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Mechanism of the MeOH/H_2O Substitution in a Series of Biomimetic Bimetallo Zinc-Based H_3O_2 Complexes

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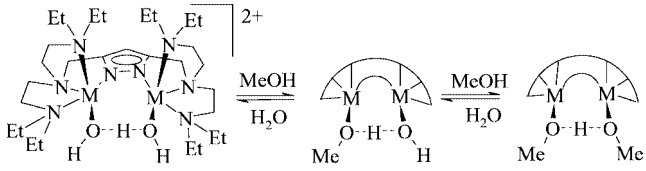
Small bimetallo biomimetic zinc-based compounds containing a bridging μ-OH functionality can be easily hydrated to yield complexes containing an intramolecular Zn–H_3O_2–Zn bridge. Because such bridges are intrinsically more nucleophilic than the corresponding μ-OH functionality, this effectively activates the complex. The Zn–H_3O_2–Zn unit is labile, and one can successively substitute the "water" and the "hydroxide" in the bridge for methanol and methoxide to form metal-bound HO–H–OMe and MeO–H–OMe functionalities. We have performed an extensive density functional investigation of this substitution mechanism for a series of bimetallo zinc complexes which have been synthesised and investigated by F. Meyer et al. There are two mechanisms for water/methanol exchange – an addition–elimination and a direct exchange mechanism. If the metal ions are coordinatively unsaturated, and their ligand sphere does not sterically hinder the approach of the methanol, both pathways compete with each other. For coordinatively saturated bimetallo complexes with larger ligand spheres, only the direct exchange mechanism is possible. Regardless of the mechanism operating, the exchange is facile and is controlled by the relative thermodynamic stability of the intermediates.

Introduction

Binuclear metallo-hydrolases have been recognised as a wide class of enzymes which contain two divalent metal ions in close proximity to each other (3.5–4.5 Å apart) in the active site, that work together in a cocatalytic manner to activate various organic substrates for hydrolysis.[1] The resting state of these enzymes often contains a μ-hydroxide bridge where a deprotonated water molecule is shared between the ions.[1] This μ-OH linkage can be relatively easily hydrated to form an intramolecular M–H_3O_2–M functionality. This is not surprising because $H_3O_2^-$ anions are quite stable in the gas phase[2] and can even be crystallised as isolated $H_3O_2^-$ anions in the solid state.[3] In the meantime, small inorganic complexes containing such H_3O_2 linkages have been reported for most of the first-row transition-metal ions (V,[4] Cr,[5,6] Fe,[7] Co,[6,8] Ni,[9,10] Cu[10] and Zn[11]), as well as for Mo,[12] W[12] and Ru.[13] In several cases, F. Meyer et al. have shown that it is possible to *selectively* obtain the μ-OH or the M–H_3O_2–M form by fine-tuning the ligand environment.[9b,14] In addition, one can replace the μ-OH and/or the H_3O_2 functionality with other ligands; for example fluoride,[15] chloride,[16] nitriles,[9d] N=C=O,[9e] carboxylates,[9e,9f] urea,[9a,9b] or N_3^-.[17]

The pyrazolate dinucleating ligand **1a** developed by F. Meyer et al. leads to the urease biomimetic $\mathbf{1_{Ni}a}$ in the presence of nickel ions.[9a] The M–H_3O_2–M functionality in $\mathbf{1_{Ni}a}$ is rather labile, as extensive kinetic studies have shown (Scheme 1).[9a] If $\mathbf{1_{Ni}a}$ is dissolved in absolute methanol, a rapid ligand exchange occurs and a CH_3O–H–OCH_3 bridged species $\mathbf{1_{Ni}c}$ can be isolated.[9a] In methanol/water mixtures, an equilibrium between three different species ($\mathbf{1_{Ni}a}$, $\mathbf{1_{Ni}b}$ and $\mathbf{1_{Ni}c}$) occurs. At low water concentrations (0.1 M) the predominate species is $\mathbf{1_{Ni}b}$ which can be independently isolated.[18] Raising the H_2O concentration to 2 M shifts the equilibrium to favour $\mathbf{1_{Ni}a}$.[9a]



Scheme 1. Methanol substitution in the H_3O_2 bridge of a binuclear urease biomimetic developed by F. Meyer et al.

Meyer's pyrazolate ligand **1a** can also be used to obtain the corresponding zinc ($\mathbf{1_{Zn}a}$)[18] and cobalt ($\mathbf{1_{Co}a}$)[19] "H_3O_2" complexes; both of which are possible functional models for binuclear phosphatases and/or peptidases. As for the nickel complex $\mathbf{1_{Ni}a}$, the M–H_3O_2–M functionality

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Supporting information for this article is available on the WWW under http://www.eurjic.org or from the author.

in $\mathbf{1}_{Zn}\mathbf{a}$ and $\mathbf{1}_{Co}\mathbf{a}$ is relatively labile and can be successively exchanged with methanol in the same manner as illustrated in Scheme 1.[18,19]

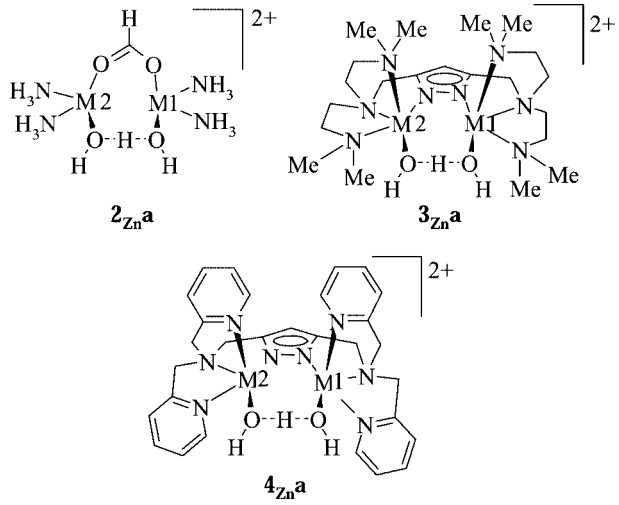
Many mononuclear zinc complexes (biomimetics for carbonic anhydrase,[20] for example) contain a metal-bound hydroxide ligand. Although the pK_a value of water (15.7) and methanol (15.1) are very similar, the Zn–OH form usually predominates in methanolic solutions, rather than the corresponding M–OCH_3 form.[21] In contrast to this, F. Meyer et al. have clearly demonstrated that, for the binuclear analogues, it is possible to select which form is present ($\mathbf{1}_{M}\mathbf{a}$, $\mathbf{1}_{M}\mathbf{b}$ or $\mathbf{1}_{M}\mathbf{c}$) by carefully controlling the reaction conditions.[18,19] This could possibly open new synthetic applications for functional binuclear biomimetica, and we have therefore, in co-operation with the research group of F. Meyer, recently become interested in the mechanism of this water/methanol exchange reaction.

