

Theoretical study of nitrile hydrolysis reaction on Zn(II) ion exchanged zeolites

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Abstract

The hydrolysis of acetonitrile catalyzed by Zn^{2+} ion exchanged zeolites has been studied theoretically by DFT (Density Functional Theory). A 4T cluster ($\text{Si}/\text{Al} = 1$) with zinc in the cation position has been chosen to model the zeolite site. The action of the metal ion is found to be analogous to that of the hydrolyzing enzymes, especially *carbonic anhydrase*. The primary reaction of Zn^{2+} with H_2O is a dissociate reaction, in which ZnOH^+ species is formed together with a zeolitic proton.

Many alternate reaction paths have been analyzed and their reaction energy diagrams, including transition states, are presented. The hydrolysis reaction can be divided in three parts: hydration, isomerization and product desorption. The rate-limiting step is the nucleophilic attack of water molecule during the hydration reaction.

Water molecules play an important role in many elementary reaction steps. It may act as proton donor in the hydration and tautomerization steps and facilitates the desorption of reaction products that inhibit the reaction. A detailed comparison is made with related enzymatic reactions. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Ab-initio; Hydrolysis; Lewis acid site; Zeolites; Water molecule

1. Introduction

During the past 15–20 years there has been a significant increase and interest in the use of enzymes as catalysts for organic synthesis. There are two major reasons for the widespread use of these catalysts: (i) a variety of substrates can be reacted with a high selectivity and yield, moreover (ii) enzymes are extremely easy to manipulate. In particular, hydrolytic enzymes (e.g. lipases, esterases and acylases) have been proved to be particularly useful and widely used in organic synthesis [1].

In the specific case of hydrolysis of nitriles, this reaction represents a potentially useful synthetic method for either amide or carboxylic acids [2], taking into account that the current carboxylic acid production process is considered to be environmentally unfriendly and such acids have very high industrial demand.

The hydrolysis reaction can be performed in two different ways: directly to organic acids (using *nitrilase*) or initially via amides (using *nitrile hydratase*) which is hydrolyzed in a consecutive step to organic acids (using *amidase*). Generally, the guideline is to perform the hydrolysis of aliphatic nitriles via two steps and aromatic nitriles via a single step pathway. Several groups have been studying successfully these enzymatic hydrolysis reactions [3–8]. The yields obtained are reasonable and the selectivity

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of the desired product in some cases is higher than 95%.

An industrial application of enzymatic hydrolysis is acrylamide production. *Nitrile hydratase* is used to convert acrylonitrile into the corresponding amide [9]. This process, compared to the current route using copper catalyst, has several advantages [9]: better conversion, thus there is no need to recover the nitrile and low reaction temperature and pressure.

The general disadvantage of enzymatic catalysts, however, are their instability or low activity under high temperature conditions, which are normally necessary for high conversion.

Similarly, zeolites, which are crystalline microporous aluminosilicate materials formed by a combination from Si and Al atoms linked tetrahedrally by O atom bridges, are also subject of large interest from a scientific and industrial points of view and are widely used to catalyze several petrochemical processes [10].

These materials have unique defined pore system, cation exchange capacity and high stability (thermal and chemical). In its protonic form (H^+), zeolites catalyze proton donor reactions (acid catalyzed reactions): activation of C–H and C–C bonds [11–13], formation of dimethyl ether [14–16], hydrolysis of organic compounds [17–22] and opening of organic rings [23]. Recently, zeolites have been used for fine chemical synthesis, where selectivity of the desired compound is very important: S_N type reactions, carbocationic rearrangements, additions and β -elimination reactions [24–27].

The combination of the special characteristics of both types of catalysts: high selectivity and yield of enzymes and unique pore system and high stability of zeolites can be very useful to improve the catalytic activity for several reactions. Lately, studies have been performed in this direction. For example, zeolites substitute enzymes in the hydrolysis of fructose and glucose precursors. In this case, high temperature reactions could be used to improve both activity and selectivity [28]. Zeolites have also been used as a solid support for enzymes. Enzymes have been immobilized by adsorption [29,30] or catalytically active molecules have been synthesized inside of the micropores (zeolite or mesoporous support), the so-called “Ship-in-the-bottle” method [31–36].

Our interest is to study theoretically the nitrile hydrolysis reaction catalyzed by zeolites, whilst combin-

ing the special features of enzymes. One way to investigate this is to mimic the enzyme active site inside of the zeolite frame.

The enzyme active site for hydrolysis has been indicated, in some cases, to be metal cations: Fe^{3+} or Co^{3+} in *nitrile hydratase* [3,8]; Zn^{2+} in *carbonic anhydrase* [8,37–47]; *alcohol dehydrogenase* [48] or *zinc-peptidases* [49] and Ca^{2+} in the *staphylococcal nuclease* [37,38] being common examples. The most suitable active site for hydrolysis can be determined by analyzing four states along the reaction pathway: (1) interaction between the reactant and the active site; (2) formation of OH^- nucleophile; (3) subsequent OH^- nucleophilic attack on the reactant; and (4) product desorption.

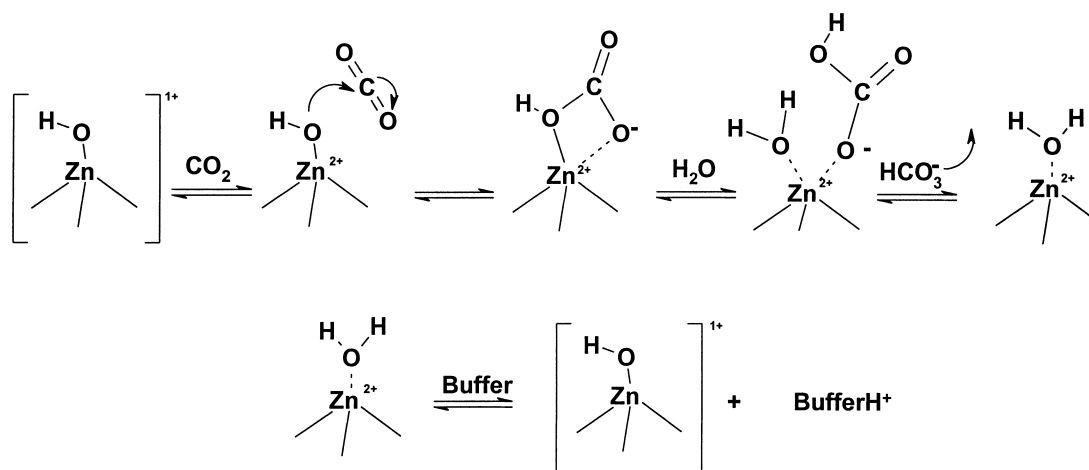
One example of this mechanism is *carbonic anhydrase* found in the red blood cells of living organisms [39–47]. This enzyme performs hydration of CO_2 to HCO_3^- . The zinc cation activates a water molecule by creating $ZnOH^+$. The reaction proceeds via OH^- nucleophilic attack on CO_2 (see Scheme 1).

This active site (Zn^{2+} cations) can also be found in some substituted zeolites: zinc containing zeolites catalyze dehydrogenation of light paraffins such as ethane [50–53]; aromatization of in situ generated ethylene [54]; propane [55] and hydration of acetylene [56–60], which has a similar mechanism to one found for *carbonic anhydrase*. Zinc ion exchanged zeolites can be prepared by different methods, such as solid-state ion exchange, chemical vapor deposition [61,62] or by ion exchange and impregnation [52,53].

Based on the active site found in *carbonic anhydrase* and for acetylene hydration, our model was chosen to be a 4T ring (with Si/Al = 1), in which both Brønsted site protons were substituted by zinc ion. The model allows one to study directly the catalytic effect of the substituted cation (Zn^{+2}) on the nitrile hydrolysis, similar to catalytic effect found for CO_2 hydrolysis on the *carbonic anhydrase*.

The chosen probe molecule is acetonitrile, since it is the smallest nitrile molecule being applied in either experimental [17,19,63,64] or theoretical [18,22,65] studies.

Furthermore, the nitrile hydrolysis has also been studied experimentally using other catalysts [17–19,22,66–73], which gives an interesting data set for further comparisons.

Scheme 1. Enzymatic CO₂ hydration.

2. Methods

A 4T cluster fragment with $(\text{Al}(\text{H}_2)\text{OSi}(\text{H})_2\text{OH})_n$ basic unit ($n = 2$) is used to model the zeolite acid site (see Fig. 1). The initial geometry was taken from

the faujasite X-ray results available in the Insight II package [74]. Studies were limited to the small size cluster to save computational time and to focus on the different elementary reaction steps, the primary interest of this work.

