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Ab initio study of solvent effects on the acetohydroxamic acid deprotonation processes

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Abstract

The structures of the aggregates of the neutral and anionic forms of acetohydroxamic acid $CH_3CONHOH$ (AH) with a water molecule have been calculated at the MP2(FC)/AUG-cc-pVDZ level of theory, for evaluating the effect of intermolecular hydrogen bonds formation on the deprotonation processes of AH. Considering the molecules to be isolated, the *Z*-amide is the most stable neutral form whereas the *E*-amide + H_2O system represents the most stable aggregate. In the system *Z*-amide + H_2O the intramolecular hydrogen bond is preserved. The theoretical results obtained clarify the interpretation of NMR studies in acetone solution (with residual water), as well as the kinetics of complex formation in aqueous solution between Ni(II) and hydroxamics acids investigated by spectrophotometric and stopped-flow techniques. In the gas phase, the *Z*-amide species and the less stable *Z*-imide form undergo deprotonation, giving rise to two stable anions. Upon deprotonation the *E* forms can produce three stable anions.

The aim of this paper is to compare ab initio calculations performed in solution using two different approaches where the solvent is treated as a continuum of constant permittivity. Two different solvents are studied: acetone and water. The calculated solvation energies in water with the PCM model directly applied on the isolated species are compared to those determined building the molecular aggregates with one water molecule. In all cases studied, the N-deprotonation of the *Z*-amide is the most probable process. Since more than one deprotonation process has been experimentally observed, the relative probabilities of the O-deprotonation of the *Z*-amide, and the N- and O-deprotonation of the *E*-amide forms are discussed. The probability of N-deprotonation from the *Z*-amide form increases in acetone.
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Keywords: Acetohydroxamic acid; Ab initio; PCM; Anions

1. Introduction

Hydroxamic acids (R-CONHOH) are chemical species that have biological activity and medical applications. The knowledge of the ionization sites and the protonation–deprotonation mechanisms is essential for understanding the role they play in biological and complexation processes [1].

In previous studies, a sequence of hydroxamic acids was investigated through experimental and theoretical procedures [2–7]. The protonation and deprotonation sites of the simplest acid, the acetohydroxamic acid (AH), have been explored using the Møller–Plesset theory, considering the molecule to be isolated and in aqueous solution [2–4]. Density functional theory has been applied on larger systems such as benzohydroxamic and salicilhydroxamic acids [5,7].

AH is a non-rigid molecule that shows amide–imide tautomerism. AH exhibits *Z*(*cis*)-*E*(*trans*) isomerization due to internal rotation around the C–N bond. In the gas phase, the *Z* and *E* forms are of relatively similar stability but

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their interconversion is hindered by barriers greater than 25 kcal/mol. Hence, four neutral forms of AH must be considered when referring to this molecule and studying its protonation/deprotonation processes. Ab initio calculations indicate that Z-amide is the most stable form of the neutral AH molecule [2,4]. It stabilizes by the formation of an intramolecular hydrogen bond. NMR measurements of hydroxamic acids in water and in acetone provide evidence for the existence of Z and E isomers [4–7].

At high acidity levels the neutral AH molecule can accept a proton. AH exhibits two protonation sites, the carbonyl oxygen and the nitrogen atom. In a dioxane/water mixture, RHF calculations predict the existence of a third cation of low stability, where the proton is bonded to the OH oxygen [2,3]. The MP2 free energies of formation of the two most stable cations in solution, $CH_3COH–NHOH^+$ (COH^+) and $CH_3CO–NH_2OH^+$ (NH^+), have been evaluated to be -160.2 and -157.6 kcal/mol, respectively. The carbonyl oxygen site is the most active protonation centre in solution and in the gas phase.

A large controversy precedes the study of the AH deprotonation sites [8–23]. Two possible atomic centres, the nitrogen (NH) and the oxygen (OH), compete as favourite sites. Initially, it was accepted that hydroxamic acids were O-acids [11–15], but extensive IR and UV measurements in dioxane and aqueous alcohol solutions [16] indicate that hydroxamic acids are N-acids, a conclusion also supported by ^{17}O NMR and FT-IR studies of the benzohydroxamate ion in methanol [11,17]. Potentiometric measurements compatible with O- and N-deprotonation of hydroxamic acids have been reported [8–10,18–21]. However, irregularities attributed to solvent effects have been observed [8–10,13,15,20–23]. Dynamic NMR and NOESY (1D and 2D) experimental results obtained for different hydroxamic acids and their anions have shown that N-deprotonation and O-deprotonation are possible [5].