There are fundamentally two possible mechanisms for the substitution of water bound in a bimetallo H_3O_2 linkage; both of which we considered in this study – an addition–elimination and a direct exchange mechanism. In the addition–elimination variant, the methanol first binds to one of the metal ions and, in a second step, displaces the water in the H_3O_2 bridge. Such an addition–elimination mechanism requires a free binding position at the metal ion, thus implicating a certain coordinative flexibility for the transition-metal ions involved. In the second variant, the methanol directly attacks the H_3O_2 bridge and replaces water through a direct exchange mechanism.

Results and Discussion

Model Systems

We selected three different model systems for study – a very simple carboxylate-bridged complex $\mathbf{2}_{Zn}\mathbf{a}$ (Scheme 2) which simulates the active site of many hydrolases containing two tetrahedrally coordinated metal ions held together by a bridging carboxylate ligand.[1] Compound $\mathbf{2}_{Zn}\mathbf{a}$ is small enough to investigate the hypersurface of these substitution reactions in detail. We then investigated the effect of the ligand sphere and the metal coordination geometry on the fundamental mechanism by means of Meyer's pyrazolate ligand-based complex $\mathbf{1}_{Zn}\mathbf{a}$,[18,19] and substituting the *N*-ethyl groups for *N*-methyl in order to reduce the calculational demand somewhat. This resulted in the model system $\mathbf{3}_{Zn}\mathbf{a}$. Increasing the complexity of the system, we then substituted the amino arms by pyridyl arms to yield the complex $\mathbf{4}_{Zn}\mathbf{a}$, which has also been reported by Meyer et al. to undergo reversible substitution by MeOH according to Scheme 1.[19] Both models $\mathbf{3}_{Zn}\mathbf{a}$ and $\mathbf{4}_{Zn}\mathbf{a}$ contain pentacoordinate metal ions. A comparison of all three of these models should allow us to determine how steric and electronic effects originating from the ligand sphere affects the intrinsic substitution mechanism(s). In all models, the ligand environments are symmetric for both metal cations. In the case of an asymmetric environment, the H_3O_2 functionality becomes polarised (as we have recently demonstrated for a computational model of the active site of bovine lens leucine aminopeptidase[22]) and one would need to investigate which "water" would be initially substituted. We selected zinc, because many of the natural systems are zinc-based hydrolases[1] and now report our findings in the present article. In continuance of our investigations, we are now calculating the cobalt analogues because many mechanistic investigations employ Co^{2+}-substituted enzymes due to the spectroscopic silence of Zn^{2+}.[23] It is quite often assumed that the mode of action of the Co^{2+}-substituted analogue parallels that of the natural Zn^{2+}-system – an assumption which we are now beginning to investigate in detail for these model compounds.