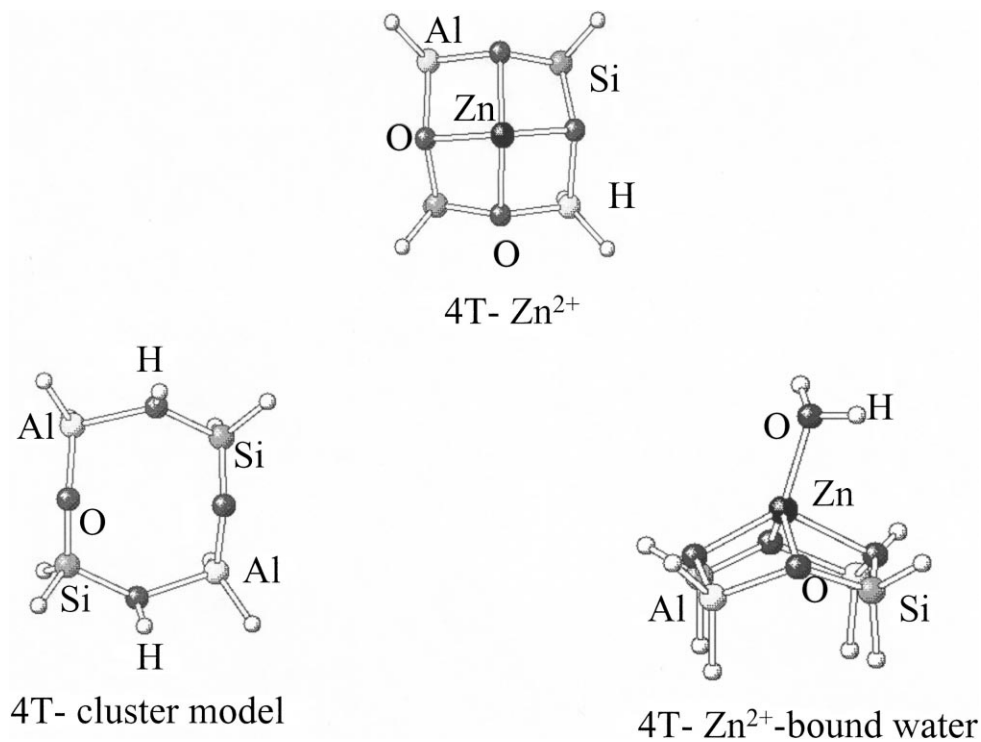


Fig. 1. Cluster models and active sites.

The choice of H-terminated Si group rather than OH-terminated group is used to avoid problems such as intramolecular hydrogen bonds, which can result in significant artifacts [75]. It has been shown that the clusters provide qualitatively interesting results, although activation energies are typically 10 kJ/mol higher than those found for extrapolated bulk zeolite reactions. The use of such clusters has been extensively discussed elsewhere [75–77].

All calculations have been performed using double zeta valence plus polarization (DZVP) function for all atoms. This basis set is designed to provide double $-\zeta$ quality in the valence orbital region and a single function to represent the less chemically reactive core orbital [78]. This basis set incorporates polarization functions on all atoms, except for hydrogen. A second auxiliary basis set (A1) was also used to expand the electron density in a set of a single-particle Gaussian-type functions [79] typically used by default in the DGauss package code [80]. Large basis set, double $-\zeta$ type, has been shown accurate in energy predictions and geometry configurations [81].

Density functional theory (DFT) has been used in this study. The Becke exchange energy [82] plus Lee–Yang–Parr correlation functional (BLYP) [83] have been employed. These functionals give acceptable values for molecular energies and reasonable values for geometries [81].

Frequency calculations were performed in order to verify the stationary point geometries. These tests result in no imaginary frequencies, which indicate that these stationary points were local minima, or in one imaginary frequency, which corresponds to transition state [84].

All energies were corrected using zero-point energy (ZPE). The chosen basis set was previously optimized for use in order to minimize the basis set superposition error (BSSE), as suggested by Radzio et al. [85].

No symmetry constraints have been used in the present work. Some extra transition states were calculated by including water molecules to our system. Furthermore, one geometry configuration was calculated by using “water rings” (with seven and five water molecules).

3. Results and discussion

Three specific points will be analyzed for the nitrile hydrolysis reaction. Initially, the active site for both Zn cation exchanged zeolite and *carbonic anhydrase* enzyme will be compared. In the second part, the reaction path will be discussed by studying different mechanisms, which depend on the activated reactant (water or acetonitrile). In parallel, the ancillary effect of water molecule will be verified, analyzing the changes in the activation energy and desorption energy of acetamide.

3.1. Active site study

Strong Lewis acids such as a divalent metal cations are found to be the active site in different ligand environment: dirhenium [73] and palladium(II) complexes [70] in acetonitrile hydrolysis; Ce(III) and Cd(II) exchanged zeolites for phenylacetylene hydration [67]; copper(II) in copper-containing micelles [86] for amide and ester hydrolysis; zinc cation in *carbonic anhydrase* for CO₂ hydrolysis [39–47]; zinc cation in polyamine complexes for different hydrolysis reactions [87] and also in zeolites for acetylene hydrolysis [56–60].

Carbonic anhydrase is surrounded by one water molecule (so-called Zn-bound water) and three chains of histidine amino-acids. In polyamines (triamines), it replaces protons inside of polycyclic-amine cavity. In these catalysts, the water molecule is considered as the fourth ligand. In zeolites, zinc ion substitutes protons, being surrounded by oxygen atoms from the frame [55,58,61,62,88,89]. The coordination number, however, depends on the degree of hydration. Roessner and coworkers [88] indicated that zinc has octahedral coordination in MFI, since the hydrate shell around zinc ion contains six water molecules, but a decrease in the coordination number was observed on elevation of temperature. Iglesias and coworkers [55], also studying Zn–H–MFI, found that zinc coordination is only four after thermal dehydration.

In the present work, zinc is tetra-coordinated in the 4T cluster (Fig. 1), similar to the active systems mentioned. Comparing the distances Zn–O in our model with the distances found for Zn–N in enzymes and Zn–O in zeolites, the geometric similarity becomes more evident, see Table 1. Its coordination

Table 1
Distance between Zn ion and the ligands (in Å)

	Distance Zn-X	
	X=O	X=N
Enzymes	2.12 [40]-water	2.06, 1.99 [40]
	2.0 [41]-water	2.1 [41]
	1.92 [43]-water	1.97, 1.94 [43]
	2.04 [48]-water	2.25 [48]
Zeolites	2.09 [55]	–
	1.56 [88]	
	1.97, 1.99 [89]	
Polyamines		2.00, 2.04, 2.01 [87]
This work	2.08 (frame)	
	2.13 (frame), 2.11-water	

number also changes with the degree of hydration. From tetra-coordinated in Zn-zeolite model (Fig. 1a) to 4 + 1 coordination in Zn-bounded water-Zeolite model (Fig. 1b). This 4 + 1 coordination of the zinc cation is also found in *carbonic anhydrase* upon CO₂ adsorption [43].

Another interesting point about the zinc position is that it prefers coordination out of the plane of the oxygen atoms. This was not observed in other zeolite model calculations, where Co²⁺ and Zn²⁺ stayed in the plane of oxygen atoms in a six and five-ring models, respectively [90,91]. This position is very important for the accessibility of the active site, which has been verified for tetraaminecyclam [87] and for *carbonic anhydrase* [45,46].

However, the zinc ion must be activated by formation of a ZnOH⁺ species. This is the known mechanism for CO₂ hydrolysis, illustrated in Scheme 1. This activation proceeds via dissociation of a water molecule. This activation is known to occur in systems such as: Zn-zeolites [55,92]; Zn-polycyclic-amines [87,93,94]; Cu-containing micelles [86]; palladium(II) [70] and dirhenium complexes [73]. In an interesting study of MnO₂ as a catalyst for acrylonitrile hydration in liquid phase, zinc was used to substitute protons in hydroxyl groups formed on the oxide surface [66], which were claimed to be the active centers. After the proton substitution there was no activity for the related reaction. Nothing was discussed, however, about zinc ion inactivity, since, even water molecules were present in the reaction medium. But the formation

of ZnOH⁺ was impossible, due to the lack of basic oxygen, free on the surface.

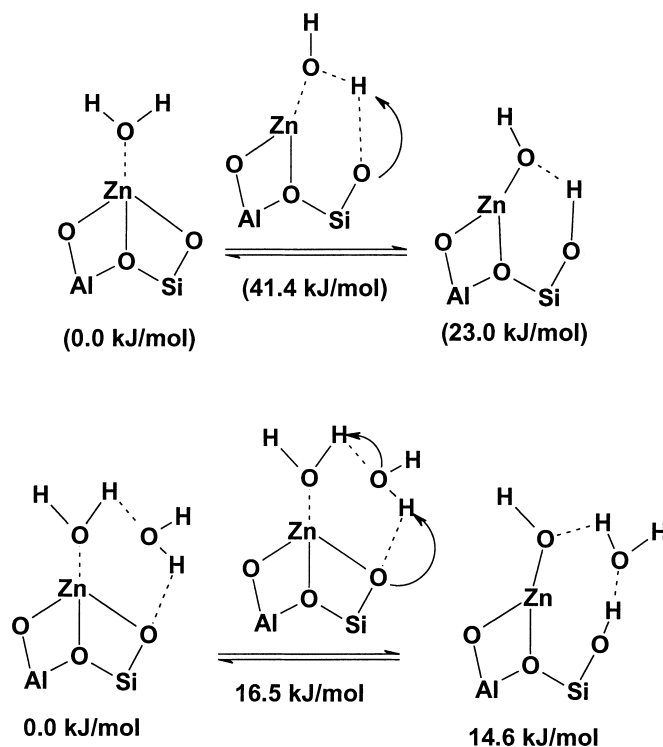
In the case of enzymes, this Zn-bound water dissociation is considered the rate-limiting step (see Scheme 1). Several mechanisms have been proposed for this proton transfer: (i) intramolecular proton shuttle between one histidine group and the Zn-bound water [42]; (ii) transfer the proton by a bridge of water molecules to the histidine group [44–46]; and (iii) transfer by external buffer [39,40], including the bicarbonate just formed in the reaction [45].

