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# Effects of complexation with sulfuric acid on the Photodissociation of Protonated Cinchona Alkaloids in the gas phase

Feriel Ben Nasr,<sup>a,d</sup> Ivan Alata,<sup>a</sup> Debora Scuderi,<sup>b</sup> Valeria Lepère,<sup>a</sup> Valerie Brenner,<sup>c</sup>  
Nejm-Eddine Jaïdane,<sup>d</sup> Anne Zehnacker<sup>\*a</sup>

*a) Institut des Sciences Moléculaires d'Orsay (ISMO), CNRS, Univ. Paris-Sud,  
Université Paris-Saclay, F-91405 Orsay, France*

*b) Univ. Paris-Sud, Laboratoire de Chimie Physique, UMR8000, and CNRS,  
Orsay, F-91405 France*

*c) LIDYL, CEA, CNRS, F-91191 Gif-sur-Yvette, France*

*d) Laboratoire de Spectroscopie Atomique, Moléculaire et Applications  
(LSAMA) Université de Tunis El Manar, LSAMA, Tunis 1060, Tunisia*

\*e-mail [anne.zehnacker-rentien@u-psud.fr](mailto:anne.zehnacker-rentien@u-psud.fr)

## **Abstract**

The role of complexation with sulfuric acid on the photodissociation of protonated cinchona alkaloids, namely cinchonidine (Cd), quinine (Qn) and quinidine (Qd), is studied by combining laser spectroscopy with quantum chemical calculations. The protonated complexes are structurally characterized in a room-temperature ion trap by means of Infra-Red Multiple Photon dissociation (IRMPD) spectroscopy in the fingerprint and the  $\nu(\text{XH})$  ( $\text{X}=\text{C}, \text{N}, \text{O}$ ) stretch regions. Comparison with density functional theory calculations including dispersion (DFT-D) unambiguously shows that the complex consists of a doubly protonated cinchona alkaloid strongly bound to a bisulfate  $\text{HSO}_4^-$  anion, which bridges the two protonated sites of the cinchona alkaloid. UV excitation of the complex does not induce loss of specific photo fragments. Indeed the UV-induced fragmentation pattern is identical to that observed in collision-induced dissociation experiments. This contrasts with the photodissociation observed in the protonated monomer or dimer, for which photo-specific fragments were observed. Analysis of the nature of the first electronic transitions at the second order approximate coupled-cluster level (CC2) explains the difference in behavior of the complex relative to the monomer or dimer towards UV excitation.

## Introduction

Exposure of biomolecules like proteins or DNA to UV light leads to structural damages, which in turn alter their biological functions, an exemplary case being mutagenic and carcinogenic effects caused by UV radiations on DNA.<sup>1-3</sup> These damages may be increased in the presence of sensitizing drugs.<sup>4</sup> Understanding the protection mechanisms of biomolecules against UV-induced damages has prompted numerous studies, both in the biomolecules themselves and in model systems.<sup>5</sup> For example, the photochemistry and photophysics of individual DNA bases have been intensively studied in solution.<sup>6-10</sup> The solvent, water in a biological context, plays an important role in the deactivation process, by stabilizing polar or charged species, modifying the excited-state energetics, or acting as a thermal bath. Gas-phase experiments are therefore required to get information on the molecule properties without the participation of the solvent. They have been conducted on small biomolecules such as DNA bases<sup>11-13</sup> and peptides and allow getting information on the photophysical processes at play in the chromophore.<sup>8, 14-22</sup> Many studies have been devoted to the electronic excited states of protonated biomolecules isolated in the gas phase, either under supersonic expansion conditions,<sup>23, 24</sup> in room-temperature ion traps,<sup>15, 25-31</sup> and more recently in cryogenic ion traps.<sup>32-40</sup> Of special interest are the aza-aromatic molecules due to their complex photophysical behavior related to several close-lying electronic transitions.<sup>29, 30, 37, 41, 42</sup>

We have recently studied aza-aromatic molecules, namely, cinchona alkaloids. Cinchona alkaloids, among which quinine is the most famous, originate from the bark of Cinchona trees and are widely used in chemistry or medicine.<sup>43-48</sup> However, photosensitizing effects have been observed in the treated patients.<sup>49</sup> This justifies the studies of photophysical and photochemical processes in quinine, in its free base or sulfate forms.

The cinchona alkaloids, quinine (Qn), quinidine (Qd), cinchonidine (Cd) and cinchonine (Cn) are displayed in **Figure 1**. They consist of an aliphatic bicyclic tertiary amine, the alkaloid part, which is substituted by a vinyl group at C<sub>3</sub> and linked to a planar aromatic quinoline ring *via* an OH-containing flexible linker C<sub>8</sub>C<sub>9</sub>. These natural molecules are classified into pairs, *i.e.* Qd/Qn and Cd/Cn, which only differ by the chirality of C<sub>8</sub> and C<sub>9</sub>. Qd/Qn differ from Cd/Cn by the presence of a methoxy substituent on the aromatic ring. Cinchona alkaloids contain two basic nitrogens (N<sub>alk</sub> and N<sub>arom</sub> in **Figure 1**). The alkaloid nitrogen N<sub>alk</sub> is the most basic site and is protonated in our experimental conditions. When not specified otherwise, CdH<sup>+</sup> denotes cinchonidine protonated on N<sub>alk</sub>. Protonation on N<sub>arom</sub> will be denoted by CdN<sub>arom</sub>H<sup>+</sup>. Doubly protonated cinchonidine (noted CdH<sub>2</sub><sup>2+</sup> in what follows) is formed in acidic solution (pH below <~4-5). Cinchona alkaloids possess different transitions in the near UV region. The ππ\* transition localized on the aromatic ring is

optically active while the  $n\pi^*$  transitions involving the quinoline or the alkaloid nitrogen lone pair have much weaker oscillator strength.<sup>50, 51</sup> Like for other aza-aromatic molecules,<sup>30</sup> protonation removes the  $n\pi^*$  excited state involving the alkaloid nitrogen lone pair from the transition manifold. This results in high fluorescence quantum yield.<sup>52</sup>

We have previously reported that protonated cinchona alkaloids show complex photochemical properties in the gas phase, using MS<sup>3</sup> experiments involving IR characterization of the UV fragments.<sup>53-57</sup> Based on IR spectra of the photofragments, combined with CC2 calculations, we have proposed that UV-induced C<sub>8</sub>C<sub>9</sub> bond cleavage happens through conformation-dependent reactions involving coupled electron and proton transfers.<sup>53</sup> The mechanism is modified in the protonated dimer, for which a photo-induced proton transfer, followed by dissociation of the complex, results to a metastable molecule protonated on the aromatic nitrogen, CdN<sub>arom</sub>H<sup>+</sup>.<sup>54, 57, 58</sup>

We extend here these studies to the complexes of cinchona alkaloids with sulfuric acid. Indeed, drugs based on cinchona alkaloids are used under their sulfate form and the above-mentioned complexes are spontaneously formed in the electrospray. The complexes are studied by multistage mass spectrometry (MS<sup>n</sup>) coupled with laser spectroscopy. We first resort to Infra-Red Multiple Photon Dissociation (IRMPD) spectroscopy, combined with quantum chemical calculations, to determine the structure of the protonated complexes of cinchona alkaloids with sulfuric acid. H<sub>2</sub>SO<sub>4</sub> is a strong di-acid; in water at neutral pH, the most abundant species is SO<sub>4</sub><sup>2-</sup> and the concentration in H<sub>2</sub>SO<sub>4</sub> is negligible. In contrast, H<sub>2</sub>SO<sub>4</sub> is stable in the gas phase<sup>59, 60</sup> while isolated HSO<sub>4</sub><sup>-</sup> has never been observed. Rare gas matrices are an intermediate case in which H<sub>2</sub>SO<sub>4</sub> is observed when isolated or included in a 1:1 complex with NH<sub>3</sub>.<sup>61</sup> However, for more basic environments, proton transfer takes place and an ion pair containing HSO<sub>4</sub><sup>-</sup> is formed.

This study first aims at defining which forms of Cd, CdH<sup>+</sup> or CdH<sub>2</sub><sup>2+</sup>, and sulfuric acid, H<sub>2</sub>SO<sub>4</sub>, HSO<sub>4</sub><sup>-</sup> or SO<sub>4</sub><sup>2-</sup>, are contained in the protonated complex. We can exclude SO<sub>4</sub><sup>2-</sup> because there are only two stable protonation sites in the Cd molecule. However, should we describe the complex in terms of CdH<sup>+</sup>:H<sub>2</sub>SO<sub>4</sub> or CdH<sub>2</sub><sup>2+</sup>:HSO<sub>4</sub><sup>-</sup>? Furthermore, UV irradiation only results to dissociation of the complex into protonated monomers, in contrast to protonated monomers and dimers that yield specific fragments under UV excitation. The second goal of this study is then to explain the absence of specific photofragments of the complex, in terms of structure and nature of the electronic excited states calculated at the CC2 level. The present study focuses first on Cd, and is extended to Qn and Qd, which have a methoxy substituent on the aromatic ring. Moreover, Qn and Qd differ from each other by the chirality of C<sub>8</sub> and C<sub>9</sub>, which is 8S/9R in Qn, as it is in Cd, and 8R/9S in Qd. We will assess whether the structure of the complexes or their photodissociation mechanism is affected by this change in absolute configuration.

## ***Experimental and theoretical methods:***

### **a) Experimental method:**

The experimental set-up has been described in details elsewhere.<sup>53</sup> The multistage mass spectrometry ( $MS^n$ ) experiments were based on a modified Paul ion trap (Bruker, Esquire 3000+).<sup>62</sup> Ions were generated by electrospraying a 10  $\mu$ M solution of the alkaloids or their sulfate in a 50:50 water/methanol mixture, adding 2  $\mu$ l of 98% formic acid to assist the protonation. The electrospray ionization (ESI) conditions were those already described for these systems.<sup>57, 63</sup> The alkaloids under study as well as their sulfates were obtained from Sigma-Aldrich and were used without further purification.

Collision-induced dissociation (CID) spectra were obtained in a  $MS^2$  experiment by mass selection of the parent in a  $\pm 5$  Da window. The parent was fragmented in the Paul ion trap by collision with He, applying a radiofrequency (RF) voltage of variable amplitude during 200 ms.

The IRMPD spectra were recorded resorting to a  $MS^2$  scheme involving IR irradiation in the above-mentioned Paul ion trap, equipped with a diamond window. The spectra were recorded in the 800-1800  $cm^{-1}$  range using the infrared free electron laser (FEL) at the “Centre Laser Infrarouge d’Orsay CLIO”.<sup>64</sup> The spectral bandwidth was typically 1% of the central wavelength and the power of the order of 0.8W. The 2800-4000  $cm^{-1}$  range was covered by a tabletop IR Optical Parametric Oscillator/Amplifier (OPO/OPA) (LaserVision 10 Hz repetition rate, pulses duration 4-6 ns, spectral bandwidth 3  $cm^{-1}$ , IR power of  $\sim 200$  mW). The IR laser was focused on the center of the trap by a parabolic Oxygen-Free High-Thermal Conductivity (OFHC) copper mirror with focal length of 350 mm. A synchronized  $CO_2$  laser (Universal Laser system 10 W at cw operation, centered at  $\lambda = 10.6$   $\mu$ m) was co-focused with the FEL or OPO source to enhance the fragmentation yield.

The fourth harmonic (266 nm) of a 10 Hz Nd-YAG laser (Minilite Continuum 500  $\mu$ J/pulse, pulse duration 5 ns) was used to electronically excite the systems, hence inducing their photodissociation. The UV laser was slightly focused on the center of the trap by a 1000 mm focal length quartz lens. The protonated complex built from cinchonidine and sulfuric acid ( $m/z$  324) was isolated in a 5 Da window and fragmented by irradiation at 266 nm during 1 s. The photo-fragments were isolated and characterized by IRMPD based on a  $MS^3$  scheme reported previously.<sup>53, 54, 58</sup>

### **b) Theoretical methods:**

The potential energy surface (PES) of the complexes of cinchonidine was first explored with a force field using the Maestro program, a part of the Schrödinger package.<sup>65</sup> Exploration with two

force fields, MMFFs and OPLS2003, generated similar structures.<sup>66, 67</sup> These force fields were already used successfully for exploring the potential-energy surface of neutral or protonated quinine as well as its protonated dimer.<sup>57, 68</sup> The structures with energy below 21 kJ/mol relative to the most stable one were fully optimized within the frame of the density functional theory (DFT) including empirical dispersion (DFT-D3),<sup>69, 70</sup> at the B3LYP-D3/6-31++G(d,p) level<sup>71-73</sup> and the harmonic frequencies were calculated at the same level of theory for structures which correspond to true minima. This level is known to yield frequencies in good agreement with experimental values.<sup>70, 72, 74, 75</sup> The “tight” criterion and fine grid were used so that the convergence threshold was set to  $6 \cdot 10^{-5}$  and  $1.5 \cdot 10^{-5}$  au for the maximum displacements and forces, respectively. In order to take into account the anharmonicity, the harmonic frequencies were corrected by mode-dependent scaling factors. These scaling factors were determined as the average of the ratio of the experimental frequencies to the calculated values of the studied molecules as described in section c).

Basis-set superposition error (BSSE) effects on both the geometry and energetics were taken into account. The geometry optimization was performed considering the BSSE term and the energetic was calculated using the counterpoise method.<sup>76</sup> In what follows, the stability of the complexes is given in terms of Gibbs energy  $\Delta G$  relative to the most stable structure taken as the zero of the scale. The BSSE corrections does not amount to more of 5% of the relative Gibbs energy and hardly modify the geometry. For example, the  $N_{\text{alk}}\text{H}^+ \dots \text{O}^-$  distance and  $N_{\text{alk}}\text{H}^+ \dots \text{O}^-$  angle are modified by less than 0.1 % in the most stable form of  $\text{CdH}_2^{2+}:\text{HSO}_4^-$  (*vide infra*). The difference is slightly larger for the  $\text{CdH}^+:\text{H}_2\text{SO}_4^-$  complexes, 0.3% and 1% for the most stable forms. Furthermore, BSSE corrections hardly modify the calculated harmonic frequencies of the most stable form of  $\text{CdH}_2^{2+}:\text{HSO}_4^-$ . The BSSE-corrected frequencies differ only by less than 0.1% from the non-BSSE-corrected ones in the  $\nu(\text{XH})$  range, a discrepancy smaller than the experimental resolution ( $4 \text{ cm}^{-1}$ ). The discrepancy is slightly larger in the fingerprint region, but remains smaller than 0.3%, except for the  $\beta(N_{\text{alk}}\text{H}^+)$  mode (0.6%). The intermolecular modes are more affected (1 to 3%). The most modified mode is the hindered rotation of  $\text{HSO}_4^-$  (cogwheel motion) for which the discrepancy between the two calculated frequencies is 5%.