$\mathbf{2}_{Zn}\mathbf{a}$ $\mathbf{3}_{Zn}\mathbf{a}$

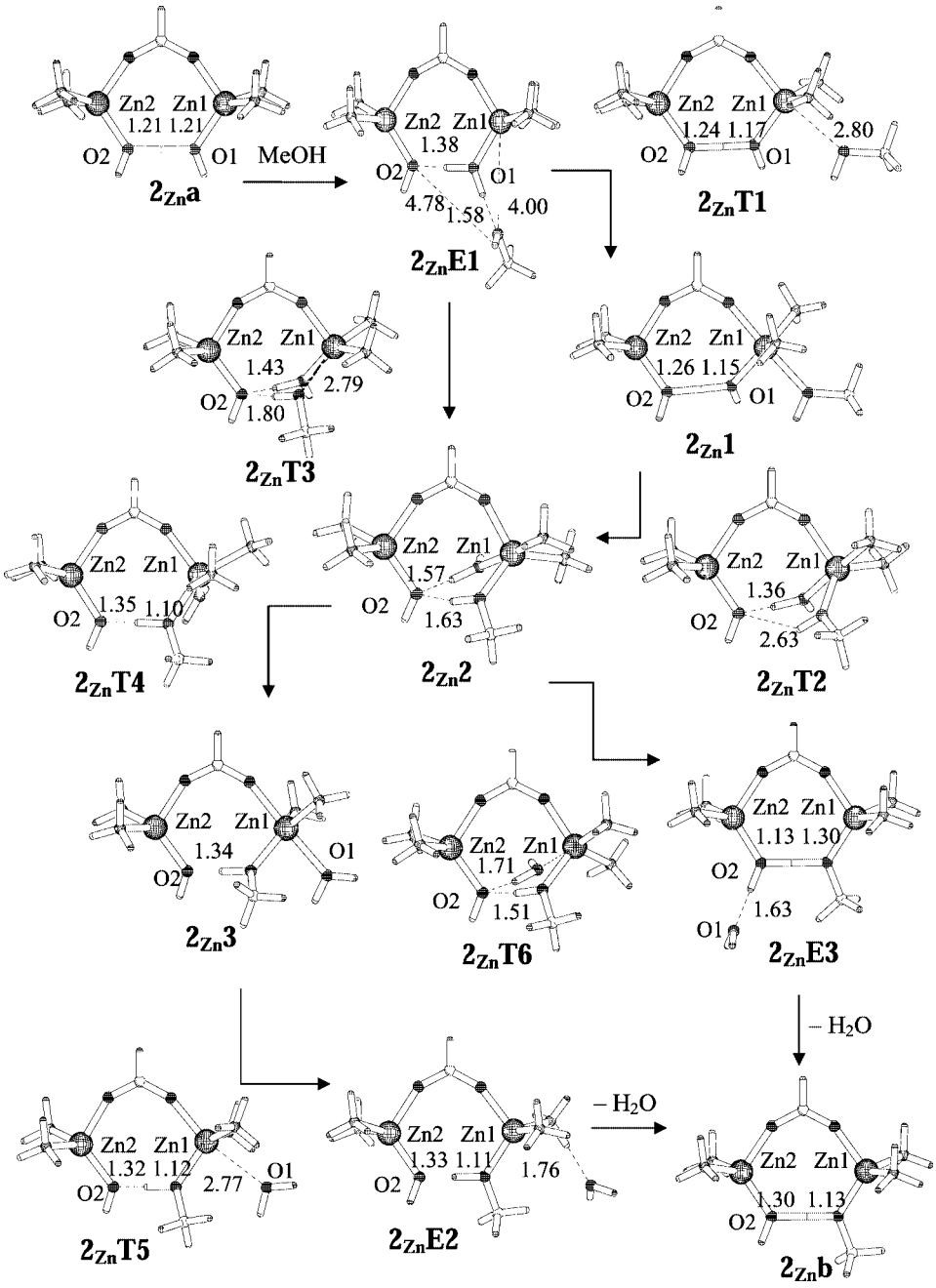
$\mathbf{4}_{Zn}\mathbf{a}$

Scheme 2. Model compounds selected for study.

Substitution Mechanism

Extensive calculations on the smallest model system $\mathbf{2}_{Zn}\mathbf{a}$ revealed that the hypersurface for the second methanol substitution is fundamentally the same as for the first. The following discussion therefore focuses on the mechanism of the first methanol/water exchange which is illustrated in Scheme 3 and Figure 1. The structures of the intermediates/transition structures involved in the second substitution can be found in the supporting information (Scheme S1 in the Supporting Information, for details see the footnote on the first page of this article).

As a methanol approaches the H_3O_2 bridge in compound $\mathbf{2}_{Zn}\mathbf{a}$, it interacts with the bridge to form a hydrogen-bonded initial encounter complex $\mathbf{2}_{Zn}\mathbf{E1}$. The methanolic oxygen is within electrostatic range (contact) of Zn1. In addition, the methanolic proton just barely "sees" the O2 in the H_3O_2 bridge. Each of these two rather weak electrostatic contacts is capable of opening up a different substitution pathway. If the MeOH swings up over transition structure $\mathbf{2}_{Zn}\mathbf{T1}$ and binds to Zn1 to generate the stable intermediate $\mathbf{2}_{Zn}\mathbf{1}$, a two-step addition–elimination mechanism is accessed. Addition of the MeOH triggers a conformational change from a tetrahedral to a trigonal bipyramidal binding situation at Zn1. This is a very low energy process with



Scheme 3. Mechanism of the first H_2O/MeOH substitution in the model complex $\mathbf{2}_{Zn}$.

an activation barrier of only 3.3 kcal/mol respective to the encounter complex $\mathbf{2}_{Zn}$**E1** (Table 1). The differential coordination of the metal ions slightly polarises the H_3O_2 bridge in the direction of a Zn1-bound hydroxide and a Zn2-bound water in $\mathbf{2}_{Zn}$**1**. The barrier for hydrogen transfer is extremely low (less than 1 kcal/mol) and the hydrogen can easily move between both oxygen atoms in the bridge. In the second step of this addition–elimination pathway, a pseudorotation on Zn1 over the transition structure $\mathbf{2}_{Zn}$**T2** swings the MeOH into the plane of the bridge which begins to disrupt the H_3O_2 functionality. This coupled process exhibits a somewhat higher barrier (6.6 kcal/mol respective to $\mathbf{2}_{Zn}$**1**). The barrier is approximately additive, because 2–3 kcal/mol are needed for the pseudorotation and 3–4 kcal/mol for bridge distortion. In the course of this process, the methanolic proton builds a strong hydrogen bond to O2 which transfers the bridging hydrogen to O1. The stable intermediate $\mathbf{2}_{Zn}$**2** is generated, in which the MeOH and the (formerly bridging) water are now both bound in a lateral manner to Zn1 and a hydroxide (O2) is localised on Zn2.

In an alternative mechanism, intermediate $\mathbf{2}_{Zn}$**2** can be accessed in a one-step manner from the initial encounter complex $\mathbf{2}_{Zn}$**E1**. In this second pathway, the MeOH swings towards the H_3O_2 bridge over transition structure $\mathbf{2}_{Zn}$**T3** and inserts itself between the metal ions. In the absence of steric effects originating from the ligand sphere, the effective