In our model, this activation process occurs by intramolecular proton transfer. The proton is transferred to the frame oxygen, thus creating a Brønsted site (see Scheme 2). It will be demonstrated, later that this Brønsted site can also participate in the hydration of acetonitrile, as well as in acetamide desorption from the active site. This water molecule dissociation has a low activation energy (41.4 kJ/mol), and is endothermic reaction, +23.0 kJ/mol. The calculated equilibrium constant for dissociation at room temperature by Eq. (1) was found to be equal to 2.5×10^{-5} . This result agrees with previous experimental work, which showed that ZnOH⁺ is not thermally stable and undergoes dehydration by coupling with acidic OH groups to form water [55].

$${}_T K^0 = \exp\left(\frac{-\Delta_{t,T} G^0}{RT}\right) \quad (1)$$

The computed activation energy for water molecule dissociation is in good agreement with theoretical calculations for enzymatic systems: it is around 37 kJ/mol for *carbonic anhydrase* [46] and 38.5 kJ/mol for *alcohol dehydrogenase* [48].

In *carbonic anhydrase*, the addition of water molecules, assisting the proton transfer, decreases the activation barrier from around 140 kJ/mol to a previous given value of 37 kJ/mol [46]. In our model, the presence of a second water molecule (see Scheme 2) decreases the activation barrier to the value of 16.5 kJ/mol and increases the equilibrium constant for the proton dissociation to 1.0×10^{-4} . This value is 40 times higher than the original value, which indicates that water molecule assists the proton transfer in our model. There is not a large energy gain in this water addition, one possible explanation is that the nature of the H-bond has not changed in both cases. These H-bonds can not be considered weak interaction, in



Scheme 2. Dissociation of zinc-bounded water.

which the O–O distance is shown to go from 2.8 to 3.0 Å [95]. For example, in the absence of water molecule the O–O distance (OH group from zinc and OH from the Brønsted site) is 2.69 Å and it becomes 2.64 Å in the presence of water (between OH (Zn^{2+}) and O (water)) and 2.57 Å for O (water) and OH (the Brønsted site).

The dissociation of a water molecule is not the rate-limiting step for the acetonitrile hydration by zeolitic Zn^{2+} ion. This is in contrast to the enzymatic case [39–47].

3.2. Reaction mechanisms

The mechanism of nitrile hydrolysis can be divided in three different steps: hydration, isomerization and product desorption. The hydration step includes two different parts: activation of the reactant and nucleophilic attack by water. The isomerization step is the transformation (tautomerization) of the iminol intermediate into acetamide, studied by many other au-

thors [17,18,22,69,72,96]. Finally, the desorption of acetamide occurs followed by restoration of the active site.

3.3. The hydration step

Both reactants (water and acetonitrile) compete for the active site. This does not occur in enzymes, because the water molecule is already one of the zinc ligands [39–47]. The interaction of these molecules has been studied previously for different metal cations: Pd^{2+} [70], K^+ [97] and Zn^{2+} exchanged zeolites [98]. For *cis*-[Pd (ethane-diamine) (H_2O) $_2$] $^{2+}$ [70], the equilibrium constant for displacement of a water ligand by acetonitrile at 293 K is about 22 $\text{K}/\text{dm}^3 \text{mol}^{-1}$. In potassium ion clusters [97] binding energies for gas phase have been calculated using the ab-initio RHF method, acetonitrile is shown to bind stronger than water molecule. The latter study indicates that acetonitrile binds better to Zn^{2+} ion than the Brønsted site. This means that acetonitrile as a ligand is pre-

Table 2
Hydration mechanisms: reaction and activation energies (in kJ/mol)

Hydration mechanism		
	Energy cost	Activation energy
Step from model A		
0 → 1	-115.2 (water adsorption)	-
1 → 3	+23.0	41.4
3 → 4	-22.7 (acetonitrile adsorption)	-
4 → 6	+14.6	37.0
6 → 8	+12.6	25.8
Step from model B		
4 → 6	-6.9	62.2
Step from model C		
3 → 4	-8.1 (acetonitrile adsorption)	-
4 → 6	+12.6	25.8
Step from model D		
3 → 4	-73.0 (acetonitrile adsorption)	-
4 → 6	+69.9	122.3
Step from model E		
0 → 1	-125.5 (acetonitrile adsorption)	-
1 → 2	-58.1 (water adsorption)	-
2 → 4	+18.4	+42.2
4 → 6	+69.9	122.3
Step from model F		
1 → 3	-118.5	+186.3
Step from model G		
1 → 2	-22.3 (water adsorption)	-
2 → 4	+52.5	+66.9

ferred to water on such cations. In our work, the same trend is observed. The acetonitrile binding energy is -125.5 kJ/mol, while the water binding energy is only -115.2 kJ/mol (see Table 2).

This small binding energy difference does not eliminate the possibility of water activation. Water can also bind to the zinc ion when acetonitrile is already adsorbed and in this case its binding energy decreases to -58.1 kJ/mol. The zinc cation has now an increased coordination to 6, which has been found experimentally for Zn-zeolites [88]. The activation of a water molecule by the zinc ion (formation of ZnOH^+) happens in the second step of the mechanism.

In enzymatic system, theoretical calculation has shown that the water binding energy has a higher value than ours: -146.9 kJ/mol [38]. In the studied model, a water molecule is the fourth ligand on the zinc ion with the other three ligands being neutral.

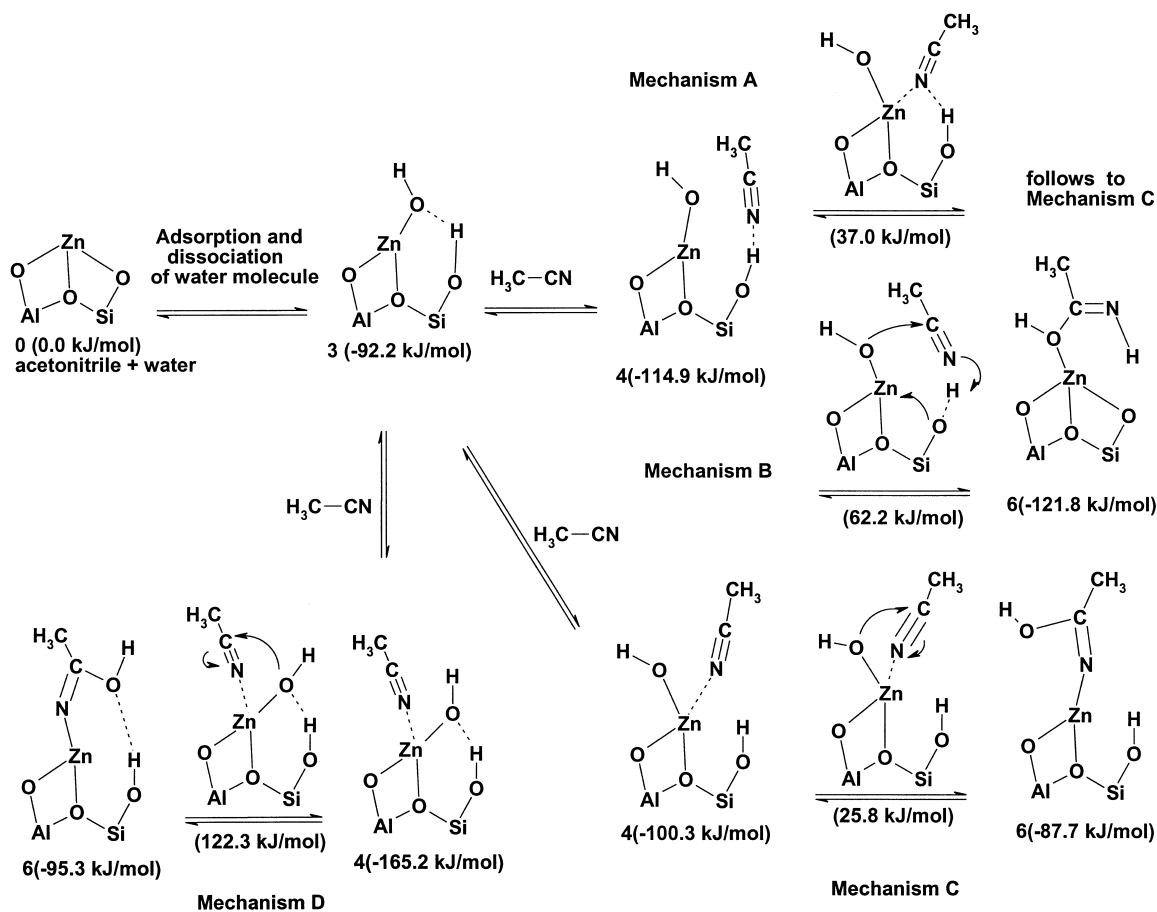
The mechanisms based in water activation will initially be discussed. There are four different paths, the main difference is related to how acetonitrile is activated and reacts with a water molecule (see Scheme 3a).