The majority of the ab initio studies on acid–base properties of hydroxamic acids appear to confirm the NH-acidity [4,9,24–29]; most studies concern the smallest species, the formohydroxamic acid [26–29]. In an earlier study [4], we have demonstrated that the Z-amide and the less stable Z-imide forms of AH undergo deprotonation, giving rise to two stable anions. Upon deprotonation the E forms (E-amide and E-imide) can produce three stable anions. On the basis of the MP2/PCM/AUG-cc-pVDZ relative energies of the most stable anion and neutral forms, the N-deprotonation of the amide (Z or E) structure appears to be the most likely process. The thermodynamic properties corresponding to the most probable processes have been evaluated within the ideal gas model. The Gibbs free energy corresponding to the most probable process, the N-deprotonation of the Z-amide, has been calculated to be 332 kcal/mol at 298.15 K, which is in good agreement with the experimental value (339 kcal/mol) [20]. Gibbs free energy values for the O-deprotonation of the Z-amide and the N- and O-deprotonations of the E-amide have been

determined to be 349.2, 341.7 and 342.0 kcal/mol, respectively.

NMR measurements have provided evidence for the existence of Z and E isomers of both the neutral and anionic forms of AH in water. The NMR acid dissociation constants of the two isomers were consistent with their spectrophotometric and potentiometric evaluation [4]. As experiments show, there is a significant influence of the environment on the deprotonation processes of AH. Furthermore, the interaction with water is a fundamental tool to learn the complexation mechanisms of the AH with transition metals [30]. For this reason, our previous ab initio calculations have been performed in solution as well, considering water as a continuous medium of constant permittivity [4]. The polarizable continuum method (PCM) [31,32], as implemented in Gaussian 98 [33], was directly applied on the neutral and anionic forms of AH. As observed for the isolated molecule, the N-deprotonation is the most probable process in the presence of water as solvent. However, the solvent decreases the probability difference between the possible deprotonation processes, making more difficult the characterization of other deprotonation sites in AH.

The PCM method is the most frequently used method to study solvent effects. Some features, such as the way the solvent cavity is described, represent an efficient improvement from previous methods. However, the capability of the method for describing the effect of the formation of hydrogen bonds between the solvent and the solvate are always a matter of controversy. In the present study, we aim at improving the model previously used [4] to provide a better characterization of the complete set of deprotonation sites in AH. We attempt to explicitly incorporate the intermolecular solute–solvent interactions by working with the aggregates of the neutral and anionic species of AH with a water molecule. Thus, the solvent effects are considered in two steps. Initially, the energies and structures of the molecular aggregates $AH + H_2O$ and $A^- + H_2O$ are determined, and afterwards, the PCM method is applied on the aggregates.

Due to the relative small size of the AH molecule, it is possible to compare different theoretical approaches without excessive computational cost. AH is a good example for testing models that can be used in future studies of larger hydroxamic acids.

In addition, since acetone is one of the solvents most commonly used in the experimental studies of hydroxamic acids and because it allows the study of NMR effects inaccessible in water, the solvent effects of acetone on the deprotonation processes of AH are also studied.

2. Computational details

Electronic structure and solvent effects calculations have been performed using the Gaussian 98 set of programs (revision A.1x) [33]. The geometries of the aggregates of acetohydroxamic acid and water ($AH + H_2O$) and

acetohydroxamic acid anions and water (A^- + H_2O) have been optimized at the MP2/AUG-cc-pVDZ level, using as the starting point the calculated geometries of the neutral and anionic forms of AH at the same level of theory [4]. The basis set chosen contains diffuse orbitals suitable for the appropriate description of the anions charge distribution. Solvent effects in water and acetone have been calculated by means of the PCM method [31,32] in which the solvent is considered a continuum dielectric, characterized by a constant permittivity. The dielectric constants of acetone and water have been set to 20.59 and 78.45, respectively, at 298.15 K.

3. Results and discussion

As explained before [4], due to the amide–imide tautomerism and the coexistence of Z and E forms of AH, four neutral forms of the acid must be considered when studying its deprotonation processes. Hence the Z and E isomers are treated as independent species and are assumed to coexist giving rise to different deprotonation processes. The probability of the processes involving the E forms must be taken into consideration for a proper interpretation of the deprotonation mechanism.