Quinine and quinidine differ from cinchonidine by the presence of a methoxy  $\text{OCH}_3$  substituent in the aromatic ring. This leads to additional conformational flexibility, with two classes of conformers corresponding to the  $\text{OCH}_3$  in cis or trans position, as observed in 2-methoxynaphthalene.<sup>77</sup> The complexes containing quinine and quinidine were then calculated using those containing cinchonidine as starting points. The chirality of the chiral centers was modified when necessary and the methoxy group was added, in the two possible positions.

The calculations were done using the Gaussian 09 package.<sup>78</sup> Obtained conformers structures were drawn with the Gabedit software.<sup>79</sup> Assignment was based on spectroscopic criteria (good match between calculated and experimental frequencies) and thermodynamics, favoring the most stable structures.

The electronic excited states of the protonated monomers and complexes were calculated at the CC2 level of theory.<sup>80</sup> The calculations were performed using the resolution-of-the-identity (RI) approximation<sup>81</sup> and the correlation-consistent polarized valence double- $\zeta$  (cc-pVDZ) basis set.<sup>82</sup> The ground state of the most stable structure assigned to the experiment was calculated at the RI-CC2 level, keeping the DFT-D geometry. Vertical excitation energies were then calculated at the RI-CC2 level considering six excited states. 22 core orbitals were frozen for the protonated cinchonidine monomers and 31 for the complex. The CC2 convergence was set at  $10^{-7}$ . This method has been used on numerous protonated organic molecules and satisfactorily reproduces the  $S_{1\leftarrow 0}$  transition energy.<sup>83</sup> All the calculations were done using the Turbomole V6.6 program package.<sup>84</sup> The difference in density between the ground state and the electronic excited states were calculated using the density analysis of Turbomole and plotted using the VMD software.<sup>85</sup>

### c) Isolated systems

The vibrational spectroscopy of the molecular sub-units is summarized here. Comparison between the experimental vibrational frequencies determined previously or in this work and those calculated here are used for determining the scaling factors used.

***H<sub>2</sub>SO<sub>4</sub> and HSO<sub>4</sub>***: The vibrational spectroscopy of H<sub>2</sub>SO<sub>4</sub> is well known in the gas phase<sup>59, 60</sup> and in low-temperature matrices.<sup>86</sup> In the 3  $\mu\text{m}$  region, the infra-red spectrum of H<sub>2</sub>SO<sub>4</sub> vapours shows an intense band at 3609.2  $\text{cm}^{-1}$  assigned to the  $\nu(\text{OH})$  stretch.<sup>59</sup> The scaling factor in this range is determined as the ratio between experimental and calculated (3755  $\text{cm}^{-1}$ ) frequencies of the H<sub>2</sub>SO<sub>4</sub>  $\nu(\text{OH})$  stretch, it amounts to 0,961. This scaling factor is of the same order as those defined for the B3LYP functional associated with other Pople basis sets.<sup>87</sup>

The experimental spectrum of H<sub>2</sub>SO<sub>4</sub> in the fingerprint region (800-1800  $\text{cm}^{-1}$ ) is dominated by two intense features at 1220.1 and 1464.7  $\text{cm}^{-1}$  assigned to the  $\nu(\text{SO}_2)$  symmetric and antisymmetric stretches, respectively. The band located at 1157.1  $\text{cm}^{-1}$  is assigned to the  $\beta(\text{SOH})$  asymmetric bend while that at 834.1 and 891.4  $\text{cm}^{-1}$  are attributed to the  $\text{S}(\text{OH})_2$  symmetric and asymmetric stretches. As we shall see later, the vibrational modes of the complexes involve stretching and bending motions extensively delocalized on the OH and CO groups. For this reasons, we have treated the stretching and bending modes on the same footing. The scaling factor in the



fingerprint region is determined as the average ratio between experimental and calculated frequencies of the  $\beta(\text{SO}_2)$  and  $\beta(\text{OH})$  bends, and  $\nu_s(\text{OH})_2$  and  $\nu(\text{SO}_2)$  stretches. The obtained scaling factor is 1,060. This value reproduces well the experimental IR spectra of  $\text{H}_2\text{SO}_4$  in the low frequencies region and scaling factors  $>1$  are generally used for SO containing species.<sup>88-90</sup>

Less is known on the infrared spectroscopy of the bisulfate anion  $\text{HSO}_4^-$ , which has been studied mostly in the condensed phase, for example in sulfuric acid solutions<sup>91, 92</sup> or thin films,<sup>93</sup> or in strongly bound complexes under cryogenic matrix<sup>61</sup> or gas-phase conditions.<sup>90</sup> Due to the absence of experimental data in isolated conditions, we will use the same scaling factors as for  $\text{H}_2\text{SO}_4$ .

**$\text{CdH}^+$ ,  $\text{QnH}^+$  and  $\text{QdH}^+$ :** The conformational landscape of neutral cinchona alkaloids has been extensively studied by Bürgi *et al.* and Caner *et al.*<sup>94-96</sup> The same nomenclature as for the neutral systems is used for all protonated states,<sup>97</sup> as described previously.<sup>53</sup> The details of the nomenclature are given in the electronic supplementary information (ESI†). Briefly, the structures can be separated in two classes: in the “Closed” structures, the alkaloid is folded over the aromatic ring while in the “Open” structures, it is extended outwards.

The vibrational spectroscopy of gas-phase Cd is not known. However, Qn and Qd have been studied previously under jet-cooled conditions by IR-UV double resonance spectroscopy.<sup>68</sup> The experimental frequency of  $3650\text{ cm}^{-1}$  observed in both molecules, a typical free  $\nu(\text{OH})$  stretch value, has been assigned to the  $\nu(\text{OH})$  stretch of the most stable  $\gamma$ -open conformer for which the calculated value is  $3821\text{ cm}^{-1}$ , which leads to a scaling factor of 0.955. The experimental  $\nu(\text{OH})$  frequency does not change much upon protonation on the alkaloid nitrogen; it is measured at  $\sim 3650\text{ cm}^{-1}$  in  $\text{CdH}^+$ ,  $\text{QnH}^+$ , or  $\text{QdH}^+$  by IRMPD spectroscopy.<sup>56</sup> It does not change substantially with the protonation on the aromatic nitrogen and appears at the same value in  $\text{CdN}_{\text{arom}}\text{H}^+$ . The average scaling factor of the  $\nu(\text{OH})$  stretch of the protonated species is then taken equal to 0.955, the same value as determined for neutral Qn under supersonic-jet conditions.

The  $\nu(\text{N}_{\text{alk}}\text{H}^+)$  stretch frequency is sensitive to conformation and hydrogen bond formation.<sup>56</sup> The cinchonidine protonated monomers and dimers ( $\nu(\text{N}_{\text{alk}}\text{H}^+)$  stretch frequency ranging from  $3209$  to  $3300\text{ cm}^{-1}$ ) were used to determine the average scaling factor, which amounts to 0.970.<sup>54</sup>

The  $\nu(\text{N}_{\text{arom}}\text{H}^+)$  stretch is experimentally observed at  $3470\text{ cm}^{-1}$ , in the monomer and the dimer. The calculated value does not depend on the conformer and yields a scaling factor of 0.971.

We can anticipate from what is known on the isolated systems that free  $\nu(\text{OH})$  stretches should appear around  $3650\text{ cm}^{-1}$  whatever the protonation state of the molecule. For protonation on  $\text{N}_{\text{alk}}$ ,  $\nu(\text{N}_{\text{alk}}\text{H}^+)$  is expected at  $3280\text{ cm}^{-1}$  for a free  $\text{N}_{\text{alk}}\text{H}^+$  and strongly shifted down in energy when it is involved in an intermolecular hydrogen bond.<sup>56</sup> Finally, for protonation on  $\text{N}_{\text{arom}}$ ,  $\nu(\text{N}_{\text{arom}}\text{H}^+)$  is expected around  $3470\text{ cm}^{-1}$  range and is not sensitive to the environment.<sup>58</sup> The standard deviation

between calculated and experimental frequencies of the reference structures allow us to assume an error of  $\sim 20\text{ cm}^{-1}$  on the calculated frequencies.

## **Results:**

### **1. Structural studies**

#### **1.1. Experimental IRMPD spectra**

The IRMPD spectra obtained by electro-spraying a solution of cinchonidine sulfate are shown in **Figure 3** and **Figure 5**. The  $3\ \mu\text{m}$  region shows two narrow bands in the region of the free  $\nu(\text{OH})$ . The presence of two bands in this region allows ruling out the presence of  $\text{SO}_4^{2-}$ ; one of these bands belongs to  $\text{CdH}^+$  and the other one to  $\text{H}_2\text{SO}_4$  or  $\text{HSO}_4^-$ . The band at  $3652\text{ cm}^{-1}$  is typical of the free  $\nu(\text{OH})$  of Cd but is not informative about the protonation site of Cd. The intense band at  $3621\text{ cm}^{-1}$  appears in the range of the free  $\nu(\text{OH})$  of  $\text{H}_2\text{SO}_4$  or  $\text{HSO}_4^-$ , but does not allow deducing whether the system contains  $\text{H}_2\text{SO}_4$  or  $\text{HSO}_4^-$ . Finally, a broad band appears at  $3396\text{ cm}^{-1}$ . This range corresponds either to  $\nu(\text{N}_{\text{arom}}\text{H}^+)$  or to intermolecular hydrogen-bonded  $\nu(\text{OH})$ . We will therefore consider the two species  $\text{H}_2\text{SO}_4$  and  $\text{HSO}_4^-$  and calculate both  $\text{CdH}^+:\text{H}_2\text{SO}_4$  and  $\text{CdH}_2^{2+}:\text{HSO}_4^-$  complexes. The fingerprint region is dominated by an intense band centered at  $1040\text{ cm}^{-1}$  followed by congested features spreading up to  $1400\text{ cm}^{-1}$ .

#### **1.2. Calculated structure of the $\text{CdH}^+:\text{H}_2\text{SO}_4$ complex**

The most stable structures of the complexes are presented in **Figure 2**. The most important structural parameters are listed in **Table 1** and the relative energies in **Table 3**.

All the calculated conformations are strongly bound by an intermolecular  $\text{NH}^{\delta\text{q}}\dots\delta\text{q}'\text{O}$  interaction that links  $\text{N}_{\text{alk}}\text{H}^+$  and the SO group of sulfuric acid ( $d=1.84$  to  $1.88\ \text{\AA}$ ). NBO analysis of the electron density and orbital populations is reported in the ESI† and shows that this interaction is mostly electrostatic in nature. It manifests itself by a substantial red shift of the  $\nu(\text{N}_{\text{alk}}\text{H}^+)$  stretch frequency at  $3291\text{ cm}^{-1}$ , while the  $\nu(\text{OH})$  frequencies remain unchanged relative to the bare molecules, reflecting the free nature of the  $\text{H}_2\text{SO}_4$  hydroxyls.

In Anti- $\gamma$ -open', one of the OH groups of  $\text{H}_2\text{SO}_4$  interacts with the aromatic ring, more precisely the  $\text{C}_6$  ring without nitrogen, denoted as  $\text{arom}_\text{C}$  in what follows ( $\text{OH}\dots\pi_{\text{arom}_\text{C}}$  interaction). The  $\text{OH}\dots\text{X}$  distance, where X is the center of the  $\text{arom}_\text{C}$  ring, is  $3.30\ \text{\AA}$ . Due to this interaction, the  $\nu(\text{OH})$  frequency of the interacting OH group of  $\text{H}_2\text{SO}_4$  is shifted down in energy to  $3429\text{ cm}^{-1}$ .

The complexes with the Closed conformers are more compact, with shorter distances between H<sub>2</sub>SO<sub>4</sub> and the aromatic ring. Anti- $\gamma$ -closed and Anti- $\gamma$ -closed' exhibit an OH... $\pi_{\text{aromC}}$  interaction, with a OH...X distance of 2.58 Å, much shorter than in Anti- $\gamma$ -open'. In Anti- $\gamma$ -closed', a strong OH...N<sub>arom</sub> hydrogen bond bridges H<sub>2</sub>SO<sub>4</sub> and the aromatic nitrogen (d=1.58 Å). This interaction results to a strong down shift of the H<sub>2</sub>SO<sub>4</sub>  $\nu(\text{OH})$  frequency, down to 2343 cm<sup>-1</sup>.

The calculated spectra of the CdH<sup>+</sup>:H<sub>2</sub>SO<sub>4</sub> structures are shown in **Figure 3**. The free  $\nu(\text{OH})$  stretches localized on CdH<sup>+</sup> and H<sub>2</sub>SO<sub>4</sub> are calculated in the 3550-3650 cm<sup>-1</sup> range for all the structures. When one hydroxyl group of H<sub>2</sub>SO<sub>4</sub> interacts with the aromatic  $\pi$  electrons, like in Anti- $\gamma$ -open', its  $\nu(\text{OH})$  frequency is shifted down to the 3400-3450 cm<sup>-1</sup> range. When one hydroxyl group of H<sub>2</sub>SO<sub>4</sub> interacts with N<sub>arom</sub>, its  $\nu(\text{OH})$  frequency is shifted further down to ~ 3300 cm<sup>-1</sup> in Anti- $\gamma$ -closed' and 2343 cm<sup>-1</sup> in Anti- $\gamma$ -closed, which is out of our experimental range and is not presented in **Figure 3**. The  $\nu(\text{N}_{\text{alk}}\text{H}^+)$  stretch is calculated in the 3170-3270 cm<sup>-1</sup> range in all the CdH<sup>+</sup>:H<sub>2</sub>SO<sub>4</sub> complexes indicating that it is involved in a strong interaction.

In the fingerprint region, the two  $\beta(\text{OH})$  bending modes of H<sub>2</sub>SO<sub>4</sub> are calculated in the 1150-1200 and 1250-1300 cm<sup>-1</sup> range. They are the most intense calculated transitions, together with the  $\nu(\text{S-OH})$  stretch at ~900 cm<sup>-1</sup> and the two  $\nu(\text{SO})$  stretches in the 1300- 1450 cm<sup>-1</sup> region.