In mechanism A, water is activated by dissociation of the OH bond. This dissociation produces a Brønsted site, on which acetonitrile adsorbs. Then acetonitrile is transferred from the Brønsted to the Lewis site. This is relatively easy (37.0 kJ/mol), but the result is not stable because of two factors: a relatively strong H-bond (distance N–O, 2.79 Å) is broken and the OH group changes its position by acetonitrile repulsion. Since acetonitrile is adsorbed on the zinc ion, the nucleophilic attack by OH occurs with very low activation energy (25.8 kJ/mol). This activation energy is lower than previously calculated for the *carbonic anhydrase* mechanism 54.8 kJ/mol (semi-empirical) [45] and to the experimental value for the β -lactam hydration by ZnOH^+ -macrocylic tetraamine (around 49 kJ/mol) [93]. All energy costs and activation energy can be seen in Table 2.

In mechanism B, acetonitrile is protonated by the Brønsted site simultaneously with the OH nucleophilic attack (concerted reaction). In this case, the bi-functionality of zeolites has been used. Acetonitrile does not need to be transferred to the zinc ion to be activated. However, the activation energy of the nucleophilic attack increases to 62.2 kJ/mol in comparison with mechanism A. This mechanism has two major drawbacks: the intermediate is very stable and the NH group is not activated by the zinc cation, which will be important for the next reaction step — isomerization.

Mechanism C is slightly different from mechanisms A and B. Acetonitrile adsorbs directly on the Lewis site (Zn^{2+}). Compared with the previous mechanisms (see Scheme 3a), this path initially has two advantages: fewer number of steps and lower activation energy. Acetonitrile adsorption on the zinc cation, however, is not favorable compared to the Brønsted site (see Table 2). Acetonitrile adsorption is slightly exothermic (-8.1 kJ/mol). The nucleophilic attack of OH is the same shown in mechanism A.

Interestingly, acetonitrile adsorption can result in two different configurations (4) (see structures number 4 for mechanisms C and D). The main difference is the side, where acetonitrile is adsorbed related to



Scheme 3. Hydration mechanisms: (a) water molecule activation and (b) acetonitrile activation.

OH group. In mechanism D, acetonitrile is adsorbed in the left side of OH group. This group suffers a repulsion and moves towards the Brønsted site. Due to the strong H-bond formed, the new configuration is more stable by 64.9 kJ/mol, in the present case this O–O distance is 2.49 Å (ZnOH⁺ and the Brønsted site oxygen), compared with the O–O distance <2.5 Å [95].

Based on these results, the hydration mechanism starting with water activation might be represented by both C and D mechanisms. Even though acetonitrile prefers to adsorb as configuration D(4), the activation energy of the nucleophilic attack is about 96.7 kJ/mol lower in mechanism C.

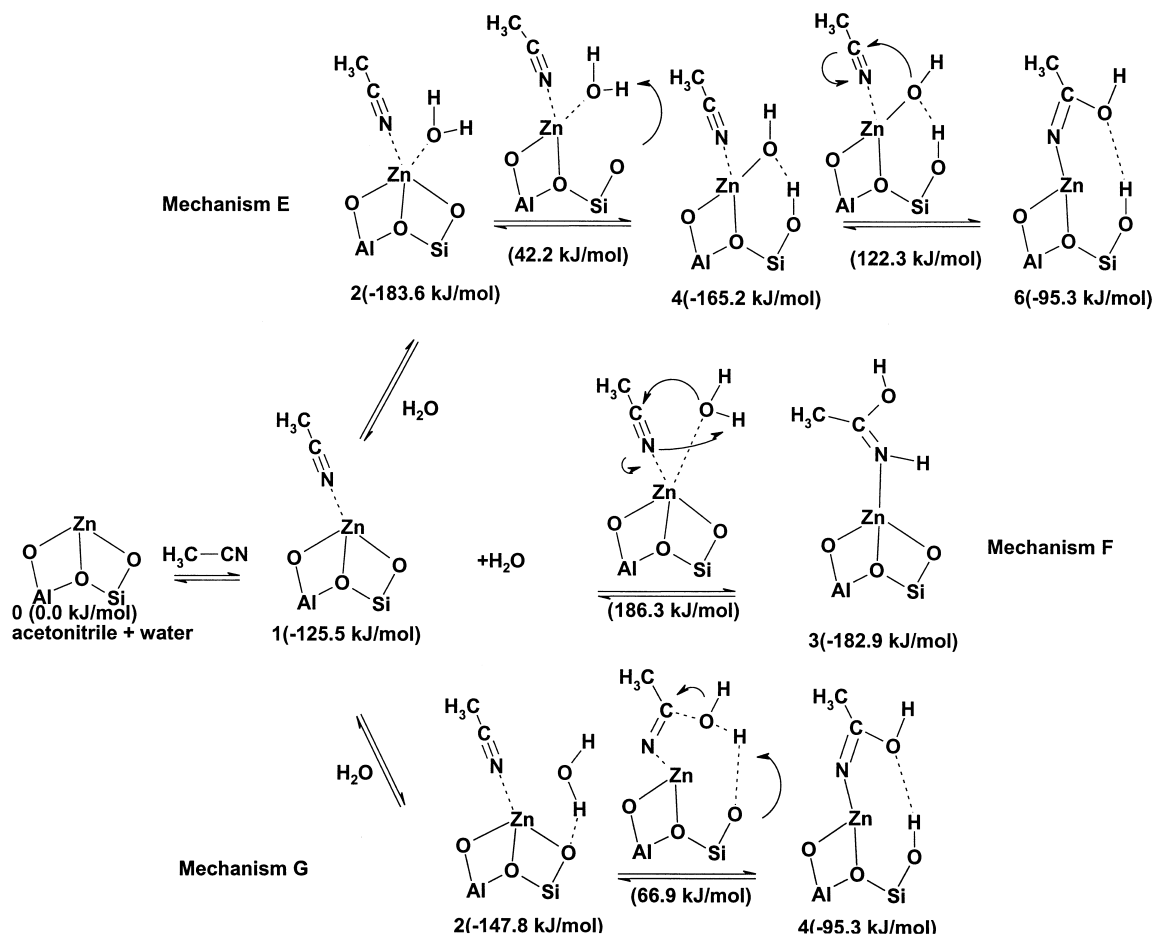
These mechanisms (C and D) might produce different optical isomers because of the relative position

of OH group. This would be an interesting probe to distinguish one mechanism from another.

As seen before, acetonitrile interacts strongly with the Lewis site. Three different reaction paths have been analyzed starting in this way (Scheme 3b).

In mechanism E, even after acetonitrile adsorption, water can bind to the Lewis acid. This adsorption is favorable, but less than the value found for mechanisms A, B, C and D. Theoretical studies of Cu⁺ and Cu(OH)⁺ in zeolites also indicate that the water binding energy decreases when a second water molecule is adsorbed to the metal ion [99,100].

Water dissociation requires more energy (42.2 kJ/mol). Interestingly, this dissociation energy has the same value found in the previous mechanisms, which



Scheme 3. (Continued).

indicates that the presence of acetonitrile does not influence the dissociation reaction. The nucleophilic attack is similar to the one found for mechanism D, therefore both intermediate configurations are identical.