The Z-amidic and Z-imidic forms can produce two different anions: Z-Ia and Z-II, where the remaining hydrogen is binding the NO oxygen and the nitrogen,

respectively (see Fig. 2 of Ref. [4]). The E-amidic and E-imidic forms can produce three different anions: E-Ia, E-II and E-Ib, where the remaining hydrogen is binding the NO oxygen, the nitrogen and the CO oxygen, respectively (see Fig. 4 of Ref. [4]). The Z and E forms of Ia and II are stable, but the anion Z-Ib displays instability at the MP2/AUG-cc-pVDZ level. Z-Ia, the most stable anion, stabilizes by the formation of an intramolecular hydrogen bond.

Fig. 1 shows the most stable aggregates of the four neutral forms of AH with one water molecule, and Figs. 2 and 3 display the aggregates of the Z and E anions of AH, respectively. The relative energies and solvation free energies of the neutral forms of AH are displayed in Table 1. This table summarizes previous and current work on these species: for the molecules and for the aggregates with a water molecule, both in the gas phase and in solution. Calculations on the molecules in acetone are also reported. Table 2 shows the same information for the anions of AH.

Table 3 shows the thermodynamic properties of the most probable deprotonation processes of AH, and Table 4 displays the calculated dipole moments. Dipole moments are indicated because this property is closely related to the environmental effects described by the PCM method.