### 1.3. Calculated structure of the CdH<sub>2</sub><sup>2+</sup>:HSO<sub>4</sub><sup>-</sup> complex

The most stable structures of the CdH<sub>2</sub><sup>2+</sup>:HSO<sub>4</sub><sup>-</sup> complex are presented in **Figure 4**. The structural parameters are listed in **Table 2** and the energies in **Table 3**. Two of these complexes contain the Open form of CdH<sub>2</sub><sup>2+</sup> and three the Closed form. They all involve strong electrostatic interactions between the bisulfate anion and the protonated nitrogen atoms. These interactions are mostly electrostatic, like that described above. The electrostatic interactions between two charged species being stronger than that between a charged species and a neutral entity. All the CdH<sub>2</sub><sup>2+</sup>:HSO<sub>4</sub><sup>-</sup> complexes are then much more stable than the corresponding CdH<sup>+</sup>:H<sub>2</sub>SO<sub>4</sub> structures, the energy difference between them being 7 kcal/mol or more.

The structures containing Open and Closed conformations of CdH<sub>2</sub><sup>2+</sup> strongly differ from each other. When CdH<sub>2</sub><sup>2+</sup> is Open, stabilization mostly arises from the N<sub>alk</sub>H<sup>+</sup> $\delta^q$ ...<sup>- $\delta^q$</sup> O interaction. This ionic interaction is strong, as it can be assessed from the short (1.58 Å) distance between N<sub>alk</sub>H<sup>+</sup> $\delta^q$  and O<sup>- $\delta^q$</sup> , and purely electrostatic. The quinoline ring and HSO<sub>4</sub><sup>-</sup> are distant by more than 6.0 Å. The Anti- $\beta$ -open structure involves an additional OH...O<sup>- $\delta^q$</sup>  hydrogen bond relative to Syn- $\gamma$ -open, from the OH of CdH<sub>2</sub><sup>2+</sup> to one oxygen atom of HSO<sub>4</sub><sup>-</sup>. The corresponding OH...O<sup>- $\delta^q$</sup>  distances are 1.87 and 4.11 Å in Anti- $\beta$ -open and Syn- $\gamma$ -open, respectively. This hydrogen bond

contributes to the stabilization of Anti- $\beta$ -open, which is more stable than the Syn- $\gamma$ -open by  $\sim 2$  kcal/mol.

The complexes with the Closed conformers involve an additional interaction between  $O^{\delta q}$  of  $HSO_4^-$  and the  $N_{arom}H^+$  group of  $CdH_2^{2+}$ , which allows  $HSO_4^-$  to bridge the two protonated nitrogen atoms. This interaction is not as strong as  $N_{alk}H^{\delta q} \dots O^{\delta q}$ , because of the larger ( $> 2.3 \text{ \AA}$ ) distance between the two sites. Again, it is purely electrostatic. The geometry of the complex results from a compromise between these two interactions, but that involving the  $N_{alk}H^+$  group is dominant and dictates the  $N_{alk}H^{\delta q} \dots O^{\delta q}$  distance, quasi identical (1.64 to 1.60  $\text{\AA}$ ) to that calculated for the Open complexes (1.58 to 1.57  $\text{\AA}$ ). The  $N_{arom}H^{\delta q} \dots O^{\delta q}$  interaction stabilizes the complexes containing Closed forms by more than 2 kcal/mol relative to those with Open forms.

The spectra calculated for the  $Cd_2H^{2+} : HSO_4^-$  structures are shown in **Figure 5**. The  $\nu(OH)$  stretches localized on  $Cd_2H^{2+}$  and  $HSO_4^-$  are calculated in the 3580-3680  $\text{cm}^{-1}$  range, as expected for free OH, for all the structures, except Anti- $\beta$ -open in which the  $Cd_2H^{2+}$   $\nu(OH)$  is shifted down to 3380  $\text{cm}^{-1}$  because the OH group acts as an hydrogen bond donor to an oxygen of  $HSO_4^-$ . The spectrum of Syn- $\gamma$ -open stands out by the presence of an intense transition at 3106  $\text{cm}^{-1}$  due to the aromatic  $\nu(C_3H)$  stretching mode gaining intensity through the interaction with the  $HSO_4^-$  ion. The calculated spectrum of all the complexes shows an intense  $\nu(N_{alk}H^+)$  stretch in the 2570 - 2700  $\text{cm}^{-1}$  region, which is out of our experimental range and not shown in Figure 5. <sup>56</sup>

The calculated  $\nu(N_{arom}H^+)$  does not vary much with the structure and is calculated at  $\sim 3465$ -3470  $\text{cm}^{-1}$  for the complexes with both Open and Closed structures. It is only shifted down by a few wavenumbers ( $< 5 \text{ cm}^{-1}$ ) in the bridged complexes with the Closed forms, with a slightly lower value in Syn- $\gamma$ -closed' than Anti- $\gamma$ -closed, in line with the more compact structure of the former.

Most of the peaks calculated in the fingerprint region correspond to vibrations localized on  $HSO_4^-$ . Syn- $\gamma$ -closed', Anti- $\gamma$ -closed and Anti- $\beta$ -open have vibrations at 1162, 1246 and 1295  $\text{cm}^{-1}$  that are described in terms of the  $\beta(OH)$  bending motion of  $HSO_4^-$  coupled with  $\nu(SO)$  stretches. Syn- $\gamma$ -open and Syn- $\gamma$ -closed have several vibrations between 1170 and 1210  $\text{cm}^{-1}$  that correspond to the  $\beta(OH)$  bending motion of  $HSO_4^-$  coupled with  $\beta(C_{aliphatic}H)$  and  $\beta(C_{aromatic}H)$  bending motions.

#### 1.4. Assignment of the observed complex

**Figure 3** compares the experiment to the spectra simulated for  $CdH^+ : H_2SO_4$ . The calculated spectrum of  $CdH^+ : H_2SO_4$  poorly reproduces the experimental data in the high frequencies range as well as in the fingerprint region. In particular, no band is observed in the range of the calculated bonded  $\nu(N_{alk}H^+)$  (3170-3300  $\text{cm}^{-1}$  range). In the fingerprint region, no strong band is observed

above  $1350\text{ cm}^{-1}$  where the two  $\nu(\text{SO})$  stretches are expected. This result allows ruling out that the observed complex is  $\text{CdH}^+:\text{H}_2\text{SO}_4$ .

**Figures 5** compares the experiment to the spectra simulated for  $\text{CdH}_2^{2+}:\text{HSO}_4^-$ . In the high frequency region, the band around  $3650\text{ cm}^{-1}$  is assigned to a free  $\nu(\text{OH})$  stretch of  $\text{CdH}_2^{2+}$ . This allows ruling Anti- $\beta$ -open for the attribution. The strong feature at  $3621\text{ cm}^{-1}$  is attributed to  $\nu(\text{OH})$  of  $\text{HSO}_4^-$  and is only slightly lower in frequency than the free  $\nu(\text{OH})$ , estimated at  $3650\text{ cm}^{-1}$  in  $\text{HSO}_4^-$ . The broader feature around  $3400\text{ cm}^{-1}$  is attributed to the  $\nu(\text{N}_{\text{arom}}\text{H}^+)$  stretch. Finally, no intense band is experimentally observed in the  $3000\text{-}3200\text{ cm}^{-1}$  region corresponding to the  $\nu(\text{CH})$  stretching modes. Thus, the observed complex cannot be Syn- $\gamma$ -open. Based on the  $3\mu\text{m}$  region, we can safely assign the observed complex to one of the calculated structures containing a Closed conformer, which all reproduce reasonably well the experimental spectrum. The experimental spectrum obtained in the fingerprint region is also satisfactorily reproduced by those calculated for the Closed structures and most of the observed peaks are assigned to transitions localized on  $\text{HSO}_4^-$ . Moreover, the energetic values listed in **Table 3** indicate that the Closed structures are by far more stable than the complexes involving neutral  $\text{H}_2\text{SO}_4$ , and more stable by several kcal/mol than the Open conformers. Anti- $\gamma$ -closed, Syn- $\gamma$ -closed' and Syn- $\gamma$ -closed are almost iso-energetic within the error. Among them, Syn- $\gamma$ -closed' displays the best match with the experimental spectrum both in the  $3\mu\text{m}$  and in the fingerprint region. We therefore assume that the observed spectrum is mainly due to Syn- $\gamma$ -closed', without excluding a contribution of the two other forms.

### 1.5. Extension to quinine and quinidine

The geometries obtained for  $\text{QnH}_2^{2+}:\text{HSO}_4^-$  are shown in **Figure 6** and **Figure 7**. The dihedral angles of the calculated complexes are listed in **Table 4** and **Table 5** and their energetics in **Table 6**. The structures obtained for  $\text{QdH}_2^{2+}:\text{HSO}_4^-$  are very similar and are shown in **Figure S1**. The energetics and the structural parameters are listed in **Tables S1** and **Table S2** of the ESI†.

The calculated complexes are similar for the cis and trans structures and resemble those obtained for  $\text{CdH}_2^{2+}:\text{HSO}_4^-$ . The presence of the  $\text{OCH}_3$  substituent slightly modifies the energetic order between the different geometries and complexes with Open forms become energetically competitive with the complexes with Closed forms. The complexes built from the Closed cis conformers resemble those obtained for  $\text{CdH}_2^{2+}:\text{HSO}_4^-$ , with  $\text{HSO}_4^-$  bridging the two protonated sites of the molecule and showing no interaction with the OH or the  $\text{OCH}_3$  groups of Qn. Cis and Trans syn- $\gamma$ -Open show no difference relative to the  $\text{CdH}_2^{2+}:\text{HSO}_4^-$  system. In contrast, the Cis-anti- $\beta$ -Open structure slightly differs from its counterpart in  $\text{CdH}_2^{2+}:\text{HSO}_4^-$  because  $\text{HSO}_4^-$  interacts not

only with the  $N_{alk}H^+$  group but also with the  $OCH_3$  group (distance of 2 Å) and the OH group of  $QnH_2^{2+}$ . These additional hydrogen bonds contribute to the stability to the complex. In Trans-syn- $\beta$ -open, only the additional interaction between  $HSO_4^-$  and OH is observed.

The IR spectra of all these complexes, the 3  $\mu$  region and the fingerprint region, are presented in **Figures 8** and **9**. In the 3  $\mu$ m region, the spectra of the cis/trans  $QnH_2^{2+}:HSO_4^-$  complexes parallel those of the  $CdH_2^{2+}:HSO_4^-$  complex. In the fingerprint region, the calculated spectra of cis/trans  $QnH_2^{2+}:HSO_4^-$  have some transitions in common with  $CdH_2^{2+}:HSO_4^-$ . Most of the differences between  $QnH_2^{2+}:HSO_4^-$  and  $CdH_2^{2+}:HSO_4^-$  are due to modes localized on the methoxy substituent. The  $\nu(CO)$  stretch of the  $OCH_3$  is calculated between  $\sim 1110\text{ cm}^{-1}$  and  $\sim 1220\text{ cm}^{-1}$ , with a weak intensity. It is higher in energy and has larger intensity in the trans forms. No particularly intense band stands out in the cis conformers. A very intense  $\beta(C_{arom}H)$  bend is calculated at  $\sim 1300\text{ cm}^{-1}$  -  $1330\text{ cm}^{-1}$  for all the trans conformers of  $QnH_2^{2+}$ , becoming the most intense in the fingerprint region. The absence of intense transition in the  $\sim 1400\text{ cm}^{-1}$  region of the experimental spectrum and the presence of bands above  $1650\text{ cm}^{-1}$  allows discarding the trans conformers.

The results obtained in the high-frequency region parallel those obtained for cinchonidine. The spectrum of the Closed cis geometries shows better correspondence with the experimental data than those of the Open cis geometries. Moreover, the cis conformers are more stable than the trans. Cis-Syn- $\gamma$ -closed, Cis-Syn- $\gamma$ -closed' and Cis-Anti- $\gamma$ -closed show good correspondence with the experiment. It is therefore likely that the observed spectrum contains contributions of these three cis Closed forms, whose relative Gibbs energy (1.0-1.5 kcal/mol) is of the order of the expected calculation error. The preference for cis forms results parallel those observed for similar systems like neutral 2-methoxynaphthalene<sup>77</sup>, Naproxene,<sup>98,99</sup> or neutral quinine and hydroquinine.<sup>68,97</sup>

No difference is experimentally observed between the complexes Qn and Qd, as it was already the case for the protonated monomers.<sup>56</sup> Qn and Qd therefore behave like true enantiomers in this context.