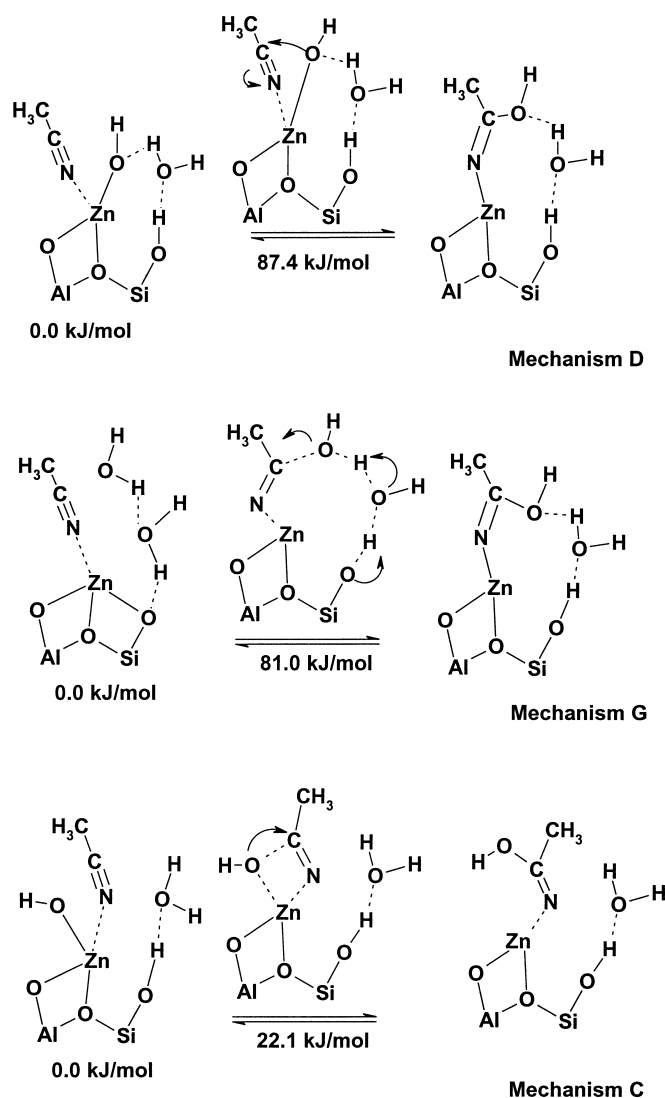
In mechanism F, acetonitrile reacts directly with water. One could expect a high activation barrier, because only acetonitrile has been activated by the catalytic site. Indeed this energy is 186.3 kJ/mol, much higher than any activation energy found so far.

In contrast to what is observed in mechanism B, the intermediate has the appropriated configuration (compare Scheme 3a — mechanism B and Scheme 3b — mechanism F), this means NH group is being activated by the active site. Furthermore, this inter-

mediate geometry is very similar to one found for mechanisms D, E.

In mechanism G, the bi-functionality of zeolites has been verified once more. The water molecule is activated by the basic oxygen atom from the zeolite frame. The nucleophilic attack occurs simultaneously with the Brønsted site formation (dissociation of water). It is the only case, in which the dissociation of water and the nucleophilic attack are coupled in a concerted mechanism. The intermediate has also the same geometry as the previous three mechanisms.

A similar mechanism has been proposed for this reaction in an experimental study using hydroxylated zirconium dioxide as catalyst [69]. Acetonitrile adsorbs on zirconium (Lewis site), while water is acti-



Scheme 4. Hydration mechanisms: water ancillary effect.

vated by the basic oxygen atom. The reaction occurs directly via nucleophilic attack on acetonitrile simultaneously with water dissociation.

Mechanism G produces a reaction diagram that is the most favorable of the paths studied here. It has the least number of steps, as well as a lower activation energy for the nucleophilic attack than mechanisms D and E. Mechanism C has the lowest activation energy for the nucleophilic attack, but it has the disadvantage of low acetonitrile binding energy: -8.1 kJ/mol.

This mechanism can, however, be an alternative for the hydration step when, water is employed in excess.

In enzymes, as mentioned before, water plays an important role during the reaction. To analyze this, three nucleophilic steps in the hydration mechanism were studied by adding one extra water molecule (Scheme 4). The first step is the nucleophilic attack as in mechanism D. In the absence of water molecules, this higher activation energy results from the cleavage of a strong H-bond (between OH group from

Table 3
Hydrolysis reaction: water ancillary effect and activation energies (in kJ/mol)

	$\Delta E_{st}(\text{Ts}), \Delta E_{st}(\text{React})$	Activation energy after adding one water molecule
Hydration mechanism		
Steps from models A, B, C and D		
1→3	−86.6, −61.8	16.5
Step from model D		
4→6	−72.7, −37.8	87.4
Step from model C		
4→6	−51.6, −47.9	22.1
Step from model G		
2→4	−46.2, −60.4	81.0
Isomerization (tautomerization)		
Step from configuration A	−108.8, −31.9	14.8
Step from configuration B	−135.6, 27.0	16.0
	Adsorption cost for an extra adsorption on Zn^{2+}	Acetamide displacement energy
Desorption of acetamide from configuration E		
Water addition	−79.0	48.1
Acetonitrile addition	−46.8	45.1
Desorption of acetamide		
Displacement of acetamide by acetonitrile		−52.7

ZnOH^+ and the Brønsted site proton). However, the presence of an extra water molecule, which is positioned between the OH group and the proton, forces the OH group to move towards the acetonitrile. This reaction occurs with a lower activation barrier. The new value found is 87.4 kJ/mol (see Table 3), which corresponds to a reduction of 34.9 kJ/mol from the original value. This new value is still higher than the activation energy found in mechanism C.

The second step is the nucleophilic attack as in mechanism G. The extra water molecule acts now as a proton donor and a nucleophilic agent simultaneously. The activation barrier is not lower, when an additional water molecule is added. Instead, the final activation energy increases to 81.0 kJ/mol (see Table 3). If one analyzes the stabilization energy of the transition state ($\Delta E_{st}(\text{Ts})$) and the reactants ($\Delta E_{st}(\text{react})$) [96], the reactants are more stabilized than the transition state. In this case, the result is not favorable, although the transition state is stabilized.

The third step is present in mechanism C. The addition of an extra water molecule decreases slightly the

activation energy for the nucleophilic attack. The new calculated activation energy is 22.1 kJ/mol and is the lowest found for the nucleophilic attack. Thus, taking into account these results, mechanism C became preferred. Mechanism G may, however, be preferred in the presence of excess of acetonitrile.

Finally, the presence of zinc ion in zeolites modifies the mechanism of acetonitrile hydration, compared with protonic zeolites [22]. Acetonitrile is not activated by protonation, but by interaction with zinc ion. Furthermore, the water molecule plays an important role in the hydration, by stabilizing the transition state, which is not found in protonic zeolites.

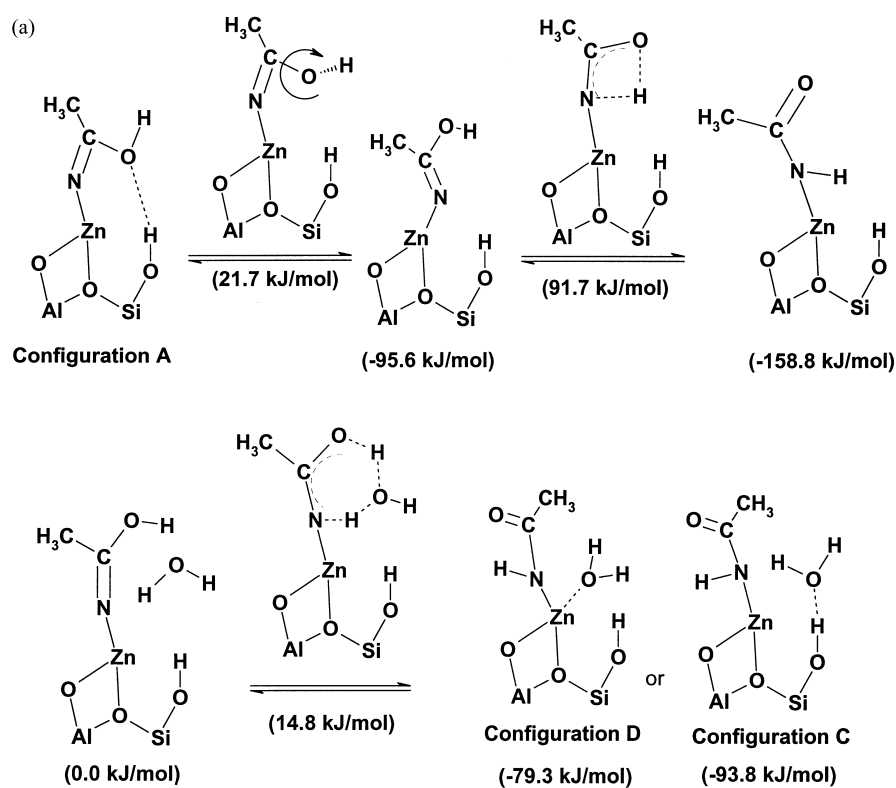
3.4. The isomerization step

Among all the mechanisms studied in Section 3.3, two were chosen to be studied using follow-up steps: C and G. From these mechanisms, two different intermediate configurations (an iminol-type compound) result (see Scheme 3). The first configuration (configuration A — Scheme 5a) has a H-bond between its