A very important result obtained in our calculations is that the relative stability of the isomers depends on the nature of the interaction with the solvent. As previously
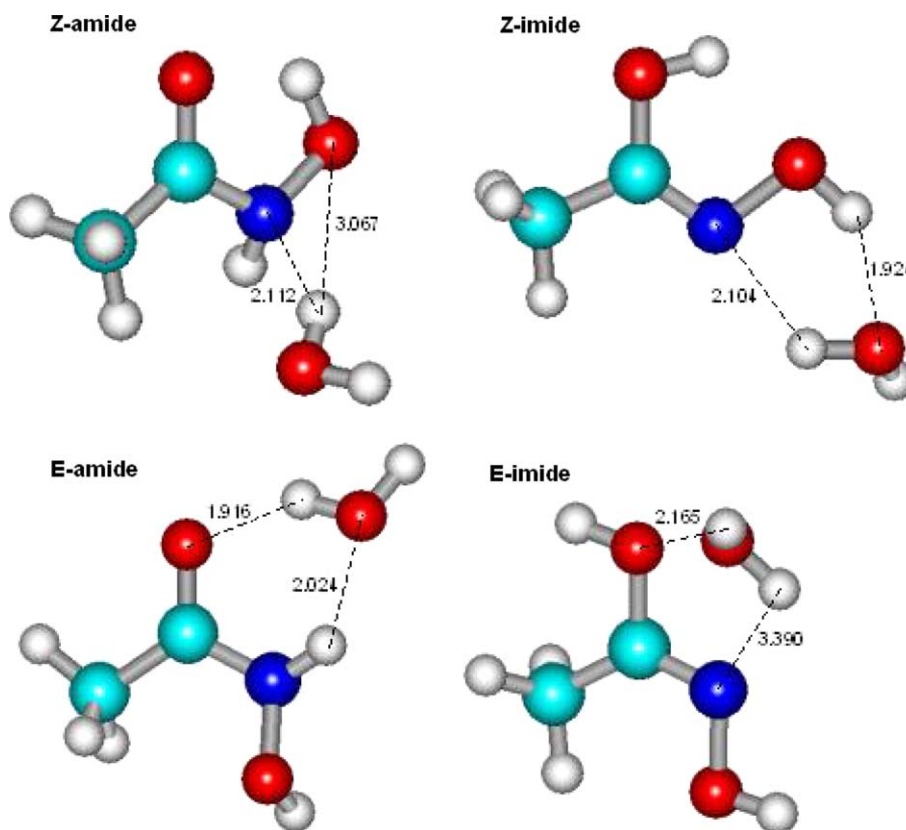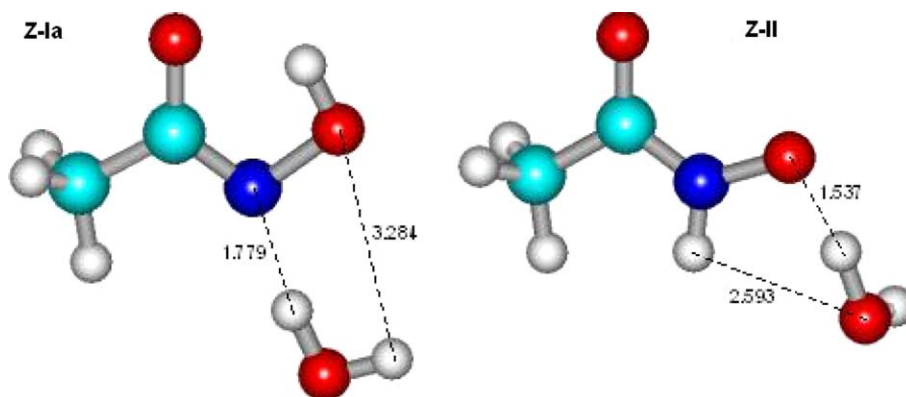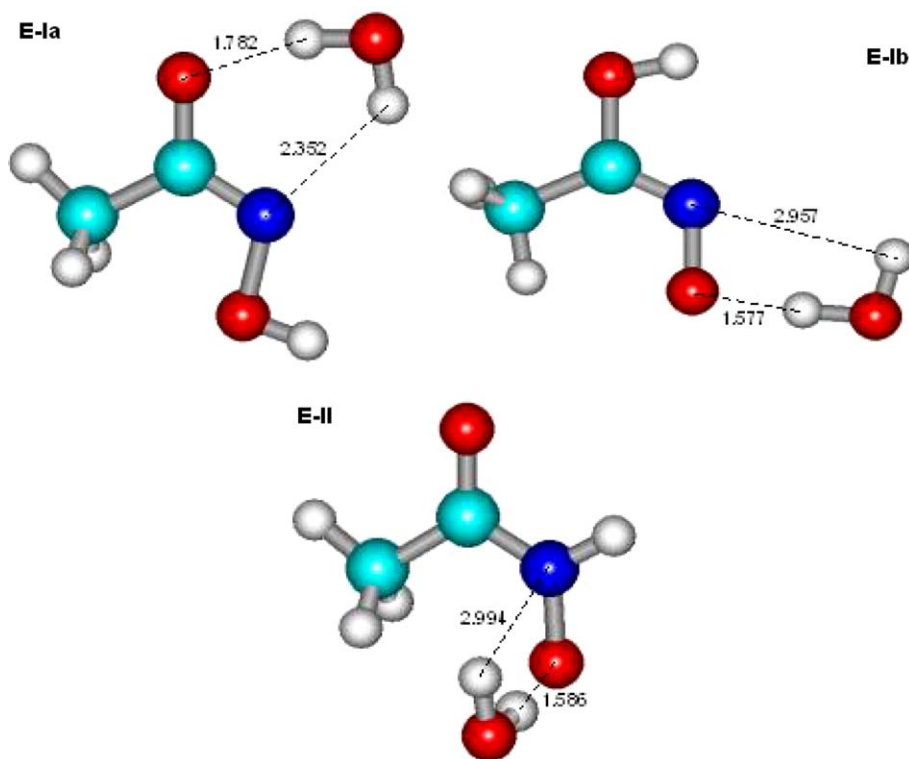

Fig. 1. The four stable neutral aggregates of AH and a water molecule.

Fig. 2. The two stable Z-anion aggregates of AH.

Fig. 3. The three stable E-anion aggregates of AH.

observed in NMR studies [6], the solvent dielectric constant significantly influences the equilibrium constant between the Z and E forms of hydroxamic acids. The addition of a water molecule (to form the aggregates) reverses the order of stability of the neutral amides in the gas phase and in water (see Table 1). As the present work shows, the E-amide + H_2O aggregate becomes 2.3 kcal/mol more stable than the Z-amide + H_2O aggregate in the gas phase, and 0.5 kcal/mol more stable in water. The reason for this change in stability lies in the structure of the aggregates and in particular in the strength of the solute–solvent hydrogen bonds formed. The E-amide + H_2O aggregate stabilizes by the formation of two hydrogen bonds, one of 1.916 Å between the C=O

oxygen and a hydrogen of water, and another one of 2.024 Å between the NH group and the oxygen in water (see Fig. 1). The characteristics of the hydrogen bond formation between the Z and E forms of AH and a solvent molecule can be used to clarify the experimental observation of benzohydroxamic acid in acetone [5]. Dynamic ^{1}H NMR studies have shown that the coalescence temperature between the two proton-singlets of the E-isomer increases from −10 to 5 °C when the proportion of residual water of the solvent is increased by 30%. This feature indicates that water hinders the interchange between the two protons of the E-NHOH group, probably due to H-bond formation, as shown in Fig. 1, in good agreement with the theoretical results for AH.