## 2. Photodissociation

### 2.1. Experimental results

The mass spectrum resulting from the photodissociation of  $CdH_2^+HSO_4^-$  at 266 nm is shown in **Figure 10**, as well as its CID spectrum. The conditions (collision voltage or UV power) have been adjusted so that the total fragmentation yield is the same for the two spectra, namely, 0.33, which allows better comparison between them. The UVPD spectrum is noisier because light scattered from the laser may create stray ions, but the two spectra show identical fragmentation

pattern, with the major fragment being the protonated monomer. In contrast with  $\text{CdH}^+$  itself, the  $\text{CdH}_2^{2+}:\text{HSO}_4^-$  complex ( $m/z$  393) does not show any specific UVPD photo-fragment, and the same behavior is observed for Qn or Qd. **Figure 10** also shows the CID spectrum of  $\text{CdH}^+$  ( $m/z$  295) produced by UV irradiation of the complex. The fragmentation pattern is the same as observed for  $\text{CdH}^+$  formed in the ESI, with the main channels being water loss ( $m/z$  277) or loss of water and methylamine ( $m/z$  246). The fragmentation efficiency for a given radiofrequency amplitude is of the same order as that of  $\text{CdH}^+$  formed in the ESI.<sup>54</sup>

## 2.2. Excited states calculations

*Vertical excitation energies and nature of the first three excited states:* The energies of the first three vertical electronic transitions of Syn- $\gamma$ -closed' are listed in **Table 7**. We have limited the table to the transitions below the energy of the UV laser (4.66 eV). Table 7 also includes the doubly protonated monomer  $\text{CdH}_2^{2+}$  for the sake of comparison. However, this doubly charged species is not stable in the gas phase and was not observed in our experimental conditions. Therefore, its PES was not fully explored. The structure of isolated  $\text{CdH}_2^{2+}$  presented in the table is a local minimum obtained by optimizing the geometry of  $\text{CdH}_2^{2+}$ , starting from the geometry contained in the  $\text{CdH}_2^{2+}:\text{HSO}_4^-$  Syn- $\gamma$ -closed' complex. Finally, the table includes the results for the corresponding monomers protonated on  $\text{N}_{\text{alk}}$  or  $\text{CdN}_{\text{arom}}\text{H}^+$ , the corresponding monomer protonated on  $\text{N}_{\text{arom}}$ , in the same geometry as contained in the complex. In short, the systems will be denoted by  $\text{CdH}_2^{2+}:\text{HSO}_4^-$ ,  $\text{CdH}_2^{2+}$ ,  $\text{CdH}^+$ , and  $\text{CdN}_{\text{arom}}\text{H}^+$  in what follows. **Figure 11** shows the difference between the electronic density of the ground state and that of the first three excited states of  $\text{CdH}^+$ ,  $\text{CdN}_{\text{arom}}\text{H}^+$ ,  $\text{CdH}_2^{2+}$  and  $\text{CdH}_2^{2+}:\text{HSO}_4^-$ . In the discussion that follows, the canonical occupied HF orbitals delocalized all over the two aromatic rings will be denoted by  $\pi_{\text{arom}}$  and the unoccupied one by  $\pi^*_{\text{arom}}$ , while the occupied orbitals localized on the aza  $\text{C}_6$  ring or carbonaceous  $\text{C}_6$  ring will be denoted by  $\pi_{\text{aromN}}$  or  $\pi_{\text{aromC}}$ , respectively. Similarly, the unoccupied ones will be denoted by  $\pi^*_{\text{aromN}}$  or  $\pi^*_{\text{aromC}}$  respectively. The  $\text{N}_{\text{alk}}$  and  $\text{N}_{\text{arom}}$  lone pairs will be denoted by  $n_{\text{Nalk}}$  and  $n_{\text{Narom}}$ , respectively. Finally, the canonical HF orbitals localized on the alkaloid  $\text{C}=\text{C}$  group will be denoted by  $\pi_{\text{CC}}$  or  $\pi^*_{\text{CC}}$ , respectively.

The three lower-energy transitions of  $\text{CdH}^+$  involve aromatic  $\pi$  electrons as well as the lone pair located on  $\text{N}_{\text{arom}}$ , as suggested for quinoline (**Figure 11a**).<sup>100</sup> The  $\text{S}_{1\leftarrow 0}$  transition mainly involves HOMO-4 (mostly  $\text{N}_{\text{arom}}$  lone pair)  $\rightarrow$  LUMO ( $\pi^*_{\text{arom}}$ ) (68%) and HOMO-3 (mixed  $\text{N}_{\text{arom}}$  lone pair and  $\pi_{\text{arom}}$ )  $\rightarrow$  LUMO (24 %) excitations. It is therefore an intramolecular charge transfer (CT) within the aromatic ring, i.e. a  $n_{\text{arom}}\pi^*_{\text{arom}}$  CT transition. The  $\text{S}_{2\leftarrow 0}$  and  $\text{S}_{3\leftarrow 0}$  electronic

transitions are  $\pi\pi^*$  transitions localized on the aromatic ring. They involve the very same orbitals HOMO-1( $\pi_{\text{arom}}$ ) $\rightarrow$  LUMO (64%) and HOMO ( $\pi_{\text{arom}}$ )  $\rightarrow$  LUMO+1 ( $\pi^*_{\text{arom}}$ ) (30%) for  $S_{2\leftarrow 0}$  and HOMO-1  $\rightarrow$  LUMO (85%) for  $S_{3\leftarrow 0}$  as the so-called  $L_b$  and  $L_a$  electronic transitions of naphthalene derivatives.<sup>101 102 68</sup>

In  $\text{CdN}_{\text{arom}}\text{H}^+$ , (**Figure 11b**), the  $S_{1\leftarrow 0}$  transition mainly involves HOMO (mostly  $n_{\text{Nalk}}$ )  $\rightarrow$  LUMO (mostly  $\pi^*_{\text{arom}}$ ) (40%) and HOMO-1 ( $n_{\text{Nalk}}$  and  $\pi_{\text{aromC}}$ )  $\rightarrow$  LUMO (37 %) excitations. The  $S_{1\leftarrow 0}$  transition is therefore mainly an intramolecular charge transfer from  $n_{\text{Nalk}}$  to  $\pi^*_{\text{arom}}$ , *i.e.* a  $n_{\text{alk}}\pi^*_{\text{arom}}$  CT transition. The  $S_{2\leftarrow 0}$  transition is mainly a naphthalene-like  $\pi_{\text{arom}}\pi^*_{\text{arom}}$  transition that involves HOMO-2 ( $\pi_{\text{arom}}$ )  $\rightarrow$  LUMO (54%) and HOMO-1  $\rightarrow$  LUMO (31%) excitations. Finally, the  $S_{3\leftarrow 0}$  transition involves HOMO-1  $\rightarrow$  LUMO+1 ( $\pi^*_{\text{arom}}$ ) (44%) and HOMO  $\rightarrow$  LUMO+1 (35%) excitations, it is mainly a naphthalene-like  $\pi_{\text{arom}}\pi^*_{\text{arom}}$  transition.

For  $\text{CdH}_2^{2+}$ , (**Figure 11c**), both nitrogen atoms are protonated and there is no possibility for CT  $n\pi^*$  transitions involving a nitrogen lone pair. The  $S_{1\leftarrow 0}$  and  $S_{2\leftarrow 0}$  transitions are of  $\pi\pi^*$  character.  $S_{1\leftarrow 0}$  corresponds to the HOMO-1 ( $\pi_{\text{aromC}}$ )  $\rightarrow$  LUMO ( $\pi^*_{\text{arom}}$ ) (94%) excitation, while  $S_{2\leftarrow 0}$  corresponds to HOMO-2 ( $\pi_{\text{arom}}$ )  $\rightarrow$  LUMO (72%) and HOMO-1 $\rightarrow$ LUMO+1 ( $\pi_{\text{arom}}$ ) (26%), respectively. Interestingly, the  $S_{3\leftarrow 0}$  transition corresponds to an intramolecular charge-transfer from the alkaloid C=C to the aromatic ring. Indeed, it is a HOMO  $\rightarrow$  LUMO transition (95%) with the HOMO orbital being the  $\pi_{\text{C=C}}$  orbital of the C=C double bond.

In the  $\text{CdH}_2^{2+}:\text{HSO}_4^-$  complex also, both nitrogen atoms of  $\text{CdH}_2^{2+}$  are protonated and there is no possibility for intramolecular CT involving a nitrogen lone pair (**Figure 11d**). The presence of  $\text{HSO}_4^-$  completely modifies the nature of the  $S_{1\leftarrow 0}$  transition compared to  $\text{CdH}_2^{2+}$ . At equilibrium distance, the charge transfer transition involving the  $\pi_{\text{C=C}}$  orbital is out of the manifold of the transitions reached by the UV laser. The  $\pi_{\text{C=C}}$  orbital corresponds to the HOMO and is involved in none of the first five electronic transitions, and only marginally in  $S_{6\leftarrow 0}$ , which is higher in energy (5.23 eV) than the laser energy.  $S_{1\leftarrow 0}$  now corresponds to HOMO-3  $\rightarrow$  LUMO excitation (93%), with the HOMO-3 being mainly described in terms of combination of the lone pairs  $n_{\text{O}}$  of the oxygen atoms of the three S=O groups of  $\text{HSO}_4^-$ , and the LUMO being a  $\pi^*_{\text{aromN}}$  orbital. The  $S_{1\leftarrow 0}$  transition can therefore be described in terms of a  $n_{\text{O}}\pi^*_{\text{aromN}}$  intermolecular CT from the bisulfate to  $\text{CdH}_2^{2+}$ . The  $S_{2\leftarrow 0}$  and  $S_{3\leftarrow 0}$  transitions correspond to HOMO-1( $\pi_{\text{aromC}}$ )  $\rightarrow$  LUMO (81%) and to HOMO-2 ( $\pi_{\text{arom}}$ )  $\rightarrow$  LUMO, (61%), respectively. They are of  $\pi\pi^*$  nature.



### *Modification of the electronic transitions when elongating the NH bonds:*

Based on calculations of the excited states at the same level as in this work, it was proposed previously that the photoreactivity of the closed forms of  $\text{CdH}^+$  arises from proton transfer from  $\text{N}_{\text{alk}}$  to  $\text{N}_{\text{arom}}$ . The  $\text{CdN}_{\text{arom}}\text{H}^+$  formed thereby undergoes electron transfer from the  $\text{C}=\text{C}$  group of the alkaloid to  $\text{N}_{\text{arom}}$ , resulting to the formation of specific photofragments.<sup>53</sup> This was confirmed by the experimental finding that in a similar system, hydroquinine, in which the  $\text{CC}$  bond is saturated, there is no formation of photofragments.<sup>53</sup> Elongating the  $\text{N}_{\text{arom}}\text{H}^+$  bond in  $\text{CdN}_{\text{arom}}\text{H}^+$  lowers the charge-transfer transition that plays a major role in the reactivity of the cinchona alkaloids, like the charge transfer involving  $\text{CO}$  in tyrosine containing peptides.<sup>38 53</sup> We have therefore calculated the change in electron density for the first three electronic transitions of  $\text{CdH}_2^{2+}$  and  $\text{CdH}_2^{2+}:\text{HSO}_4^-$ , when elongating either the  $\text{N}_{\text{alk}}\text{H}$  or the  $\text{N}_{\text{arom}}\text{H}$  distances. The density difference between the ground state and the first three excited states of the complex is compared to that in  $\text{CdH}_2^{2+}$  in **Figure 12**. In  $\text{CdH}_2^{2+}$ , the  $\text{S}_{1\leftarrow 0}$  transition for the  $\text{N}_{\text{alk}}\text{H}^+$  bond modified from its equilibrium distance (1.023 Å) to 2.000 Å is an intramolecular charge transfer within the alkaloid part of the molecule. It is mostly a HOMO ( $\pi_{\text{C}=\text{C}}$ )  $\rightarrow$  LUMO ( $\sigma^*_{\text{N}_{\text{alk}}\text{H}^+}$ ) (96%) transition. It is therefore a CT transition from the  $\pi_{\text{C}=\text{C}}$  orbital to the  $\sigma^*_{\text{N}_{\text{alk}}\text{H}^+}$  orbital.<sup>53</sup> For the  $\text{N}_{\text{arom}}\text{H}^+$  bond elongated from its equilibrium distance (1.018 Å) to 2.000 Å the  $\text{S}_{1\leftarrow 0}$  and  $\text{S}_{2\leftarrow 0}$  are HOMO-1 ( $\pi_{\text{arom}}$ )  $\rightarrow$  LUMO ( $\sigma^*_{\text{N}_{\text{arom}}\text{H}^+}$ ) (96%) and HOMO-2 ( $\pi_{\text{arom}}$ )  $\rightarrow$  LUMO ( $\sigma^*_{\text{N}_{\text{arom}}\text{H}^+}$ ) (98%) transitions. However, the  $\text{S}_{3\leftarrow 0}$  transition is a HOMO ( $\pi_{\text{C}=\text{C}}$ )  $\rightarrow$  LUMO (97%) transition, *i.e.* a charge transfer from the  $\text{C}=\text{C}$  group localized on the alkaloid. In both cases, one of the first three electronic transitions, namely,  $\text{S}_{1\leftarrow 0}$  when elongating the  $\text{N}_{\text{alk}}\text{H}^+$  bond or  $\text{S}_{3\leftarrow 0}$ , when elongating the  $\text{N}_{\text{arom}}\text{H}^+$  bond involves charge migration from the  $\pi_{\text{C}=\text{C}}$  orbital to the  $\sigma^*_{\text{NH}^+}$ .

The  $\text{CdH}_2^{2+}:\text{HSO}_4^-$  complex behaves differently from  $\text{CdH}_2^{2+}$ . Elongating the  $\text{N}_{\text{alk}}\text{H}^+$  bond from its equilibrium distance is prevented by the cage effect due to the presence of  $\text{HSO}_4^-$ . Elongating the  $\text{N}_{\text{arom}}\text{H}$  bond from its equilibrium value (1.017 Å) to 2.000 Å has two consequences. Compared to  $\text{CdH}_2^{2+}$ , it modifies the energy order of the transition. For an identical  $\text{N}_{\text{arom}}\text{H}$  distance, of 2.000 Å,  $\text{S}_{2\leftarrow 0}$  and  $\text{S}_{3\leftarrow 0}$  in the complex are similar to  $\text{S}_{2\leftarrow 0}$  and  $\text{S}_{1\leftarrow 0}$  in  $\text{CdH}_2^{2+}$ , respectively in terms of excitations type and then electron density changes.  $\text{S}_{1\leftarrow 0}$  in the complex is the HOMO-3  $\rightarrow$  LUMO excitation (90%), with the HOMO-3 being mainly described in terms of combination of the  $n_{\text{O}}$  of the three  $\text{S}=\text{O}$  groups of  $\text{HSO}_4^-$ , and the LUMO being the  $\sigma_{\text{N}_{\text{arom}}\text{H}^+}$  orbital. It corresponds therefore to an intermolecular CT transition.

We can conclude from these results that the bisulfate anion has a protective effect and prevents photodissociation of the  $\text{CdH}_2^{2+}:\text{HSO}_4^-$  complex in two manners. Firstly, the fact that the two

nitrogen atoms,  $N_{\text{alk}}$  and  $N_{\text{arom}}$ , are protonated prevents proton transfer from  $N_{\text{alk}}$  to  $N_{\text{arom}}$ . Moreover, the short hydrogen bond between the bisulfate and  $N_{\text{alk}}$  induces a cage effect that prevents motions of the  $N_{\text{alk}}\text{H}^+$ . The second effect of the complex formation is that the CT transitions from the  $\pi_{\text{C=C}}$  orbital of the alkaloid part of the molecule to the  $\sigma^*_{\text{NalkH}^+}$  or  $\sigma^*_{\text{NaromH}^+}$  orbital are removed from the manifold accessible by the laser. Instead, the first three  $S_{n\leftarrow 0}$  transition involve  $\pi\pi^*$  excitations and then electron density changes within the quinoline ring, or charge migration from the bisulfate anion to the aza  $\text{C}_6$  ring, or to the  $\sigma^*_{\text{NaromH}^+}$ .