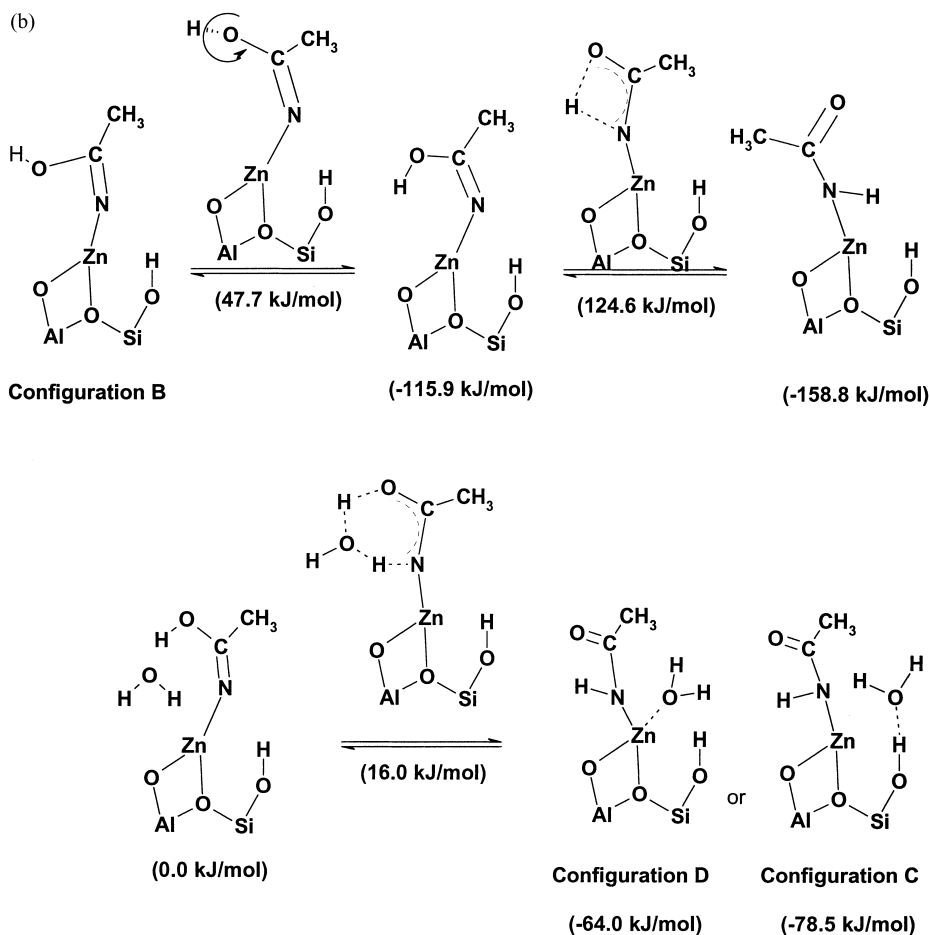
Table 4

Isomerization and desorption mechanisms: reaction and activation energies (in kJ/mol)

	Reaction energy	Activation energy
Isomerization mechanism		
Step from configuration A		
Rotation of C–OH bond	+0.3	21.7
Tautomerization	−63.2	91.7
Step from configuration B		
Rotation of C–OH bond	−28.2	47.7
Tautomerization	−42.9	124.6
Desorption of the product		
Step from configuration C		
Protonation	−35.7	1.4
Displacement of acetamide by water from configuration E	30.9	–
Water desorption from configuration E	73.3	–
Acetamide desorption from Zn-model	72.8	–
Step from configuration D		
Protonation	+19.6	43.1
Acetamide desorption from ZnOH ⁺ -model	−15.6	–



Scheme 5. Isomerization and tautomerization mechanism: water ancillary effect of (a) configuration A and (b) configuration B.



Scheme 5. (Continued).

OH group and the Brønsted site of the frame, whilst the other is configuration B (see Scheme 5b). Mechanism G results in an intermediate configuration A, whilst mechanism C results in the other intermediate configuration (B).

The isomerization mechanism is composed of two different steps: OH bond rotation and proton transfer from the OH group to nitrogen atom. The rotation requires low activation energy in the case of configuration A (see Table 4). The energy difference between the activation barrier in those two paths is mainly caused by the H-bond, which activates the OH group.

However, the second step, the proton transfer (tautomerization), requires a high activation energy: 91.7 and 124.6 kJ/mol, respectively. In both mechanisms, the proton transfer barrier is even higher than in the

previous nucleophilic attack. This higher activation barrier for the proton transfer in tautomerization has been observed previously by the authors for the same isomer on different catalysts [22,96], as well as for formohydroxamic acid tautomers, which is a parent molecule of hydroxy imine [101].

Similar to the previous case, the ancillary effect of a water molecule was studied for proton transfer. Water acts as a bridge, transferring proton from the OH group to nitrogen, see Scheme 5a and b. The original barriers decrease to the value of 14.8 and 16.0 kJ/mol, respectively. The energy gain, in these cases is 76.9 and 108.6 kJ/mol.

The same water synergistic effect, in proton transfer reactions has been observed by others: hydrolysis of N-nitrobenzenesulfonamides and H-nitrobenzamides

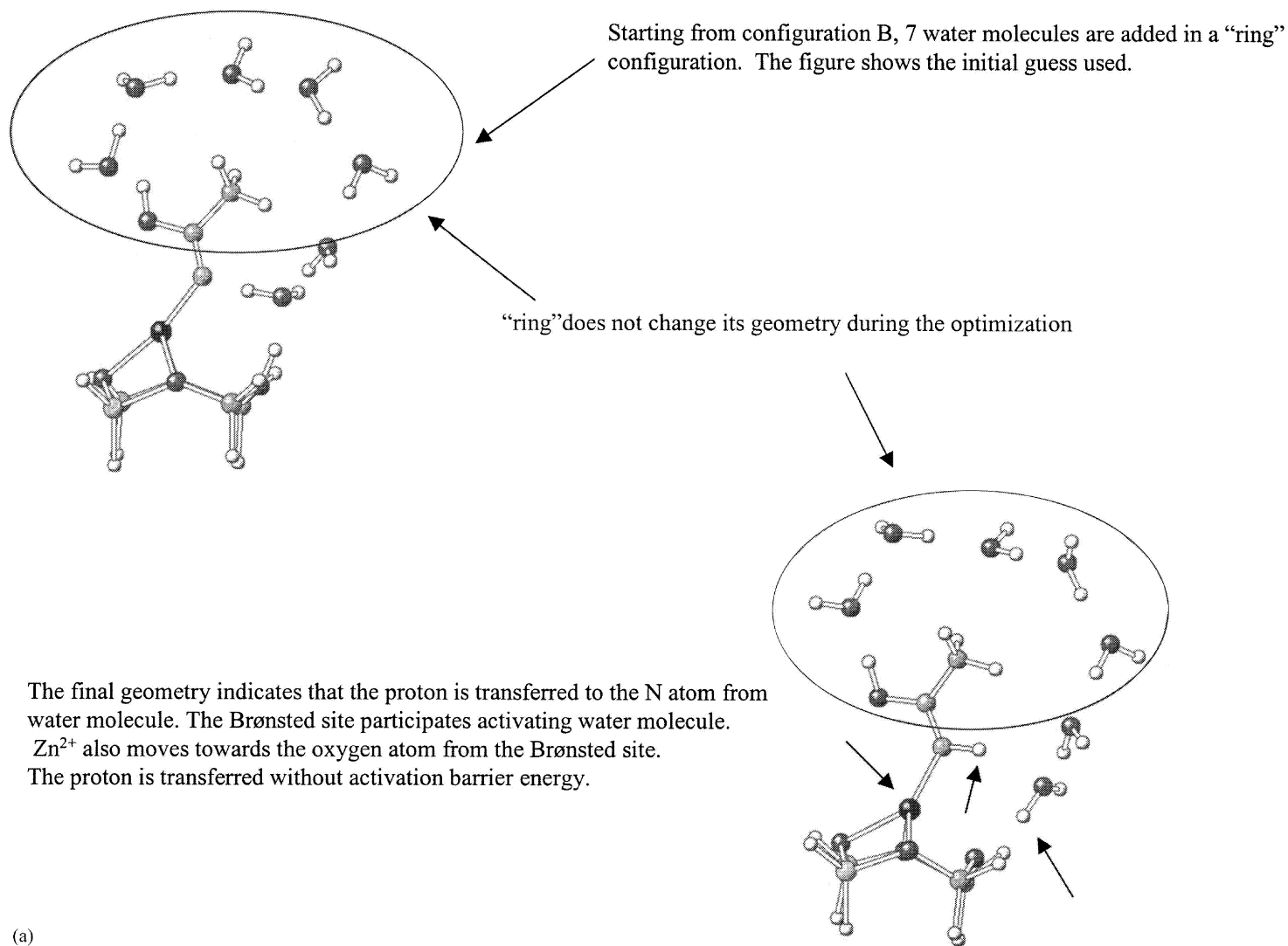
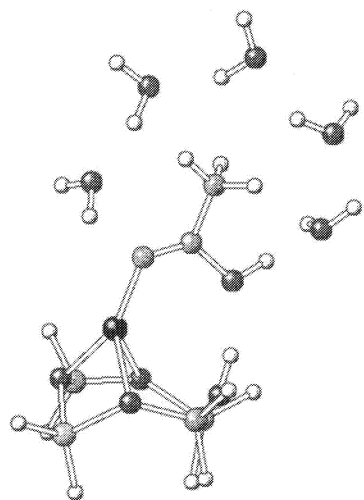
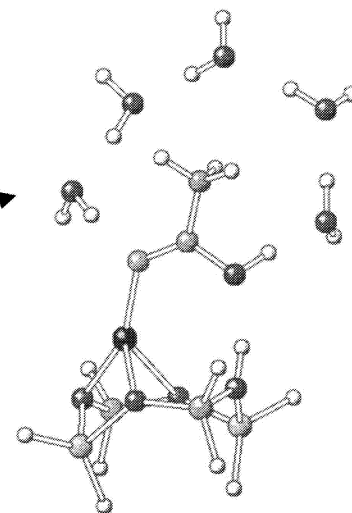


Fig. 2. (a) Water ring configurations (seven water molecules); (b) water ring configurations (five water molecules).