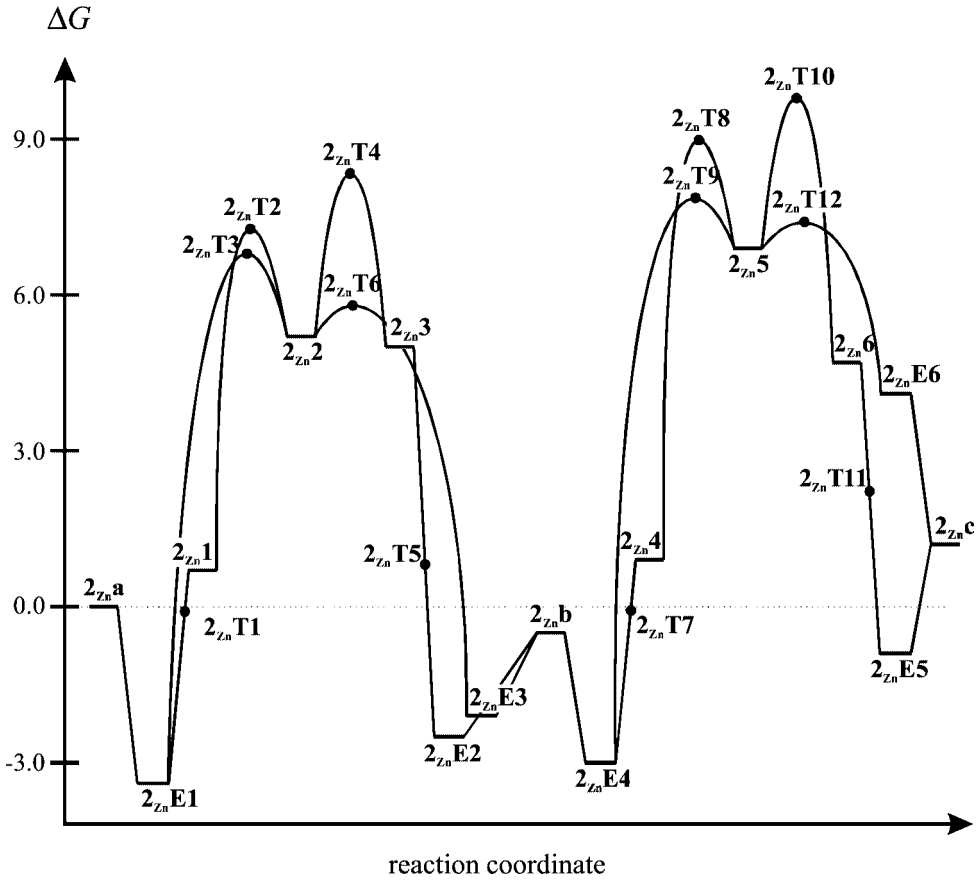


Figure 1. Energy diagram of water/methanol substitution in $\mathbf{2_{Zn}}$. Calculated at the B3LYP/aug–cc–pVTZ level of theory and given relative to $\mathbf{2_{Zn}a}$ and a free methanol.

Table 1. Relative energies (Gibb's free energies of reaction) for methanol/water exchange in the model complexes $\mathbf{2_{Zn}}$. Calculated at the B3LYP/aug-cc-pVTZ level of theory and given in kcal/mol relative to $\mathbf{2_{Zn}a}$ and a free methanol.

First substitution	ΔG	Second substitution	ΔG
$\mathbf{2_{Zn}a}$	0.0	$\mathbf{2_{Zn}b}$	–0.5
$\mathbf{2_{Zn}E1}$	–3.4	$\mathbf{2_{Zn}E4}$	–3.0
$\mathbf{2_{Zn}T1}$	–0.1	$\mathbf{2_{Zn}T7}$	–0.1
$\mathbf{2_{Zn}1}$	0.7	$\mathbf{2_{Zn}4}$	0.9
$\mathbf{2_{Zn}T2}$	7.3	$\mathbf{2_{Zn}T8}$	9.0
$\mathbf{2_{Zn}T3}$	6.8	$\mathbf{2_{Zn}T9}$	7.9
$\mathbf{2_{Zn}2}$	5.2	$\mathbf{2_{Zn}5}$	6.9
$\mathbf{2_{Zn}T4}$	8.3	$\mathbf{2_{Zn}T10}$	9.8
$\mathbf{2_{Zn}3}$	5.0	$\mathbf{2_{Zn}6}$	4.7
$\mathbf{2_{Zn}T5}$	0.8	$\mathbf{2_{Zn}T11}$	2.2
$\mathbf{2_{Zn}E2}$	–2.5	$\mathbf{2_{Zn}E5}$	–0.9
$\mathbf{2_{Zn}T6}$	5.8	$\mathbf{2_{Zn}T12}$	7.4
$\mathbf{2_{Zn}E3}$	–2.1	$\mathbf{2_{Zn}E6}$	4.1
$\mathbf{2_{Zn}b}$	–0.5	$\mathbf{2_{Zn}c}$	1.2

barriers for both processes are very similar and an equilibrium between both pathways can be expected.

Complex $\mathbf{2_{Zn}2}$ now expels the Zn1-bound water. This can again occur through either a two-step or a one-step mechanism. In the first possibility, a pseudorotation at Zn1 over transition structure $\mathbf{2_{Zn}T4}$ pulls the water down and away from its bridging position. A stable HO–H–OMe bridged species $\mathbf{2_{Zn}3}$ results which contains a pentacoordinate zinc. The activation barrier (relative to intermediate $\mathbf{2_{Zn}2}$) for this pseudorotation is with 3.1 kcal/mol again quite low. The zinc ion in $\mathbf{2_{Zn}3}$ then regains its original tetrahedral geometry by kicking out the axial water over transition structure $\mathbf{2_{Zn}T5}$. As the water leaves, it first builds an encounter complex $\mathbf{2_{Zn}E2}$ in which the departing water forms a hydrogen bond to one of the ammonia ligands before it finally departs to yield $\mathbf{2_{Zn}b}$ in which one of the waters has been substituted by methanol.

Alternatively, $\mathbf{2_{Zn}2}$ can expel the water over a one-step mechanism. The water departs over $\mathbf{2_{Zn}T6}$ in a lateral manner and simply swings down to build an encounter complex $\mathbf{2_{Zn}E3}$ before finally departing. The monosubstituted complex $\mathbf{2_{Zn}b}$ is characterised by a slightly asymmetric O–H–O bridge in which the shared hydrogen is more tightly bound to the methanol than the hydroxide.