## Conclusion

This study unambiguously shows that the complexes formed between protonated cinchonidine and sulfuric acid actually contains doubly protonated cinchonidine  $\text{CdH}_2^{2+}$  and the bisulfate anion,  $\text{HSO}_4^-$ . The cinchona alkaloid is therefore protonated on both nitrogens, the alkaloid nitrogen  $N_{\text{alk}}$  and the aromatic nitrogen  $N_{\text{arom}}$ .  $\text{HSO}_4^-$  bridges the two protonation sites so that electrostatic interactions between  $\text{CdH}_2^{2+}$  and  $\text{HSO}_4^-$  stabilize the doubly protonated species in the gas phase. The same structure as for cinchonidine is observed for quinine and quinidine. No chirality effect is observed in the structure of the complex.

The presence of bisulfate has several consequences on the photophysics of protonated cinchonidine. First, the cinchonidine contained in the complex is doubly protonated, so that the transitions involving the  $N_{\text{alk}}$  or  $N_{\text{arom}}$  lone pair are removed from the manifold. The presence of  $\text{HSO}_4^-$  also has a protective role towards photo-dissociation. It first prevents the mobility of the proton localized on  $N_{\text{alk}}$  thanks to the strong electrostatic interaction. Such a cage effect has already been observed in tryptamine, tryptophan, or cinchonidine itself, embedded in cyclodextrine.<sup>53, 103, 104</sup> This explains why the reactivity related to proton mobility, previously proposed for isolated  $\text{CdH}^+$ , is not observed here.<sup>53</sup> The second role of the bisulfate is to modify the nature of the electronic transitions. In particular, the CT transitions from  $\pi_{\text{C=C}}$  orbital to  $\sigma^*_{\text{NalkH}^+}$  or  $\sigma^*_{\text{NaromH}^+}$ , which has been supposed to play a role in the photodissociation of  $\text{CdH}^+$ , is higher than the laser energy in the complex.<sup>53</sup> This study emphasizes the role of counterions in protecting biomolecules from photodissociation. The influence of complexation by sulfuric acid on the protonated cinchona alkaloid dimers is currently in progress and will be reported in a near future.

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## Figures and Tables

**Table 1:** Significant calculated dihedral angles ( $^{\circ}$ ) and distances ( $\text{\AA}$ ) of the most stable conformers of the  $\text{CdH}^+\text{H}_2\text{SO}_4$  complex optimized at the B3LYP-D3/6-31++G(d,p) level.

Dihedral angles ( $^{\circ}$ ) and distances ( $\text{\AA}$ )	Anti- $\gamma$ -open	Anti- $\gamma$ -open'	Anti- $\gamma$ -closed	Anti- $\gamma$ -closed'
$\tau_1$ ( $\text{C}_3\text{C}_4\text{C}_9\text{C}_8$ )	100	109	68	70
$\tau_2$ ( $\text{C}_4\text{C}_9\text{C}_8\text{N}_{\text{alk}}$ )	168	164	44	54
$\tau_3$ ( $\text{N C}_8\text{C}_9\text{O}$ )	-69	-71	165	175
$\mathbf{T}_3$ ( $\text{C}_8\text{C}_9\text{O H}$ )	-179	172	172	179
$\mathbf{d}_{\text{N}_{\text{alk}}\text{H}^{\delta+} \dots \delta-\text{OS}}$	1.88	1.88	1.84	1.87
$\mathbf{d}_{\text{N}_{\text{arom}} \dots \text{HOS}}$	7.14	5.47	1.58	3.38

**Table 2:** Significant calculated dihedral angles ( $^{\circ}$ ) and distances ( $\text{\AA}$ ) of the most stable conformers of the  $\text{CdH}_2^+\text{HSO}_4^-$  complex optimized at the B3LYP-D3/6-31++G(d,p) level.

Dihedral angles ( $^{\circ}$ ) and distances ( $\text{\AA}$ )	Syn- $\gamma$ -closed	Syn- $\gamma$ -closed'	Anti- $\gamma$ -closed	Anti- $\beta$ -open	Syn- $\gamma$ -open
$\tau_1$ ( $\text{C}_3\text{C}_4\text{C}_9\text{C}_8$ )	-108	-107	68	100	-83
$\tau_2$ ( $\text{C}_4\text{C}_9\text{C}_8\text{N}_{\text{alk}}$ )	72	47	58	165	161
$\tau_3$ ( $\text{N C}_8\text{C}_9\text{O}$ )	-165	171	177	-71	-73
$\mathbf{T}_3$ ( $\text{C}_8\text{C}_9\text{O H}$ )	172	165	169	108	149
$\mathbf{d}_{\text{N}_{\text{alk}}\text{H}^{\delta+} \dots \delta-\text{OS}}$	1.64	1.62	1.6	1.57	1.58
$\mathbf{d}_{\text{N}_{\text{arom}}\text{H}^{\delta+} \dots \delta-\text{OS}}$	2.76	2.35	2.66	7.03	6.17

**Table 3:** Calculated relative electronic energy  $\Delta E$  and Gibbs free energy  $\Delta G$  including counterpoise correction, for  $\text{CdH}^+\text{H}_2\text{SO}_4$  and  $\text{CdH}_2^{2+}\text{HSO}_4^-$  at the B3LYP-D3/6-31++G (d,p) level of theory. Counterpoise correction to the energy **BSSE**. Natural charges on significant atoms **q**. The notation used for  $\text{CdH}^+$  and  $\text{CdH}^{2+}$  is taken from reference <sup>55</sup>.



Molecules	$\Delta E$ (kcal/mol) with counterpoise correction	$\Delta G$ (kcal/mol) with counterpoise correction	BSSE (kcal/mol)	q(O) (...N <sub>alk</sub> H <sup>+</sup> )	q(O) (... N <sub>arom</sub> <sup>+</sup> )	q(O) (free)	q(H) (N <sub>alk</sub> H <sup>+</sup> )	q(H) (N <sub>arom</sub> H <sup>+</sup> )	q(S)	q(H) (SOH)	q(O) (SOH)
H <sub>2</sub> SO <sub>4</sub>	-	-	-	-	-	-0.90	-	-	2.53	0.53	-0.90
CdH <sup>+</sup>	-	-	-	-	-	-	0.48	-	-	-	-
Anti $\gamma$ -closed											
CdH <sup>+</sup> H <sub>2</sub> SO <sub>4</sub>											
Anti $\gamma$ -open	17.5	14.5	2.2	-0.96	-	-0.88	0.49	-	2.57	0.55	-0.90
Anti $\gamma$ -open'	16.7	16.2	2.3	-0.94	-	-0.91	0.49	-	2.56	0.55	-0.89
Anti $\gamma$ -closed	8.0	7.5	3.0	-0.89	-	-1.01	0.51	-	2.59	0.54	-0.91
Anti $\gamma$ -closed'	14.2	13.2	2.6	-0.94	-	-0.91	0.50	-	2.57	0.55	-0.89
HSO <sub>4</sub> <sup>-</sup>	-	-				-1.02					
						-1.02	-	-	2.53	0.49	-0.97
						-1.00					
CdH <sub>2</sub> <sup>2+</sup>	-	-									
Anti- $\gamma$ -closed							0.47	0.48	-	-	-
CdH <sub>2</sub> <sup>2+</sup> HSO <sub>4</sub> <sup>-</sup>											
Anti- $\beta$ -open	3.0	2.2	2.6	-1.01	-	-0.98	0.51	0.46	2.56	0.53	-0.90
						-1.03 *					

<b>Syn-<math>\gamma</math>-open</b>	5.0	4.8	2.3	-1.01	-	-1.03 *	0.51	0.46	2.56	0.53	-0.90
<b>Syn-<math>\gamma</math>-closed'</b>	0.1	0.0	2.7	-1.04	-0.99	-0.92	0.51	0.49	2.56	0.53	-0.92
<b>Anti-<math>\gamma</math>-closed</b>	0.5	0.4	2.7	-1.03	-0.99	-0.92	0.51	0.48	2.56	0.53	-0.92
<b>Syn-<math>\gamma</math>-closed</b>	0.0	0.2	2.7	-1.02	-0.99	-1.02	0.51	0.47	2.56	0.53	-0.92

\* H bond acceptor from OH

**Table 4:** Significant calculated dihedral angles ( $^{\circ}$ ) and distances ( $\text{\AA}$ ) of the most stable conformers of the **Cis**  $\text{QnH}_2^{2+}\text{HSO}_4^-$  complex optimized at the B3LYP-D3/6-31++G(d,p) level of theory.

<b>Dihedral angles (<math>^{\circ}</math>) and distances (<math>\text{\AA}</math>)</b>	<b>Cis-Anti-<math>\beta</math>-open</b>	<b>Cis-Syn-<math>\gamma</math>-open</b>	<b>Cis-Syn-<math>\gamma</math>-closed</b>	<b>Cis-Syn-<math>\gamma</math>-closed'</b>	<b>Cis-Anti-<math>\gamma</math>-closed</b>
$\tau_1$ ( $\text{C}_3$ , $\text{C}_4$ , $\text{C}_9$ , $\text{C}_8$ )	98	-85	-110	-107	74
$\tau_2$ ( $\text{C}_4$ , $\text{C}_9$ , $\text{C}_8$ , $\text{N}_{\text{alk}}$ )	162	160	59	47	60
$\tau_3$ ( $\text{N}$ , $\text{C}_8$ , $\text{C}_9$ , $\text{O}$ )	-74	-73	-178	171	-180
$T_3$ ( $\text{C}_8$ , $\text{C}_9$ , $\text{O}$ , $\text{H}$ )	111	151	171	165	170
$d_{\text{N}_{\text{alk}}\text{H}^{+\delta} \dots -\delta\text{OS}}$	1.6	1.58	1.62	1.62	1.64
$d_{\text{N}_{\text{arom}}\text{H}^{+\delta} \dots -\delta\text{OS}}$	7.17	6.19	2.51	2.34	2.51

**Table 5:** Significant calculated dihedral angles ( $^{\circ}$ ) and distances ( $\text{\AA}$ ) of the most stable conformers of the **Trans**  $\text{QnH}_2^{2+}\text{HSO}_4^-$  complex optimized at the B3LYP-D3/6-31++G(d,p) level of theory.

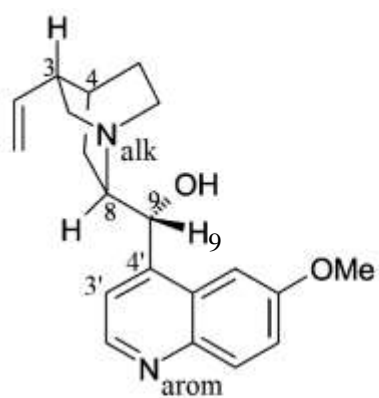
<b>Dihedral angles (<math>^{\circ}</math>) and distances (<math>\text{\AA}</math>)</b>	<b>Trans-Anti-<math>\beta</math>-open</b>	<b>Trans-Syn-<math>\gamma</math>-open</b>	<b>Trans-Syn-<math>\gamma</math>-closed</b>	<b>Trans-Syn-<math>\gamma</math>-closed'</b>	<b>Trans-Anti-<math>\gamma</math>-closed</b>
$\tau_1$ (C <sub>3</sub> C <sub>4</sub> C <sub>9</sub> C <sub>8</sub> )	103	-87	-109	-108	76
$\tau_2$ (C <sub>4</sub> C <sub>9</sub> C <sub>8</sub> N <sub>alk</sub> )	166	160	57	46	60
$\tau_3$ (N C <sub>8</sub> C <sub>9</sub> O)	-71	-74	-180	170	180
$T_3$ (C <sub>8</sub> C <sub>9</sub> O H)	106	153	171	166	169
$d_{\text{N}_{\text{alk}}\text{H}^{+\delta} \dots -\delta\text{O}_\text{S}}$	1.57	1.58	1.62	1.63	1.67
$d_{\text{N}_{\text{arom}}\text{H}^{+\delta} \dots -\delta\text{O}_\text{S}}$	7.08	6.16	2.49	2.34	2.5

**Table 6:** Calculated relative electronic energy  $\Delta E$  and Gibbs free energy  $\Delta G$  including counterpoise correction, for the most stable conformers of  $\text{QnH}_2^{2+}\text{HSO}_4^-$  at the B3LYP-D3/ 6-31++G (d,p) level of theory. Counterpoise correction to the energy **BSSE**.

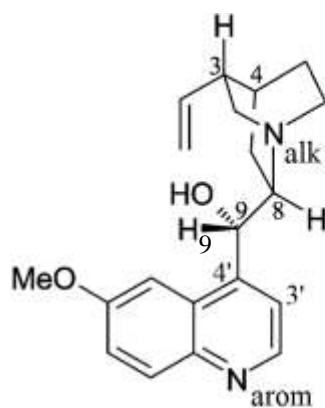
<b>Complex [QnH<sub>2</sub><sup>2+</sup>HSO<sub>4</sub><sup>-</sup>]</b>	<b><math>\Delta E</math> (kcal/mol)</b> with counterpoise correction	<b><math>\Delta G</math> (kcal/mol)</b> with counterpoise correction	<b>BSSE</b> <b>(kcal/mol)</b>
<b>Cis-Anti-<math>\beta</math>-open</b>	0.4	0.0	2.7
<b>Cis-Syn-<math>\gamma</math>-open</b>	5.9	5.0	2.3
<b>Cis-Syn-<math>\gamma</math>-closed</b>	0.0	0.6	3.0
<b>Cis-Syn-<math>\gamma</math>-closed'</b>	1.1	0.8	2.7
<b>Cis-Anti-<math>\gamma</math>-closed</b>	1.5	0.9	2.9
<b>Trans-Anti-<math>\beta</math>-open</b>	5.4	4	2.6
<b>Trans-Syn-<math>\gamma</math>-open</b>	7.1	5.9	2.3
<b>Trans-Syn-<math>\gamma</math>-closed</b>	1.2	1.7	2.9
<b>Trans-Syn-<math>\gamma</math>-closed'</b>	1.9	1.5	2.7
<b>Trans-Anti-<math>\gamma</math>-closed</b>	1.4	1.2	2.9

**Table 7:** Energy  $\Delta E_{0-1,2,3}$  (eV) of the first three vertical transitions  $S_{1,2,3\leftarrow 0}$  of the protonated monomer  $\text{CdH}^+$ , of the di-protonated monomer  $\text{CdH}_2^+$  (see text), and of the  $\text{CdH}_2^+\text{HSO}_4^-$  complex to which the experimental spectra has been assigned, all in the Syn- $\gamma$ -closed conformation. The transition energy is given relative to the ground state of the corresponding system. Only the transitions below the laser energy (4.66 eV) are considered.