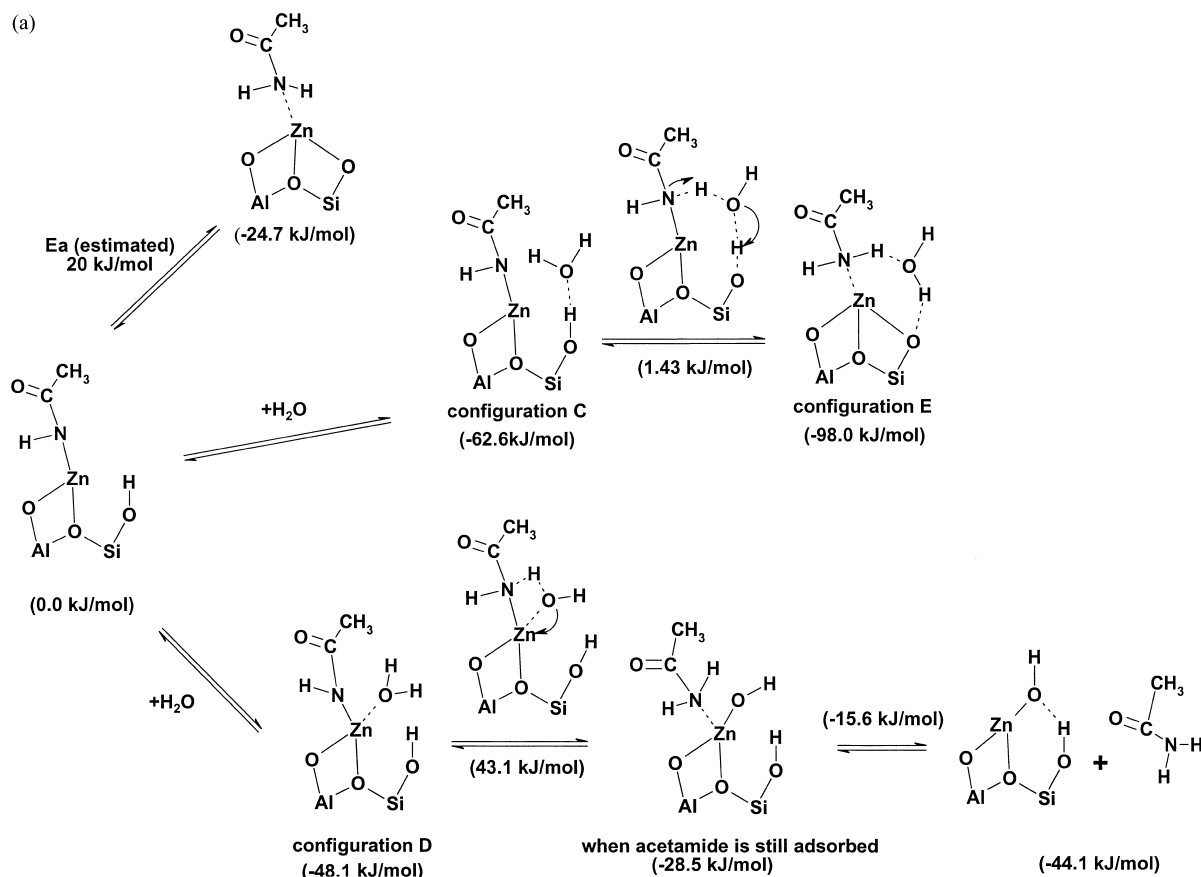
Starting from configuration A, 5 water molecules are added in a “ring” configuration. The figure shows the initial geometry.

The final geometry indicates that the proton is not transferred to the N atom, from the water molecule. In this case the Brønsted site is not close enough to activate any water molecule.



(b)

Fig. 2. (Continued).



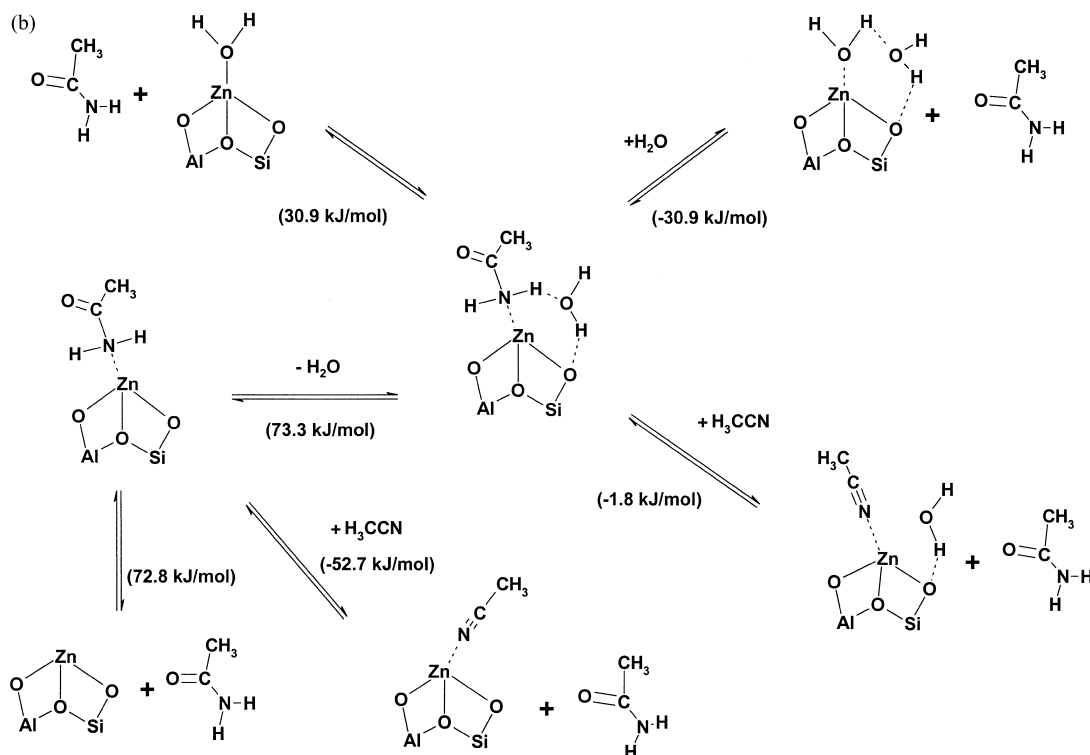
Scheme 6. (a) Proton donation to acetamide by water molecule; (b) displacement of acetamide by reactants; (c) desorption of acetamide co-promoted by adsorption of reactants.

[102]; of the parent carbodiimine [103]; of isocyanates [104]; β -lactam models [105,106]; of α -oxocarboxylic acids derivatives [107] and the internal proton transfer of zinc-bound HCO_3^- in *carbonic anhydrase* [44]. The energy gain in our tautomerization step is in good agreement with values reported in the above studies. For example in the β -lactam study, the activation energy reduction was 54.4 kJ/mol, in the parent carbodiimine hydrolysis study 48.6 kJ/mol in the α -oxocarboxylic acids derivatives hydrolysis 74.9 kJ/mol and in *carbonic anhydrase* 134.4 kJ/mol. The water molecule also plays an important role in the isomerization mechanism.

An additional study has been done using a water molecule ring. This study aimed to verify the existence of a proton shuttle during the isomerization

step. In *carbonic anhydrase*, the existence of this proton shuttle catalyzes the dissociation of zinc-bound water [39–47]. In our case, this proton shuttle was studied during the tautomerization step. Two different intermediate configurations were employed (see Fig. 2).

Configuration A needs only five water molecules, while configuration B requires seven water molecules to form a ring. During the optimization of configuration B (Fig. 2a), the proton is transferred directly without barrier to nitrogen, giving NH group as a final geometry. Only one molecule acts as a proton shuttle. The position of the other six water molecules does not change during the optimization process. The proton is transferred from the Brønsted site to nitrogen and not from OH group as had been anticipated.



Scheme 6. (Continued).