The mechanism for substitution by a second methanol is almost identical to that calculated for the first substitution and is therefore illustrated in the supporting information (Scheme S1). An incoming methanol interacts with the hydroxide in the HO–H–OMe bridge of $\mathbf{2_{Zn}b}$ to build an initial encounter complex identical to $\mathbf{2_{Zn}E3}$. A stable intermediate analogue to $\mathbf{2_{Zn}2}$ is then generated either over a two-step metal-based addition–elimination or a one-step direct insertion mechanism. A water is then eliminated through

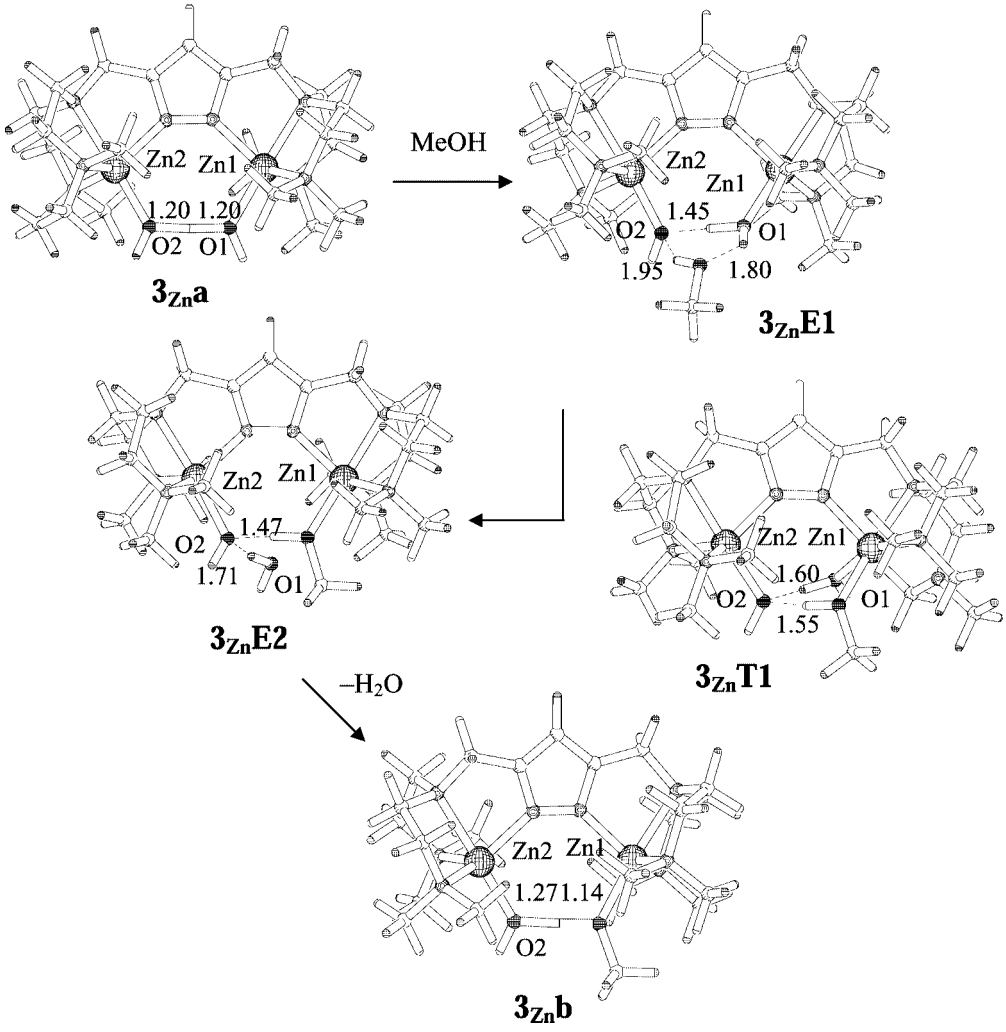
an analogous one- or two-step mechanism, which finally generates the bisubstituted product $\mathbf{2_{Zn}c}$ containing a symmetric MeO–H–OMe bridge.

As to be expected from the structural/mechanistic similarities calculated for both hypersurfaces (see Scheme 3 and Scheme S1 in the Supporting Information), the energetics of the first and the second substitution are very similar. All barriers are quite low (less than 10 kcal/mol), indicating that these processes are controlled by thermodynamic equilibrium processes. Throughout the course of these substitutions, the metal–metal distance remains with an average value of 4.57 Å quite constant.

The coordinational hypersurface is quite flat with pseudorotation barriers of only ca. 2–4 kcal/mol, thus facilitating an easy change in the coordination number. This is, in the case of zinc, not unusual[24] and is probably one of the reasons why nature often preferentially selects zinc over other transition-metal ions in the active site of multinuclear hydrolases.[1] Preliminary calculations (substitution of Co^{2+} for Zn^{2+} in model **2**) indicate that Co^{2+} ions in binuclear systems also possess a flexible coordination sphere – and the mechanism for H_2O/methanol substitution is nearly independent of the identity of the metal ion.[25]

Ligand-Sphere Effects

We then turned our attention to the sterically more demanding system $\mathbf{3_{Zn}a}$ (Scheme 2) in which both metal ions are pentacoordinate. After extensive calculations, we conclude that the steric bulk of the ligands prevents an easy expansion to an octahedral coordination sphere. We did not succeed in finding a single stable intermediate with an axial Zn–OHMe coordination analogue to the species $\mathbf{2_{Zn}1}$ (Scheme 3). The hypersurface is thus considerably simplified because only a one-step, direct substitution mechanism is possible. Although bulky, the ligand environment allows the methanol to approach the H_3O_2 bridge in $\mathbf{3_{Zn}a}$ from beneath, and an initial hydrogen-bound encounter complex $\mathbf{3_{Zn}E1}$ is formed (Scheme 4). The methanol then swings in to interact with Zn1 (which undergoes a partial pseudorotation), thus disrupting the H_3O_2 bridge. In the transition structure $\mathbf{3_{Zn}T1}$, the MeOH and the (formerly bridging) water are now bound to Zn1, which is octahedrally coordinated, and a hydroxide is localised on Zn2. Steric constraints of the ligand environment stiffens the coordination sphere of Zn1 and destabilises $\mathbf{3_{Zn}T1}$, thus leading to a much larger barrier for the substitution (17.1 kcal/mol;



Scheme 4. Mechanism of the first H_2O/MeOH substitution in model complex $\mathbf{3_{Zn}}$.