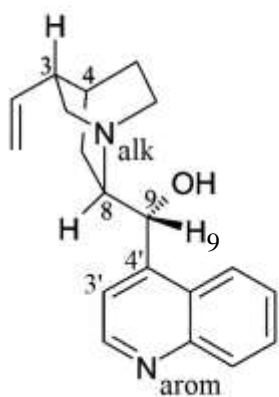
Protonated system	$\Delta E_{0-1}$	Orbitals involved in $S_{1\leftarrow 0}$	$\Delta E_{0-2}$	Orbitals involved in $S_{2\leftarrow 0}$	$\Delta E_{0-3}$	Orbitals involved in $S_{3\leftarrow 0}$
$\text{CdH}^+$	4.24	HOMO-4 $\rightarrow$ LUMO (68%) HOMO-3 $\rightarrow$ LUMO (24 %)	4.36	HOMO-1 $\rightarrow$ LUMO (64%) HOMO $\rightarrow$ LUMO+1 (30%)	4.69	HOMO-1 $\rightarrow$ LUMO (85%)
$\text{Cd N}_{\text{arom}}\text{H}^+$	2.48	HOMO $\rightarrow$ LUMO (40%) HOMO-1 $\rightarrow$ LUMO (39%) HOMO-2 $\rightarrow$ LUMO (15%)	3.98	HOMO-2 $\rightarrow$ LUMO (54%) HOMO-1 $\rightarrow$ LUMO (31%)	4.09	HOMO $\rightarrow$ LUMO+1 (44%) HOMO-1 $\rightarrow$ LUMO+1 (35%)
$\text{CdH}_2^+$	3.85	HOMO-1 $\rightarrow$ LUMO (94%)	4.29	HOMO-2 $\rightarrow$ LUMO (72%) HOMO-1 $\rightarrow$ LUMO+1 (26%)	4.63	HOMO $\rightarrow$ LUMO (95%)
$\text{CdH}_2^+\text{HSO}_4^-$	3.80	HOMO-3 $\rightarrow$ LUMO (93%)	4.09	HOMO-1 $\rightarrow$ LUMO (81%)	4.17	HOMO-2 $\rightarrow$ LUMO (61%)



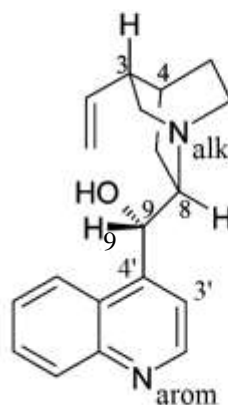
(-)-Quinine (Qn) (1S,3R,4S,8S,9R)



(+)-Quinidine (Qd)(1S,3R,4S,8R,9S)

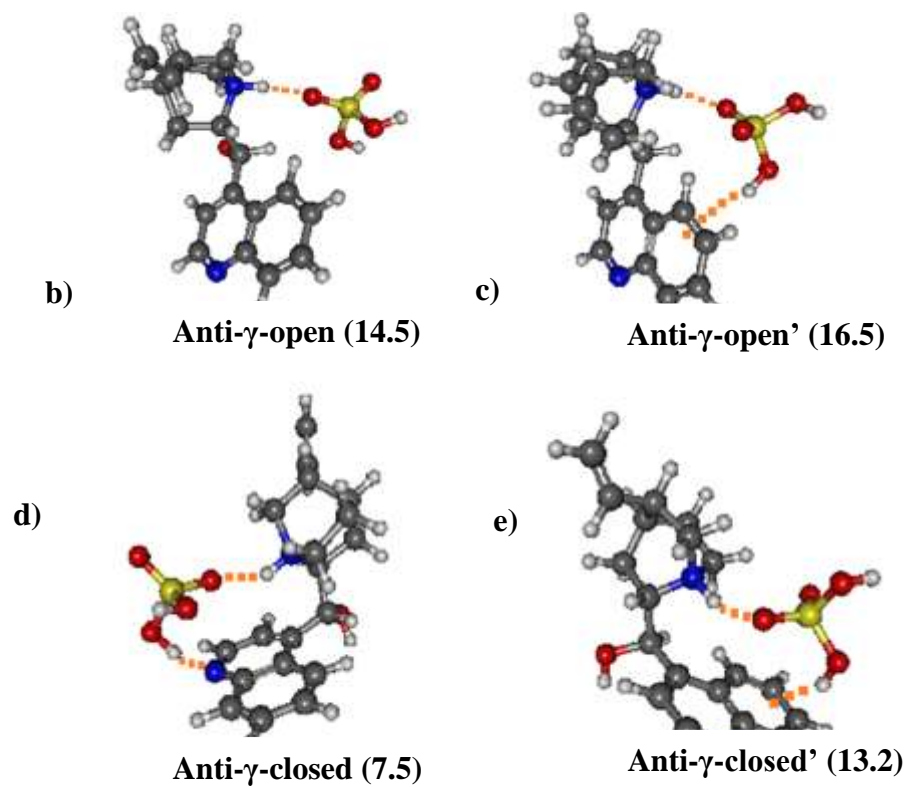


(-)-Cinchonidine (Cd) (1S,3R,4S,8S,9R)



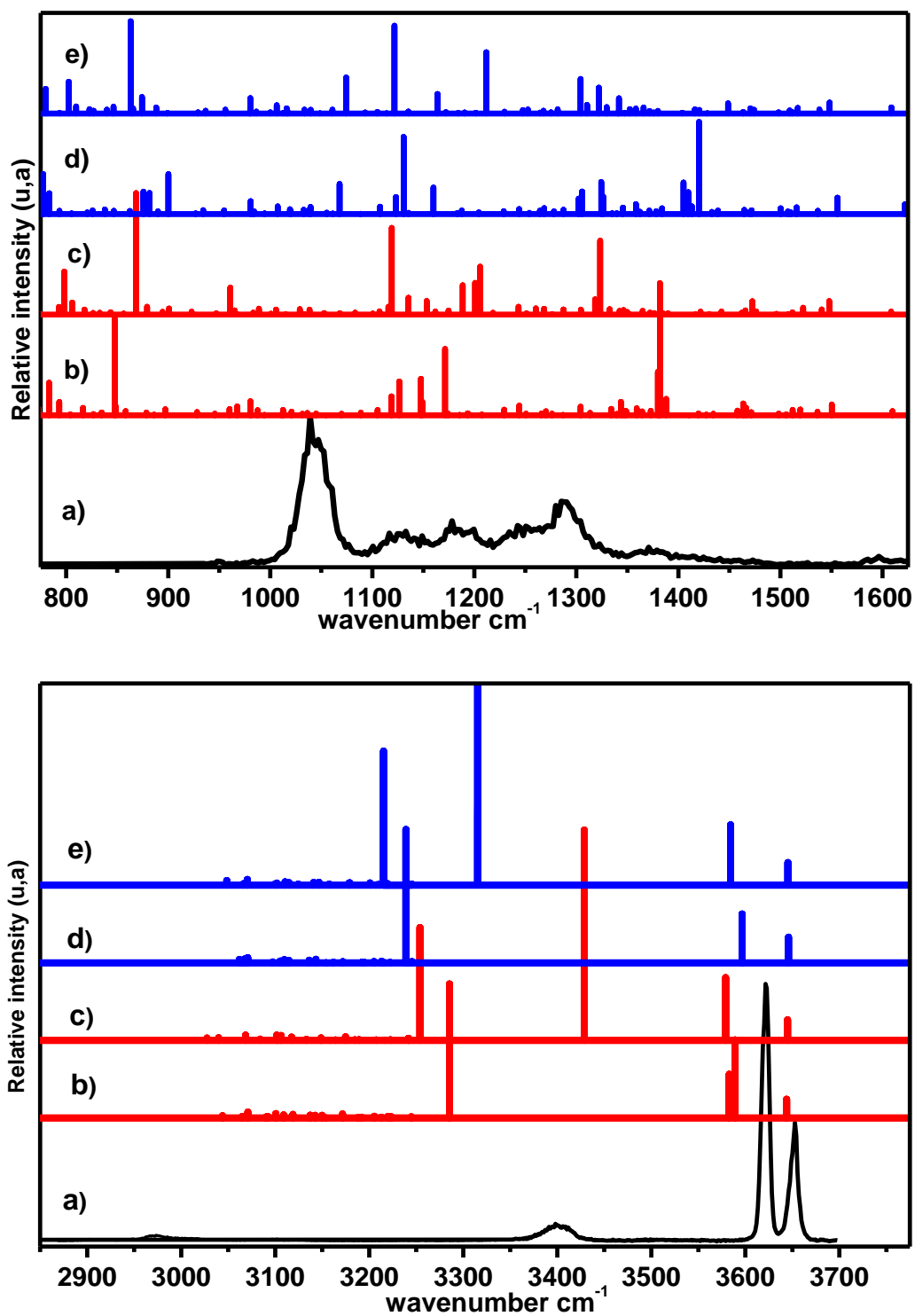
(+)-Cinchonine (Cn) (1S,3R,4S,8R,9S)

*Figure 1: Structure of the molecules under study*

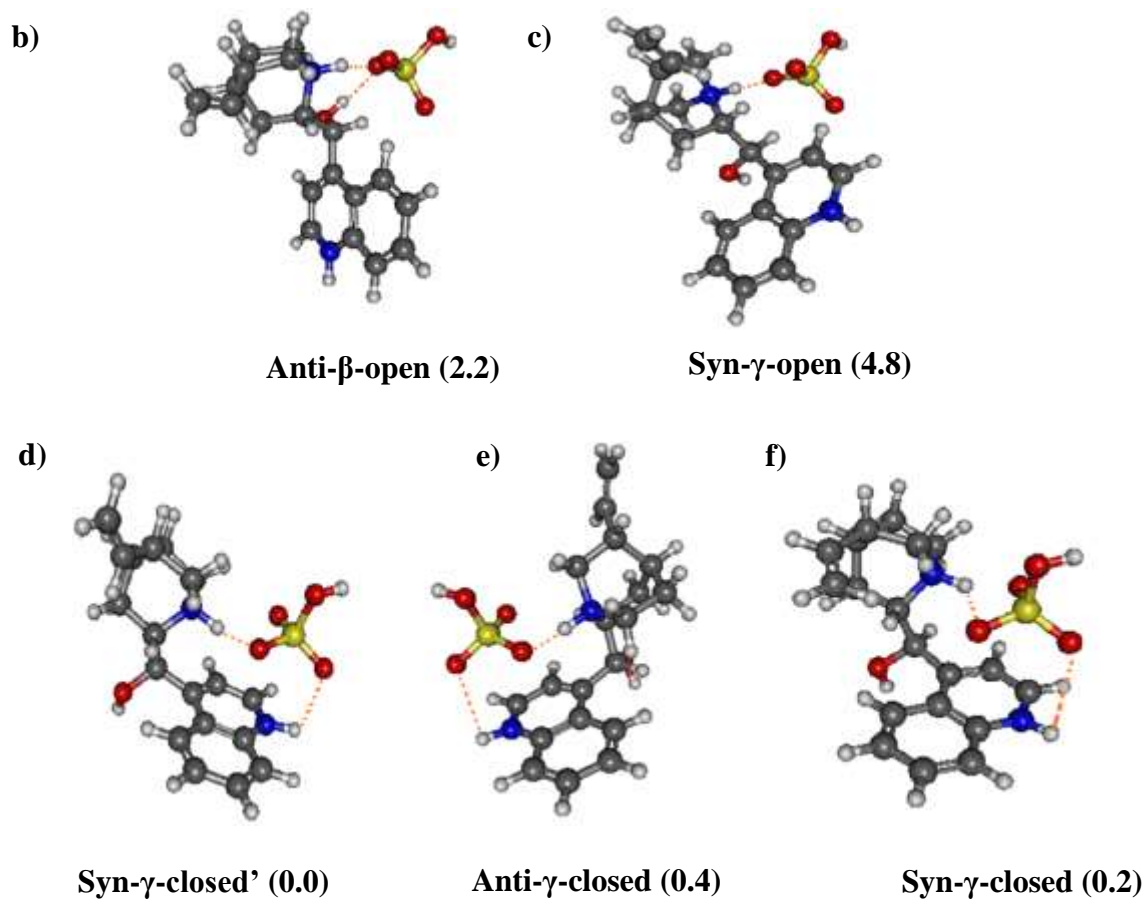


*Figure 2: Structure of the four most stable conformers of the  $\text{CdH}^+\text{H}_2\text{SO}_4$  complex calculated at the B3LYP-D3/6-31++G (d,p) level of theory. The Gibbs free energy relative to the most stable calculated complex is given in parentheses in kcal/mol*