Table 1
MP2/AUG-cc-pVDZ calculated relative energies, E_R, and solvation free energies, ΔG_s and $\Delta G_s^=$,[a] (in kcal/mol) of the neutral forms of AH

| | Gas-phase molecule [4] | Molecule | | | | Molecule + water | | |
| | | PCM acetone (present work) | | PCM water [4] | | (Present work) | PCM (present work) | |
	E_R	E_R	$\Delta G_{s(acetone)}$	E_R	$\Delta G_{s(water)}$	E_R	E_R	$\Delta G_{s(water)}^=$ [a]
Z-amide	0.0[b]	0.0[c]	−4.8	0.0[d]	−9.4	0.0[e]	0.0[f]	−16.0
Z-imide	1.1	1.9	−3.9	1.9	−8.6	2.4	1.6	−15.4
E-amide	1.6	1.2	−5.2	0.4	−10.6	−2.3	−0.5	−18.0
E-imide	5.4	5.8	−4.4	5.0	−9.8	10.3	7.5	−13.8

Calculations on the molecules and their aggregates (molecule + water), in the gas phase and in solvent (using the PCM method) are reported.
  [a] In the cases of the aggregates, the solvation free energies are calculated using Eq. (1).
  [b] $E_b = -283.673447$ a.u.
  [c] $E_c = -283.681108$ a.u.
  [d] $E_d = -283.688362$ a.u.
  [e] $E_e = -359.943205$ a.u.
  [f] $E_f = -359.959768$ a.u.

Table 2
MP2/AUG-cc-pVDZ calculated relative energies, E_R, and solvation free energies, ΔG_s and $\Delta G_s^=$,[a] (in kcal/mol) of the anionic forms of AH

| | Gas-phase anion [4] | Anion | | | | Anion + water | | |
| | | PCM acetone (present work) | | PCM water [4] | | (Present work) | PCM (present work) | |
	E_R	E_R	$\Delta G_{s(acetone)}$	E_R	$\Delta G_{s(water)}$	E_R	E_R	$\Delta G_{s(water)}^=$ [a]
Z-Ia	0.0[b]	0.0[c]	−54.5	0.0[d]	−63.2	0.0[e]	0.0[f]	−72.4
Z-II	17.2	11.5	−60.3	6.5	−74.0	10.9	2.6	−87.0
E-Ia	13.0	9.3	−58.2	6.8	−69.4	9.7	6.8	−78.6
E-Ib	28.4	25.1	−57.8	22.9	−68.7	22.7	17.3	−83.5
E-II	12.3	12.1	−54.7	8.9	−66.6	8.2	3.9	−80.7

Calculations on the molecules and their aggregates (molecule + water), in the gas phase and in solvent (using the PCM method) are reported.
  [a] In the cases of the aggregates, the solvation free energies are calculated using Eq. (1).
  [b] $E_b = -283.121064$ a.u.
  [c] $E_c = -283.207966$ a.u.
  [d] $E_d = -283.221794$ a.u.
  [e] $E_e = -359.407491$ a.u.
  [f] $E_f = -359.497302$ a.u.

Table 3
Thermodynamic properties (kcal/mol) corresponding to the most probable deprotonation processes of AH calculated at 298.15 K, in the gas phase and in water (+PCM)

| Processes (AH → A⁻ + H⁺) | Gas-phase processes [4] | | +PCM [4] | +PCM (present work) |
	D_e	ΔG^{ISO}	ΔG	$\Delta G'$
Z-forms				
R1: Z-amide → Z-Ia anion	338.3	332.0	170.7	−0.9
R2: Z-amide → Z-II anion	355.7	349.2	177.1	1.7
R3: Z-imide → Z-Ia anion	337.3	330.9	168.8	−2.6
E-forms				
RE1: E-amide → E-Ia anion	348.9	341.7	175.4	4.6
RE2: E-amide → E-II anion	348.9	342.0	178.5	2.8
RE3: E-imide → E-Ia anion	345.6	339.1	172.0	2.2
RE4: E-imide → E-Ib anion	360.5	354.4	188.0	8.2

The magnitudes reported are the dissociation energy (D_e) and the free energy change of the dissociation process in the gas phase (ΔG^{ISO}) and in solution considering the isolated molecules (ΔG)[a] and the aggregates ($\Delta G'$)[b].
  [a] Calculated using Eq. (2).
  [b] Calculated using Eq. (3).