Table 2) than for the flexible model $\mathbf{2_{Zn}}$ (for which the corresponding structure $\mathbf{2_{Zn}2}$ is a stable intermediate). The complex $\mathbf{3_{Zn}T1}$ then eliminates the water which retains electrostatic contact with O2 and departs over a second encounter complex $\mathbf{3_{Zn}E2}$. The mechanism for introducing a second MeOH into the bridge to generate $\mathbf{3_{Zn}c}$ is completely analogue. The intermediates/transition structure for this second step can be found in Scheme S2 (Supporting Information).

Table 2. Relative energies (Gibb's free energies of reaction) for methanol/water exchange in the model complexes $\mathbf{3_{Zn}}$ and $\mathbf{4_{Zn}}$. Calculated at the B3LYP/lanl2dz level of theory and given in kcal/mol relative to $\mathbf{3_{Zn}a}$ or $\mathbf{4_{Zn}a}$ and a free methanol.

	ΔG		ΔG
$\mathbf{3_{Zn}a}$	0	$\mathbf{4_{Zn}a}$	0
$\mathbf{3_{Zn}E1}$	0	$\mathbf{4_{Zn}E1}$	–4.7
$\mathbf{3_{Zn}T1}$	17.1	$\mathbf{4_{Zn}T1}$	10.5
$\mathbf{3_{Zn}E2}$	7.1	$\mathbf{4_{Zn}1}$	5.8
$\mathbf{3_{Zn}b}$	4.8	$\mathbf{4_{Zn}T2}$	7.7
$\mathbf{3_{Zn}E3}$	9.0	$\mathbf{4_{Zn}E2}$	–1.2
$\mathbf{3_{Zn}T2}$	23.6	$\mathbf{4_{Zn}b}$	3.3
$\mathbf{3_{Zn}E4}$	13.8	$\mathbf{4_{Zn}E3}$	–1.1
$\mathbf{3_{Zn}c}$	10.4	$\mathbf{4_{Zn}T3}$	15.2
		$\mathbf{4_{Zn}2}$	10.4
		$\mathbf{4_{Zn}T4}$	11.8
		$\mathbf{4_{Zn}E4}$	8.6
		$\mathbf{4_{Zn}c}$	6.9

The hypersurface is illustrated in Figure 2. Methanol exchange is an endothermic process and the intermediates $\mathbf{3_{Zn}b}$ (HO–H–OMe bridge) and $\mathbf{3_{Zn}c}$ (MeO–H–OMe) are 4.8 and 10.4 kcal/mol respectively less stable than the H_3O_2 form $\mathbf{3_{Zn}a}$. Although steric constraints have considerably increased the barriers ($\mathbf{3_{Zn}T1}$ = 17.1; $\mathbf{3_{Zn}T2}$ = 23.6 kcal/mol), they are still low enough to enable an equilibrium between the three species to take place under experimental conditions. It is therefore not surprising, that the bisubstituted form **c** can only be isolated from absolute methanol. The barrier for the second addition is higher than for the first, which corresponds well with the fact that the monosubstituted form **b** is preferred in water/methanol mixtures.[18,19]

The largest system we investigated is $\mathbf{4_{Zn}a}$ which contains *N*-pyridyl arms (Scheme 2). The methanol prefers to directly attack the H_3O_2 bridge in much the same manner as calculated for the system $\mathbf{3_{Zn}}$. An initial encounter complex $\mathbf{4_{Zn}E1}$ is formed, which then undergoes a metal-assisted insertion over $\mathbf{4_{Zn}T1}$ (Scheme 5). The *N*-pyridyl arms are not as rigid as the *N*-methyl arms in model $\mathbf{3_{Zn}}$ (the flat aromatic rings can swing out and away from the H_3O_2 functionality much better than the bulky *N*-methyl groups). The substitution barrier of $\mathbf{4_{Zn}T1}$ (10.5 kcal/mol) therefore lies considerably below that calculated for $\mathbf{3_{Zn}}$ (17.1 kcal/mol). Because of this increased flexibility, the hypersurface (Scheme 5 and Figure 2) is somewhat more complicated than for the model $\mathbf{3_{Zn}}$. There is enough room to comfortably bind both the MeOH and the water in a lateral manner to Zn1, and a stable intermediate $\mathbf{4_{Zn}1}$ results, which can be directly compared to $\mathbf{2_{Zn}2}$ calculated for the most flexible model system. The water molecule then leaves the coordination sphere of the zinc ions via the transition structure $\mathbf{4_{Zn}T2}$ to first generate the encounter complex $\mathbf{4_{Zn}E2}$ and finally the stable mixed bridged species $\mathbf{4_{Zn}b}$. As for all other models, the mechanism for the second substitution is identical to the first and is illustrated in the supporting information (Scheme S3).