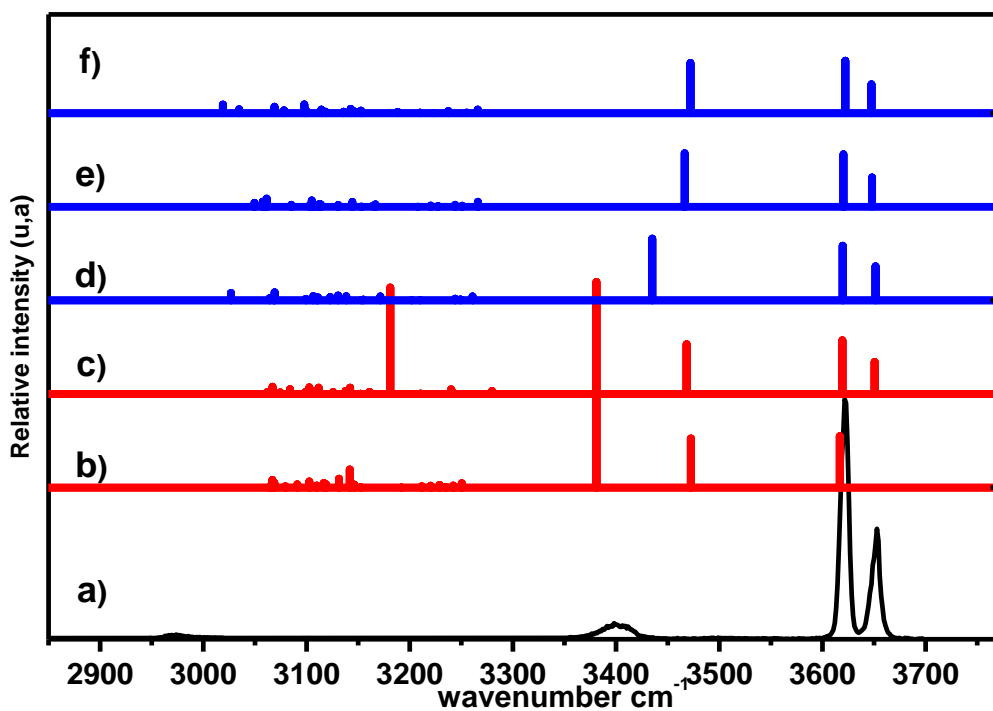
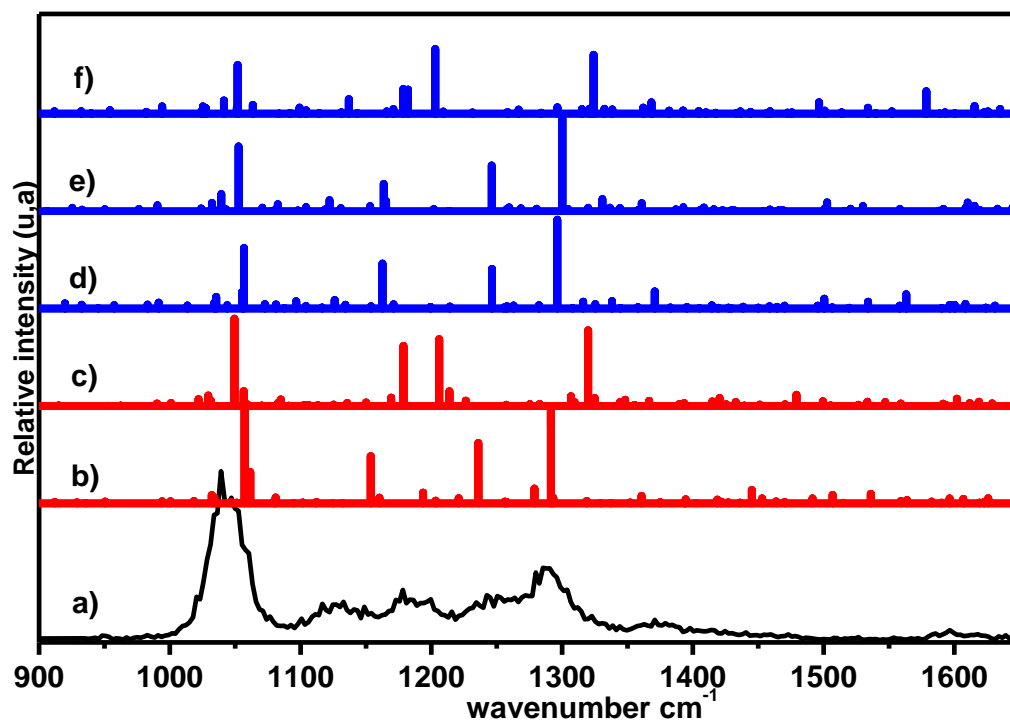




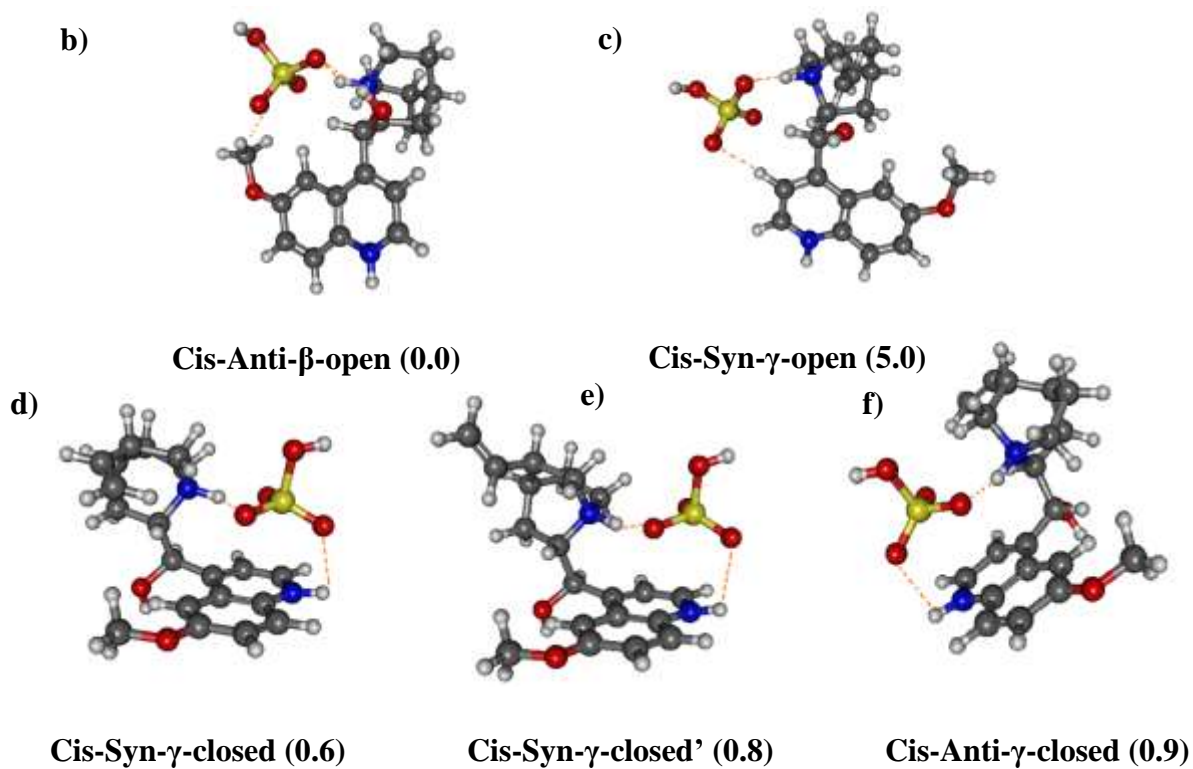
**Figure 3: Comparison between the IR experimental spectrum of  $\text{CdH}^+\text{H}_2\text{SO}_4$  (a) and the IR simulated spectra of the four most stable conformers: b) Anti- $\gamma$ -open (Figure 2b), c) Anti- $\gamma$ -open' (Figure 2c), d) Anti- $\gamma$ -closed (Figure 2d), e) Anti- $\gamma$ -closed' (Figure 2e). The spectra of the open conformers are in red and those of the closed conformers in blue. Fingerprint region (Top) and high frequency region (Bottom).**



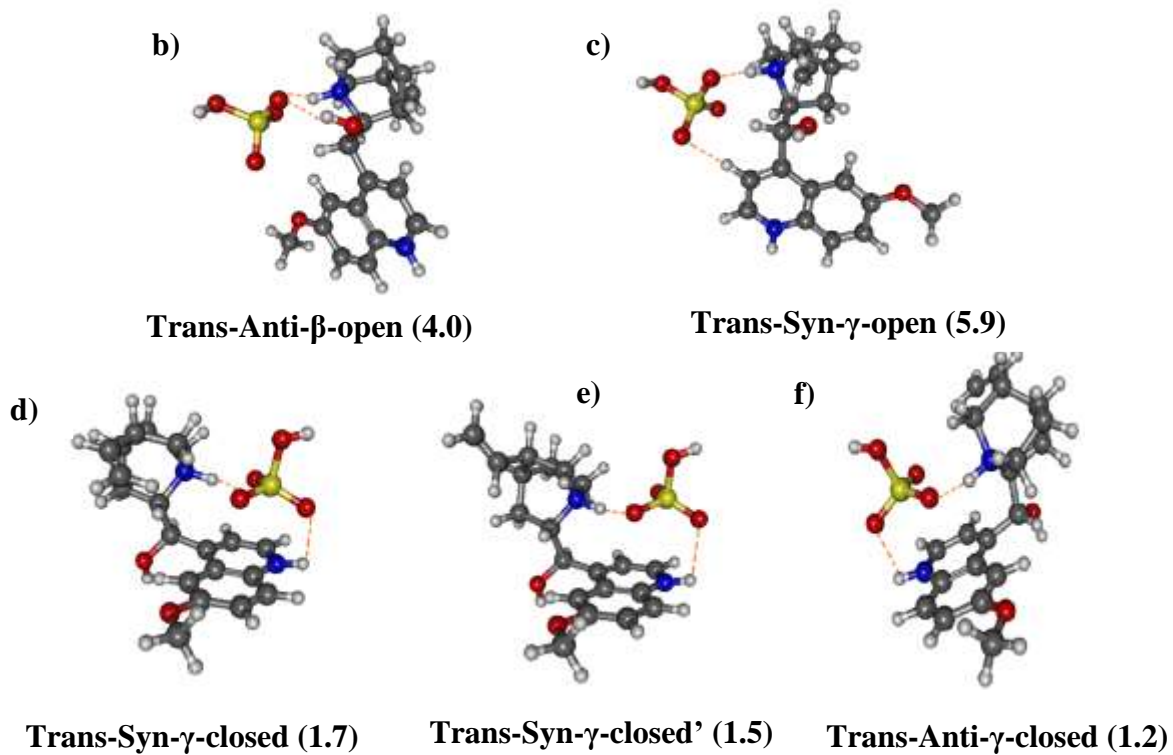
**Figure 4: Structure of the five most stable conformers of the  $\text{CdH}_2^{2+}\text{HSO}_4^-$  system optimized at the B3LYP-D3/6-31++G(d,p) level of theory. *The Gibbs free energy relative to the most stable calculated complex is given in parentheses in kcal/mol***



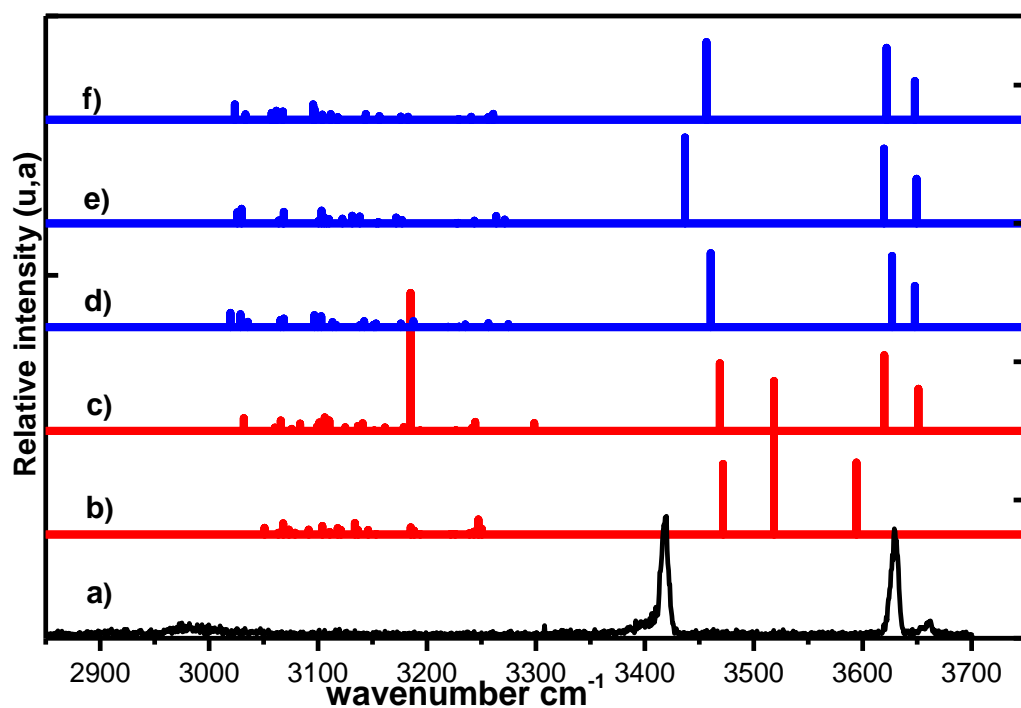
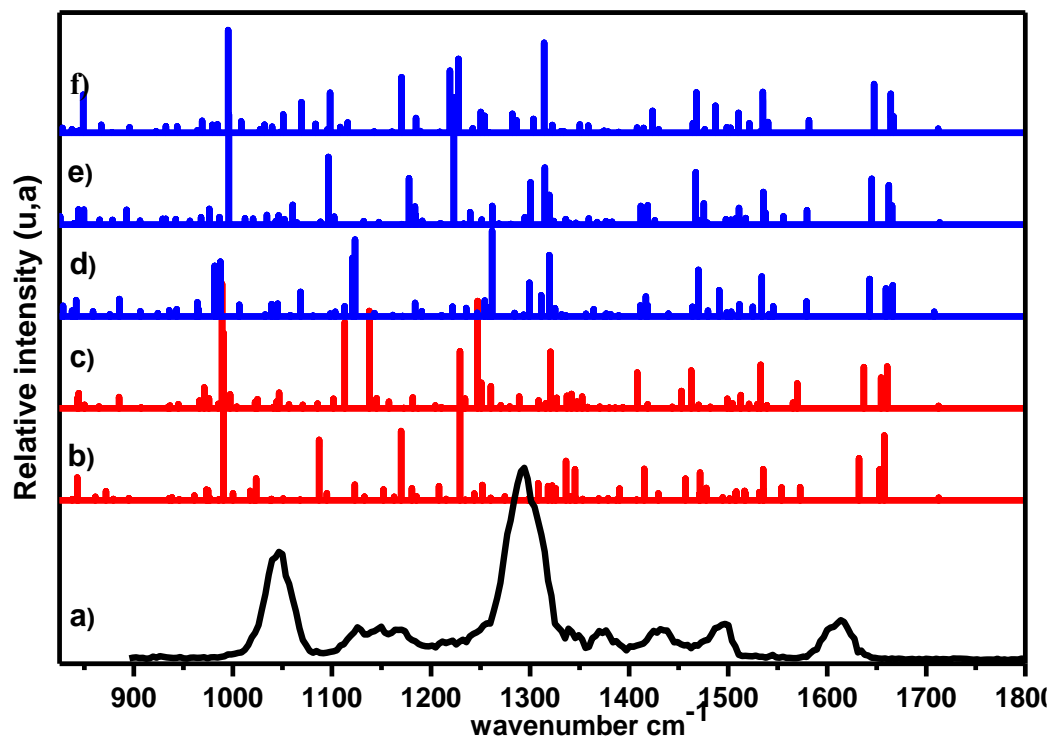
**Figure 5:** Comparison between the IR experimental spectrum (a) and those simulated for: b) Anti- $\beta$ -open (Figure 3b), c) Syn- $\gamma$ -open (Figure 3c), d) Syn- $\gamma$ -closed' (Figure 3d), e) Anti- $\gamma$ -closed (Figure 3e) and f) Syn- $\gamma$ -closed (Figure 3f) of the most stable conformers of  $\text{CdH}_2^{2+}\text{HSO}_4^-$  system. The spectra of the open conformers are in red and those of the closed conformers in blue. Fingerprint region (Top) and high frequencies region (Bottom)