The result is different for configuration A (Fig. 2b). The OH group interacts with the Brønsted site. None of water molecules are activated in this case, therefore the transfer does not occur directly as in the previous case. The new activation barrier in this case might be lower than in the previous tautomerization case (calculated with a water molecule), but this new transition state for the proton transfer was not calculated due to the high computational cost of this system.

3.5. The desorption of acetamide

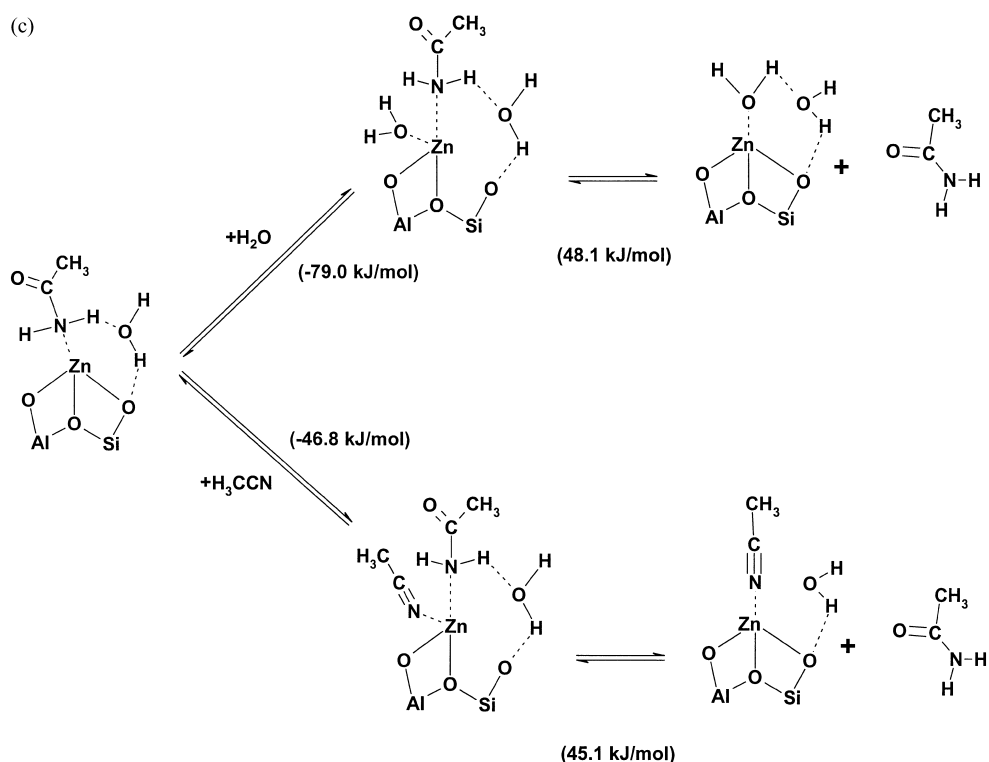
Product desorption is the next step in the studied mechanism (Scheme 4). Acetamide has, however, not yet been completely formed. One more proton is required, which may come from either the Brønsted acid site of the zeolite or a water molecule.

If the proton is donated by Brønsted acid site, the activation energy will be around 20 kJ/mol and the desorption energy will be about 72 kJ/mol. In the case

of water assisted process, a water molecule can be adsorbed in two different positions: it can interact with the Brønsted site (configuration C) or directly with the divalent Zn^{+2} ion (configuration D). The former is more stable than the latter by 14.5 kJ/mol (see Scheme 6a).

Starting with configuration C, water acts as a bridge for the Brønsted site proton. This donation requires only 1.43 kJ/mol. One can notice that the zinc ion binds to the basic oxygen atom of the cluster when acetamide is formed, since the bond between nitrogen and zinc has been weakened. This proton shuttle is similar to the one previously studied (see Fig. 2a). The Brønsted site activates the water molecule in both cases, promoting proton transfer without activation barrier. It confirms that the presence of other water molecules has no influence on the stabilization of activated water.

Acetamide interacts strongly with both water and Zn^{+2} ion. The final configuration (E) is the most sta-



Scheme 6. (Continued).

ble among all studied in this work. Consequently, acetamide, interacting with water and the Lewis acid, can inhibit the reaction, leaving the active site occupied for the hydration step.

In the case of configuration D, water molecule is activated by Zn^{2+} ion (Scheme 6a). This activation is found in *zinc-peptidases* for the opening of β -lactam rings [49]. Although, the water binding energy is -48.1 kJ/mol, the activation energy for the proton transfer is not negligible, 43.1 kJ/mol. Therefore, the proton transfer will occur by following the previous mechanism.

An interesting point is to study acetamide desorption. Acetamide can be displaced from the active site (Zn^{2+}) directly by acetonitrile, as seen in Scheme 6b. This displacement is an exothermic reaction releasing 52.7 kJ/mol. Therefore, the inhibition process verified in configuration E does not occur due to acetamide adsorption on the Lewis site but from a combination of two interaction: adsorption on Zn^{2+} ion and the

H-bond between acetamide and water molecule. In enzymes, this inhibition effect is also verified, HCO_3^- [38,44] or benzamide [108] poisoned the active site.

To break this complex (water + acetamide) 146.1 kJ/mol of energy is required (73.3 kJ/mol to desorb water and 72.8 kJ/mol to desorb acetamide), see Scheme 6b and Table 4. However, the displacement of acetamide by other molecules requires less energy. For instance, acetonitrile replaces acetamide on this complex needing almost no energy, -1.8 kJ/mol. This replacement restores the catalytic cycle observed in mechanism G (see Schemes 3b and 6b). Water molecules also promote product desorption, preventing product inhibition. In the case of one water molecule, the required energy is reduced to 30.9 kJ/mol. The effect of addition of water molecules becomes more evident, when two water molecules are employed. The displacement of acetamide becomes an exothermic process, -30.9 kJ/mol. Furthermore, the catalytic cycle is again restored in both cases,

as observed in mechanism C. In enzymatic systems, water molecules also facilitate the displacement of HCO_3^- ion, decreasing the calculated desorption energy by about 250 kJ/mol [44]. In this case, the extra water molecule acts as the fifth ligand on Zn^{+2} ion.

To test a similar effect, a second water molecule is added to configuration E in order to increase number of the ligands on the zinc ion (see Scheme 6c). The process is exothermic: -79.0 kJ/mol (see Table 3). Although, the desorption of acetamide is endothermic, 48.1 kJ/mol, the total energetic balance is, however, favorable. The metal ion prefers to maintain its 4 + 1 coordination, thus breaking one of the bonds with the oxygen of the framework.

In the case of acetonitrile co-adsorption (see Scheme 6c), the active site becomes completely filled, creating steric repulsion. Therefore, the adsorption energy is lower than the previous case, -46.8 kJ/mol. In this case, the metal ion also maintains 4 + 1 coordination. The acetamide desorption is also endothermic, requiring almost the same energy: 45.1 kJ/mol. Similarly, the total energetic balance is also favorable.

An interesting point is that acetamide desorption is also facilitated by an OH group, formed after proton donation (see Scheme 6a). Due to the strong H-bond formed between the OH group and the Brønsted site proton, acetonitrile displacement is an exothermic process: 15.6 kJ/mol. This displacement also restores the catalytic cycle observed in mechanism C.

4. Conclusions

A 4T cluster ($\text{Si}/\text{Al} = 1$), in which zinc substitutes both Brønsted sites, was used to model zinc loaded zeolites in the acetonitrile hydrolysis reaction. The zinc ion positioned in the model frame with geometry close to the enzyme *carbonic anhydrase* active site. The reactivity of metal ion is also shown to be very similar to this enzyme active site. In both cases, the zinc ion is activated by H_2O to form a ZnOH^+ species. Another interesting point is that the basic oxygen atom next to zinc ion acts in a similar way to the basic organic groups found in the *carbonic anhydrase*, promoting the dissociation of the Zn-bound water.

The hydrolysis reaction has been divided in three parts: hydration, isomerization and product desorption. In the first part seven different mechanisms have

been analyzed starting with two different activated reactants: either water or acetonitrile. Among these mechanisms, the most favorable one is extremely influenced by the reactant concentration and can be represented by different starting activation of both reactants: water and acetonitrile. The hydration mechanism has some similarities with both enzymatic CO_2 hydrolysis and zeolite catalyzed acetylene hydration. In the isomerization route, only two mechanisms have been studied, based on the intermediate configurations. Water molecules play an important role in many parts of the reaction mechanism. It acts as proton donor in hydration and tautomerization and also facilitates the displacement of the product that is a possible inhibitor of the reaction. Because of this water co-promotion effect, the rate-limiting step is the hydration. A similar role has been seen in metalloenzymatic systems, therefore water co-catalyzes equally in both environments.

Interestingly, the zinc ion exchanged zeolite promotes the hydrolysis reactions better than zeolite protonic form [22] and even some protonic enzymes as papain [109]. Moreover, the reactants can avoid product poisoning, commonly verified in *nitrilase* enzymes [102,103] and protonic zeolites [17,22].

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