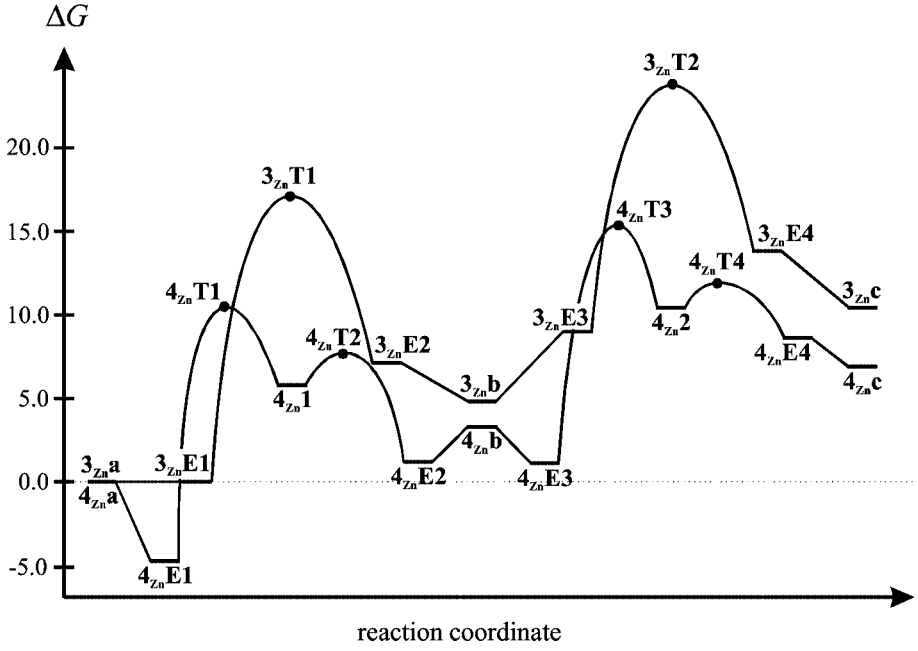
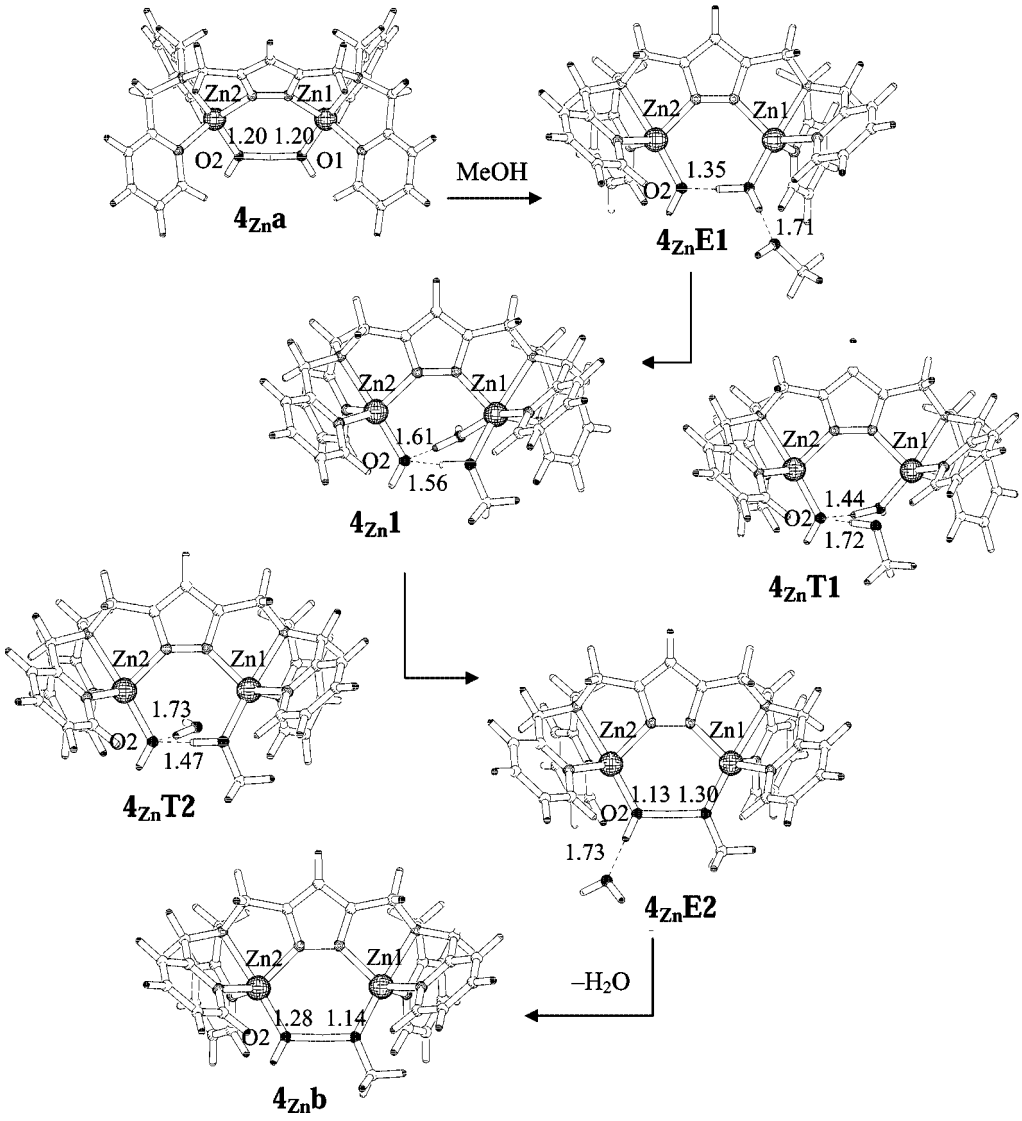


Figure 2. Energy diagram of water/methanol substitution in $\mathbf{3_{Zn}}$ and $\mathbf{4_{Zn}}$. Calculated at the B3LYP/lanl2dz level of theory and given relative to $\mathbf{3_{Zn}a}$ or $\mathbf{4_{Zn}a}$ and a free methanol.



Scheme 5. Mechanism of the first H_2O/MeOH substitution in model complex $\mathbf{4_{Zn}}$.

Relative Nucleophilicity

Biomimetic complexes containing metallated A–O–H–O–B bridges (A, B = H and/or alkyl) are potentially quite interesting for synthetic applications because the refunctionalisation of simple esters, amides, phosphates, etc. under "biological" (mild) conditions is synthetically more valuable than their simple hydrolysis. We therefore addressed two final questions of interest – which functionality, the "hydroxide" or the "methoxide" in the bridge, will be the reacting nucleophile?