Table 4
Calculated dipole moments, μ (in D), of the neutral and anionic forms of AH and their aggregates (species + water), in the gas phase and in solvent (using the PCM method) at the MP2/AUG-cc-pVDZ level of theory

	Gas-phase species [4]	Species		Species + water	
		PCM acetone (present work)	PCM water [4]	(Present work)	PCM (present work)
AH					
Z-amide	3.779	4.443	4.781	2.179	2.851
Z-imide	0.317	0.247	0.154	2.209	2.595
E-amide	3.537	4.207	4.578	2.836	3.691
E-imide	0.056	0.104	0.074	2.069	2.465
A$^-$					
Z-Ia	3.296	4.210	4.466	1.701	2.217
Z-II	7.449	9.158	9.876	7.488	9.427
E-Ia	4.421	5.612	6.051	4.976	6.229
E-Ib	5.413	7.042	7.495	6.051	7.677
E-II	2.283	2.856	2.827	2.010	2.371

In the *Z*-amide aggregate, there is only a hydrogen bond of 2.112 Å between the nitrogen and a hydrogen of water, and the intramolecular hydrogen bond of 1.936 Å is preserved. Following this result, a new interpretation of the complexation mechanism of hydroxamic acids and nickel (II) is feasible [5,6]. The kinetic study shows that both the *Z*-amide and its *Z*-II anion are capable of binding to nickel (II). While the anion reacts at a "normal" speed, the rate of replacement of a water molecule in $Ni(H_2O)_6$ by the neutral *Z*-amide is of about one order of magnitude less than expected on the basis of water exchange. The observed behaviour might be interpreted in the following three ways: (a) a slow AH or Ni–AH complex deprotonation [34], (b) a slow $Z\Delta E$ interconversion [35], or (c) that the *Z*-amide form of hydroxamic acids in aqueous solution is involved in an equilibrium between an "open" (reactive) *Z* form and a more abundant "closed" *Z* form, which is unreactive because the reaction site is blocked by the intramolecular hydrogen bond [5]. The theoretical results support interpretation (c), showing that the intramolecular hydrogen bond is stronger than the intermolecular hydrogen bond that binds the water molecule with the hydroxamate group.

Our calculations of the imides show the *Z*-form to be more stable than the *E*-form in all cases. None of the imidic forms have been experimentally observed, and our calculations of the molecules and the aggregates in water are in agreement with this fact. The *Z*-imide aggregate shows two hydrogen bonds of 2.104 and 1.924 Å between the nitrogen and a water hydrogen, and between the NOH group hydrogen and the water oxygen, respectively.

The *Z*-Ia anion is the most stable one in all cases mainly because of the intramolecular hydrogen bond that this anion exhibits (see Table 2 and Fig. 2). The order of stability of the anions and the aggregates in the gas phase is maintained. However, the energy difference between the anions in the aggregates is smaller than when the anions are isolated. Since the *Z*-II anion is the one with the greatest dipole moment in the gas phase and in the aggregate (see Table 4), it gets stabilized the most by solvation. The *Z*-II anion has the most negative solvation free energy in all cases. This finding is consistent with the experimental results that enabled the detection of the N-anion and O-anion forms [5]. The chelation process requires that the *Z*-form be O-deprotonated (*Z*-II anion) but this, of course, does not exclude the N-deprotonation (*Z*-Ia anion). However, the N anions can be partially converted to O-anions by a fast, buffer-assisted proton transfer from oxygen to nitrogen.

Tables 1 and 2 also show the MP2 solvation free energies (ΔG_s), defined as the difference between the MP2 free energies of the species in solution and in the gas phase. ΔG_s involves three non-electrostatic contributions: cavitation, dispersion and repulsion energies. For the molecular aggregates, the solvation free energy $\Delta G_s^=$ is determined by the equation:

$$\Delta G_{s(MP2)}^= = E_{MP2}^{PCM}(\text{aggregate}) - E_{MP2}(\text{isolated species}) - E_{MP2}(H_2O) \tag{1}$$

As expected, the solvation effect on the neutral forms is very small, but somewhat larger for amides as compared to imides. The solvation effect, however, is more significant for the anions.