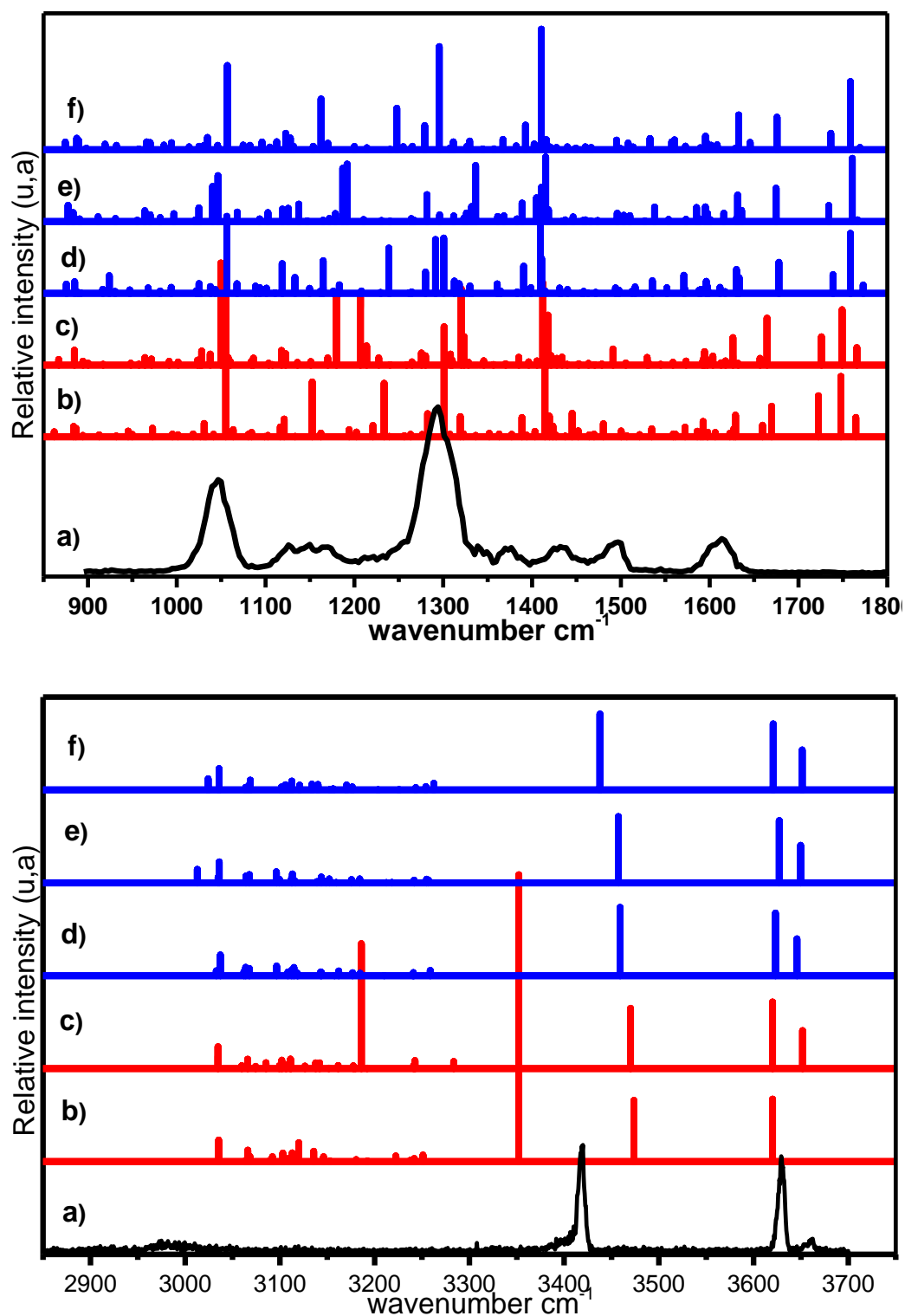
**Figure 6: Structure of the five most stable conformers of the cis  $QnH_2^+HSO_4^-$  system optimized at the B3LYP/6-31++G(d,p) level of theory. The Gibbs free energy relative to the most stable calculated complex is given in parentheses in kcal/mol**



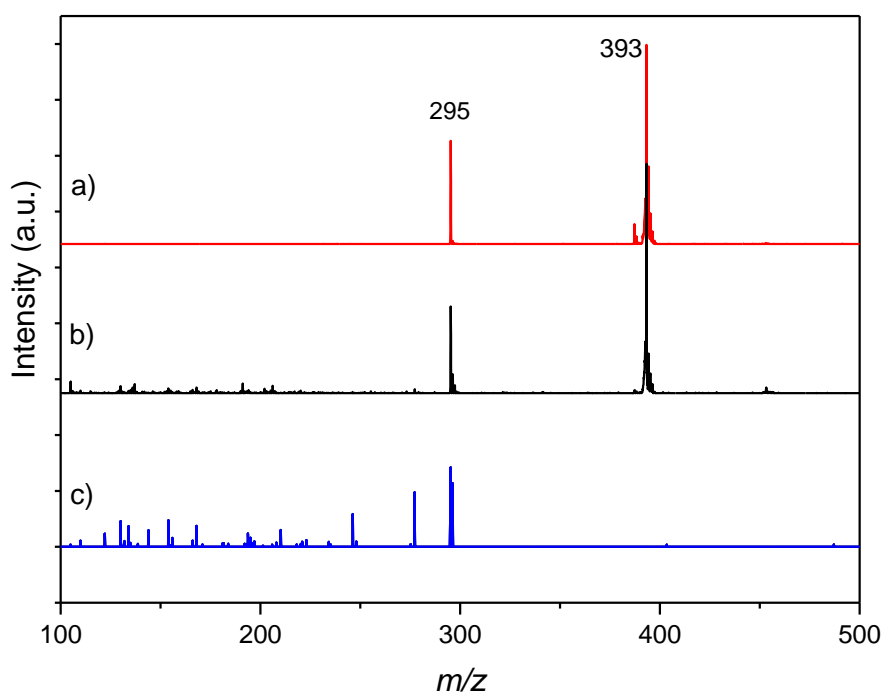
**Figure 7: Structure of the five most stable conformers of the trans QnH<sub>2</sub><sup>2+</sup>HSO<sub>4</sub><sup>-</sup> system optimized at the B3LYP-D3/6-31++G(d,p) level of theory. *The Gibbs free energy relative to the most stable calculated complex is given in parentheses in kcal/mol***



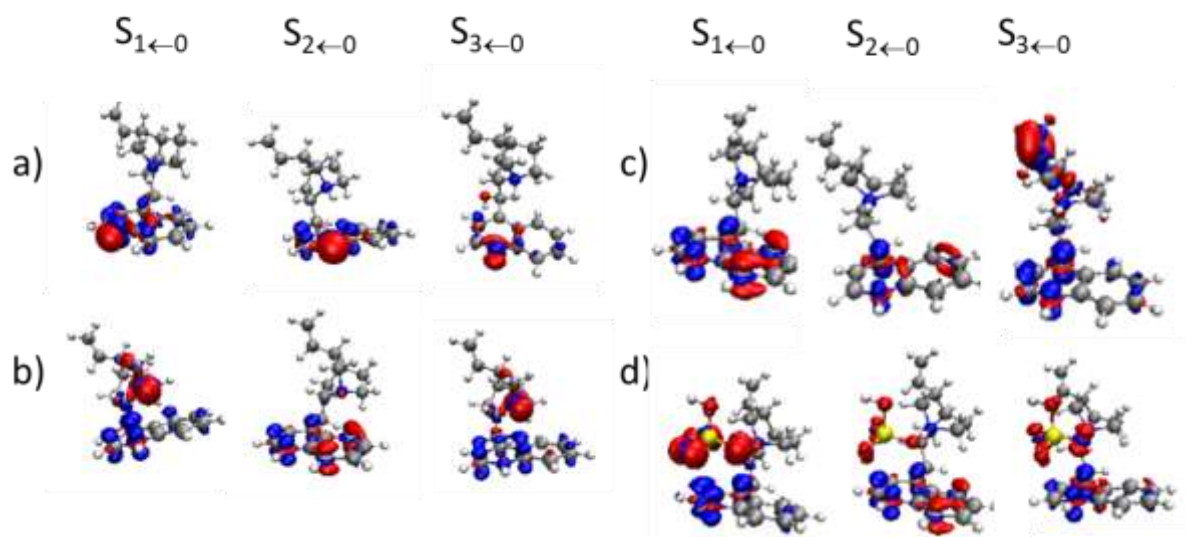
*Figure 8: Comparison between the IR experimental spectrum of  $QnH^+H_2SO_4$  (a) and the IR simulated spectra of the most stable Cis conformers: b) Cis-Anti- $\beta$ -open (Figure 6b), c) Cis-Syn- $\gamma$ -open (Figure 6c), d) Cis-Syn- $\gamma$ -closed (Figure 6d), e) Cis-Syn- $\gamma$ -closed' (Figure 6e), f) Cis-Anti- $\gamma$ -closed (Figure 6f). The spectra of the open conformers are in red and those of the closed conformers in blue. Fingerprint region (Top) and high frequencies region (Bottom)*



*Figure 9: Comparison between the IR experimental spectrum of  $QnH^+H_2SO_4$  (a) and the IR simulated spectra of the most stable Trans conformers: b) Trans-Anti- $\beta$ -open (Figure 7b), c) Trans-Syn- $\gamma$ -open (Figure 7c), d) Trans-Anti- $\gamma$ -closed (Figure 7d), e) Trans-Syn- $\gamma$ -closed (Figure 7e), f) Trans-Syn- $\gamma$ -closed' (Figure 7f) The spectra of the open conformers are in red and those of the closed conformers in blue. Fingerprint region (Top) and high frequencies region (Bottom)*

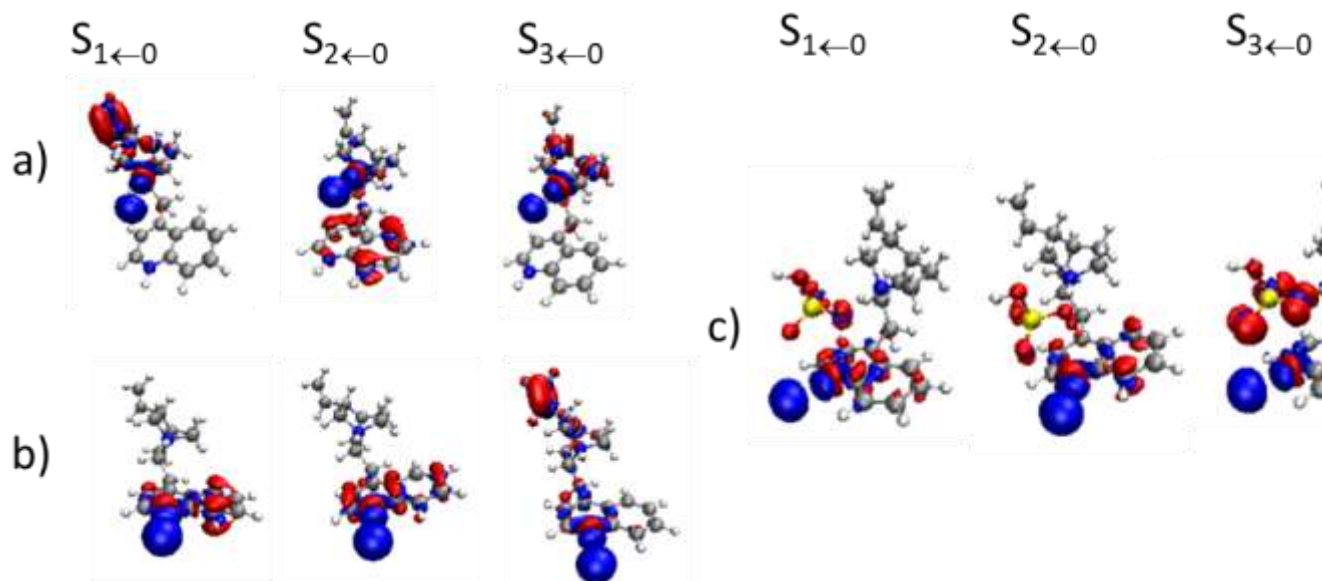


**Figure 10:** CID (a) and UVPD (b) mass spectra of the complex formed between protonated cinchonidine and sulfuric acid. The conditions are adjusted so that the fragmentation yield is  $\sim 0.33$  in both cases. CID spectrum (c) of the  $m/z$  295 fragment resulting from the photodissociation of  $m/z$  393



**Figure 11:** Difference between the electronic density of the ground state and that of the first three excited states. The isovalue is set to 0.005. The red (blue) color codes a decrease (increase) in electron density, respectively: a)  $\text{CdH}^+$ , with the proton located on  $N_{\text{alk}}$  b)  $\text{CdN}_{\text{arom}}\text{H}^+$ , with the proton located on  $N_{\text{arom}}$  c)  $\text{CdH}_2^{2+}$  with  $N_{\text{alk}}$  and  $N_{\text{arom}}$  protonated d)  $\text{CdH}_2^{2+}\text{HSO}_4^-$  complex.





**Figure 12: Difference between the electronic density of the ground state and that the first three excited states. The isovalue is set to 0.005. The red (blue) color codes a decrease (increase) in electron density, respectively: a)  $\text{CdH}_2^{2+}$ , with  $N_{\text{alkH}}$  distance of 2.0 Å b)  $\text{CdH}_2^{2+}$ , with  $N_{\text{aromH}}$  distance of 2.0 Å c)  $\text{CdH}_2^{2+}\text{HSO}_4^-$  with  $N_{\text{aromH}}$  distance of 2.0 Å**