Due to the ionic nature of the Zn–O interactions, the oxygen atoms possess two lone electron pairs (the O–H–O three-centred bond and the OH/Me bonds are covalent in nature). One lone pair (sp-hybridised) is involved in the ionic bond and thus oriented towards the zinc cation. The orbital of the remaining lone pair is approximately p in character and is the only lone pair available (and properly oriented) for nucleophilic attack on an incoming substrate. The energy of this p-type orbital can be expected to be one of the major factors determining the nucleophilicity. The higher it lies, the easier will be an attack on the $\pi_{C=O}$* orbital of a substrate.

NBO (natural bond orbital) analyses (Table 3) show small but clear trends in the p-orbital energies as a function of increasing substitution by methanol. These trends are independent of the model (ligand sphere) selected. The "H_3O_2" species $\mathbf{X_{Zn}a}$ can clearly be expected to be the least and the "methoxide" species $\mathbf{X_{Zn}c}$ the most nucleophilic. It is quite interesting that, for mixed bridges ($\mathbf{X_{Zn}b}$), the calculations predict that the "hydroxide" will always be slightly (average difference of 0.2 eV in their orbital energies) more nucleophilic than the "methoxide". This means that practical applications (refunctionalisation instead of hydrolysis) will probably have to be carried out under non-aqueous conditions. The atomic charges (q) on oxygen in

Table 3. NBO atomic charges q and the energy ε (eV) of the nucleophilic lone electron pair (p-orbital) on oxygen.

		q[a]	ε [eV][a]			q[b]	ε [eV][b]			q[b]	ε [eV][b]
$\mathbf{2_{Zn}a}$	O_{wat}	–1.17	–15.0	$\mathbf{3_{Zn}a}$	O_{wat}	–1.20	–13.1	$\mathbf{4_{Zn}a}$	O_{wat}	–1.20	–12.8
$\mathbf{2_{Zn}b}$	O_{wat}	–1.21	–14.8	$\mathbf{3_{Zn}b}$	O_{wat}	–1.23	–13.0	$\mathbf{4_{Zn}b}$	O_{wat}	–1.23	–12.6
	O_{Me}	–0.95	–14.5		O_{Me}	–0.98	–12.8		O_{Me}	–0.99	–12.4
$\mathbf{2_{Zn}c}$	O_{Me}	–0.98	–14.4	$\mathbf{3_{Zn}c}$	O_{Me}	–1.01	–12.6	$\mathbf{4_{Zn}c}$	O_{Me}	–1.01	–12.3

[a] Calculated using B3LYP/aug-cc-pVTZ wavefunctions. [b] Calculated using B3LYP/lanl2dz wavefunctions.

the bridges also show small but clear trends – opposing those calculated for the orbital energies. The oxygen atoms in the "H_3O_2" species $\mathbf{X_{Zn}a}$ are more negatively charged (average of 0.19 e) than those in the "methoxide" compounds $\mathbf{X_{Zn}c}$. This is due to the well known inductive effect of C–H bonds (partial delocalization of the negative charge on oxygen through hyperconjugation) and is a reason why charges should not be used to judge relative nucleophilicities.

Conclusion

Extensive DFT calculations on a series of model complexes have provided mechanistic details for the experimentally observed replacement of water molecules by methanol (and other alcohols) in metallated M–H_3O_2–M functionalities. This replacement can occur through two fundamentally different substitution mechanisms – an addition–elimination, controlled by the metal ions, and a direct exchange mechanism in which the metal ions function as templates. If the ligand sphere in the bimetallo complex is flexible and there are free coordination holes on the metal ions, these mechanisms compete with each other. In the case of "stiff" ligands and a higher coordination number at the central ions, only the direct exchange mechanism is feasible. Stiffening the ligand sphere leads to an increase in the energy barrier for substitution. However, this effect is not enough to effectively hinder substitution under experimental conditions, and one can expect a thermodynamic equilibrium between all three possible intermediates (H_3O_2, HOHOMe and MeOHOMe bridges) to occur. A "methoxide" in such a bridge is fundamentally more nucleophilic than an "hydroxide". The "H_3O_2" form $\mathbf{X_{Zn}a}$ is clearly less nucleophilic than the "methoxide" form $\mathbf{X_{Zn}c}$. However, the "hydroxide" in a mixed species $\mathbf{X_{Zn}b}$ is more nucleophilic than the "methanol" component; a fact which will have experimental consequences.

Computational Section

The calculations reported in this article were performed with the gradient-corrected, hybrid B3LYP[26] density functional using the Gaussian98[27] program package. In the case of the smallest model system $\mathbf{2_{Zn}}$, H, C, N and O were described with the very large correlation consistent aug-cc-pVTZ basis set.[28] The SDD basis[29] was employed for the central Zn^{2+} ions. The size of the larger models $\mathbf{3_{Zn}}$ and $\mathbf{4_{Zn}}$ limited our computational investigations to the smaller lanl2dz basis set (D95[30] basis for the first row atoms and the Los Alamos effective core potential plus DZ was used for Zn^{2+}[31]). We found this smaller basis set to deliver qualitatively and quantitatively approximately the same results as the much larger aug-cc-pVTZ basis. All species found on the hypersurface were characterised as energetical minima or transition structures by vibrational analyses at the B3LYP/aug-cc-pVTZ or B3LYP/lanl2dz level of theory. Default convergence criteria were used and no symmetry was employed in any of the calculations. All relative stabilities reported are gas phase Gibb's free energies that contain standard thermochemical (298 K) and vibrational corrections. Natural bond orbital (NBO[32]) analyses were carried out using B3LYP/aug-cc-pVTZ (model $\mathbf{2_{Zn}}$) or B3LYP/lanl2dz wavefunctions (models $\mathbf{3_{Zn}}$ and $\mathbf{4_{Zn}}$) using NBO version 5.0[33] as patched into Gaussian98.

The mechanism for substitution by a second methanol is almost identical to that calculated for the first substitution for all model complexes ($\mathbf{2_{Zn}}$, $\mathbf{3_{Zn}}$ and $\mathbf{4_{Zn}}$) and is therefore illustrated in the supporting information, Schemes S1, S2 and S3 (see footnote on the first page of this article).

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