An important objective of this study is to compare the solvation energies calculated with the PCM method directly applied on the species of Ref. [4], with the solvation energies determined by using Eq. (1). The second approach refers to the application of the PCM method to the molecular aggregates. Both methods produce very similar relative solvation free energies, although the absolute values differ by approximately 10 kcal/mol. For example, the *Z*-amide solvation energy varies from −9.4 kcal/mol when isolated, to −16.0 kcal/mol in the aggregate. Similarly, the solvation energy of the *Z*-Ia anion varies from −63.2 kcal/mol when isolated, to −72.4 kcal/mol in the aggregate. It might be inferred from these results, that the effect of the hydrogen bond formation between the solvent and the solvate on the solvation energies appears to be somehow incorporated in the PCM model, even though they are not explicitly described.

Table 3 shows the thermodynamic properties (in kcal/mol) calculated at 298.15 K corresponding to the most probable deprotonation processes of AH (see Figs. 3 and 4 in Ref. [4]). The first two columns refer to the isolated species. D_e is the dissociation energy defined as the difference between the energies at 0 K of the neutral and anionic forms connected by the different processes. The free energy change of the dissociation process in the gas phase, ΔG^{ISO}, is estimated within the ideal gas model. The Gibbs energy change of the processes in solution, ΔG, is determined by Eq. (2). When considering the aggregates, the Gibbs energy change, $\Delta G'$, is calculated using Eq. (3)

$$\Delta G = \Delta G^{ISO} - \Delta G_s(AH) + \Delta G_s(A^-) + \Delta G_s(H^+) \quad (2)$$

$$\Delta G = \Delta G^{ISO} - \Delta G_s^=(AH) + \Delta G_s^=(A^-) + \Delta G_s^=(H^+) \quad (3)$$

A^- denotes the anion of AH formed after deprotonation. We have identified two solvation free energies, ΔG_s and $\Delta G_s^=$ (see Tables 1 and 2), and two free energy changes of the dissociation processes in solution, ΔG and $\Delta G'$ (see Table 3). ΔG_s and ΔG are calculated with the PCM method directly applied on the molecules, while $\Delta G_s^=$ and $\Delta G'$ are calculated with the PCM method applied on the aggregates with a water molecule.

If the PCM is applied on the isolated species, the proton solvation energy can be calculated as the solvation energy of H_3O^+:

$$\Delta G_s(H^+) = E_{MP2}^{PCM}(H_3O^+) - E_{MP2}(H_3O^+) \quad (4)$$

The result obtained from this equation (-107.5 kcal/mol) is not in agreement with the experimental measurement (-264.61 kcal/mol) [36]. But, if the aggregate formation is considered, the solvation energy of the proton can be calculated as:

$$\Delta G_s^=(H^+) = E_{MP2}^{PCM}(H_3O^+) - E_{MP2}(H^+) - E_{MP2}(H_2O)$$
$$= E_{MP2}^{PCM}(H_3O^+) - E_{MP2}(H_2O) \quad (5)$$

The result obtained with this approach at the same level of theory (-276.52 kcal/mol), is in good agreement with the experimental result (-264.61 kcal/mol) [33].

Calculations in the gas phase and in solution (see Table 3) indicate that the N-deprotonation of the *Z*-amide (process R1) is the most probable process from a thermodynamic point of view ($\Delta G^{ISO} = 332.0$ kcal/mol, $\Delta G = 170.7$ kcal/mol and $\Delta G' = -0.9$ kcal/mol). Experimentally, two deprotonation processes are observed for AH [4]. From the experimental pK_a at 298.15 K, the aqueous ΔG obtained for the *Z* and *E* isomers is 12.3 and 12.8 kcal/mol, respectively [4]. However, from the ab initio calculations it is difficult to derive information about the nature of the other deprotonation process experimentally observed. In the gas phase, the N- and O-deprotonation of the *E*-amide show almost identical probabilities. In solution, different models produce divergent assertions. If the PCM method is directly applied on the isolated molecules, the N-deprotonation of the *E*-amide (process RE1) is more thermodynamically favoured than the O-deprotonation

(process RE2). However, if the dissociation energies are calculated after forming the aggregates, the O-deprotonation of the *E*-amide is more favoured. Our previous work on acetohydroxamic acids [4] points to the N-anion as being the most favoured species in water, but subsequent spectra performed at pH 11.5 showed that both N- and O-anions are present in similar concentrations. The formation of N- and O-anions in similar concentrations has been proposed for other hydroxamic acids [13,15,37,38].

ΔG obtained from the experimental pK [4] was smaller than the theoretical value in solution. The causes of the difference between experimental and calculated pK values are discussed in Ref. [39]. Although the present study reconfirms some of our previous results [4], the ab initio calculations do not clarify all the questions regarding the AH deprotonation. The calculations on the molecular aggregates confirm the N-deprotonation as the most probable process. In addition, if more water molecules are added to the aggregates this conclusion is not expected to change, because the force of the hydrogen bonds decreases when more water molecules are present. The solvent molecules in the primary solvation sphere produce the greatest stabilizing effect on the anions.

3.1. Calculations performed using acetone as solvent

Finally, we compare the calculations performed in acetone with those carried out in water. Acetone is one of the most commonly used solvents in the experimental studies of hydroxamic acids because of the solubility these compounds in it. Furthermore, some of the properties of acetone as a solvent (it is a dipolar aprotic solvent with a low melting point) favour the NMR observation of the hydroxamate group protons at low temperatures.

Tables 1 and 2 show the relative energies and the solvation free energies of the neutral and anionic forms of AH calculated in acetone, respectively; Table 4 displays the calculated dipole moments. In these calculations, the PCM method is directly applied to the molecules and the anions of AH. The solvation free energies of the neutral species in acetone are approximately 50% lower than the corresponding values in water. As expected, considering the permittivities of these solvents ($\varepsilon_{acetone} = 20.59$, $\varepsilon_{water} = 78.45$), the dipole moments in acetone are also lower than in water. The anion solvation energies decrease by approximately 10 kcal/mol when going from water to acetone. Since the *Z*-Ia anion is more stable in acetone than in water, the new solvent favours the N-deprotonation of the *Z*-amide.

Despite the quantitative differences, there seem to be no significant qualitative differences between the calculations in water and acetone since the stabilization order of the neutral and anionic forms of AH in water and acetone is practically the same. At the quantitative level, however, acetone is a less polar solvent than water, the solute–solvent dipole–dipole interactions in acetone are weaker and, hence, solvation free energies are smaller.

Differences concerning relative stabilities are observed for the neutral forms in the two different solvents considered. The *E*-form stabilizes significantly in water. This outcome justifies and clarifies the experimental NMR studies in acetone (with residual water) solution [5].

4. Conclusions

Our main intention in this publication has been to compare two different approaches for considering solvent effects on the deprotonation processes of AH. Experiments indicate that two different processes occur but the nature of one of the processes was not fully clarified in our previous publication on this topic [4]. We have shown that the solvent plays an important role in the deprotonation processes of AH at the molecular level. The solvent model previously considered (PCM), as well as more recently developed versions, cannot successfully characterize all solute–solvent interactions because they are unable to explicitly describe the hydrogen bond formation between solute and solvent molecules. For this reason, we decided to study the aggregates of all the neutral and anionic species considered with a water molecule and, in addition, to include solvent effects at the PCM level, in order to explicitly consider the formation of hydrogen bonds with solvent molecules. The PCM solvation model provided consistency with our previous study [4].

The relative stability of the *Z* and *E* isomers of AH depends on the nature of the interaction with the solvent, in agreement with experimental results. The calculated solvation energies in water with the PCM model directly applied on the isolated species are compared to those determined building the molecular aggregates with one water molecule. In all cases, the N-deprotonation of the *Z*-amide form of AH is the most probable process. If the aggregate formation is considered, the O-deprotonation of the *Z*-amide appears to be more probable than the N- and O-deprotonation of the *E*-amide form of AH. It was also found that the probability of N-deprotonation from the *Z*-amide form increases in acetone.

Furthermore, the theoretical results obtained on the aggregates clarify the interpretation of NMR studies in acetone with residual water, as well as the kinetics of complex formation in aqueous solution between Ni(II) and hydroxamics acids investigated by spectrophotometric and stopped-flow techniques, the intramolecular hydrogen bond preserved in the *Z*-amide + H_2O system helps clarify the complexation mechanism of AH. In the *E*-amide + H_2O system the intermolecular hydrogen bonds formed help stabilize the *E* form, in agreement with NMR results. In addition, the observed formation of the N- and O-anions in hydroxamic acids can be justified on the basis of the theoretical results obtained.

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