

Density Functional Theory Study on Vibrational Circular Dichroism as a Tool for Analysis of Intermolecular Systems: (1:1) Cysteine–Water Complex Conformations

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This paper presents a discussion of the interaction energies for selected conformers of chiral L-cysteine and their (1:1) complexes with water at the B3LYP/aug-cc-pVDZ level. From among more than forty calculated 1:1 complexes three groups of complexes were singled out and examined by the B3LYP/aug-cc-pVDZ calculated vibrational circular dichroism (VCD) spectra. On the basis of analysis of the $\nu(\text{OH})$ and $\nu(\text{NH})$ and $\beta(\text{OH}_2)$ and $\beta(\text{NH}_2)$ ranges, the VCD spectra were found to be sensitive to conformational changes and water arrangement in cysteine complexes, and to be especially useful for discriminating between different chiral forms of intermolecular hydrogen-bonding complexes. In particular, we show that the VCD modes of an achiral water molecule after complex formation acquire significant rotational strengths whose signs change in line with the geometry of the complex. Moreover, for some water arrangements the VCD spectra can be sensitive to water-wagging conformers and, in temperatures low enough, the intensive $\nu(\text{OH}_{\text{free}}^{\text{W}})$ and $\beta(\text{H}_2\text{O})$ VCD bands may be sufficiently separated to be splitted into pair of oppositely directed bands.

1. Introduction

Biomacromolecules have received rapidly increasing attention in recent years, from both experimental and theoretical bio-sciences. However, studies on small biomolecules enables theoretical treatment by methods based on first principles and thus enables establishing some elementary physicochemical relationships. A juxtaposition of experimental methods such as IR vibrational absorption, Raman, and vibrational circular dichroism (VCD) spectroscopies, as well as theoretical approaches, play an important role in providing insight into the processes that take place in proteins and peptides. It has also been known for a long time that water interactions play a vital structural role in proteins and peptides.¹ To better understand the role of water molecules for modifying the arrangement of biomolecules, one needs to investigate the consequences of hydration processes at the quantum-mechanical level.

Although known since mid 1970s,² the VCD technique is now given much attention as a probe of molecular conformation for molecules. The VCD spectrum is a difference of vibrational spectra taken with respect to left vs right circularly polarized IR light. In contrast to IR spectroscopy, VCD spectra discriminate between individual enantiomers and that is why it is suitable for the study of optically active molecules, in particular, for biomolecules.^{3,4} The IR spectra of enantiomers are identical but the VCD spectra have intensities with opposite signs. Each VCD band reports information regarding the molecular structure and the coupling of particular vibrational modes in the chiral

molecule. Thus, the VCD spectrum is a subtle, stereospecific effect associated with the interaction of a chiral molecule with light.

On the other hand, ab initio analysis is a useful approach for the determination of structural details of chiral molecules, too. The combination of experimental VCD spectra and ab initio predictions provides a powerful method for determining the absolute configuration.⁵ Most calculations of the VCD spectra deal with the single molecules, and so far, the calculations for molecular complexes are much less common.

Numerous experimental and theoretical studies were devoted to proving the advantage of engaging the VCD spectra in determination of conformational structure shaped by intramolecular hydrogen bonding.⁶ However, the subject of the influence of the intermolecular hydrogen bond was undertaken in a few papers, where geometrical arrangement of the H-bond partners was shown to be determinable based on the VCD spectra.^{7–10}

One of the first attempts to refer VCD spectra to investigations of the intermolecular hydrogen-bonding complexes were the calculations of the H-bond complex of model chiral β -lactams with HX molecules.⁸ Next, we have studied VCD spectra in determining intermolecular H-bond geometry of the complex of D-lactic acid with a water molecule.⁹ The VCD spectra were found to be sensitive to conformational changes of both free and complexed molecules and to be useful for discriminating between different chiral forms of intermolecular hydrogen-bonding complexes. We showed that the VCD modes of achiral water molecules after complex formation acquire rotational strength whose sign changes in line with the geometry of the complex.^{8,9} Recently one of the first experimental matrix isolation-VCD works by Tarczay, Magiarfalvi, and Vass for (*R*)-2-amino-1-propanol¹⁰ confirmed our prediction for the model lactic acid–water system.⁹

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The present work is a continuation of our study on both correlation between conformation of the cysteine molecule, $\text{NH}_2\text{-CH}(\text{CH}_2\text{SH})\text{COOH}$,^{12,13} and the VCD spectra and the influence of intermolecular interactions on the VCD spectra.^{8,9} Cysteine plays a key role by cross-linking proteins and by increasing the molecular stability as well as by supporting the protein secondary structure. The cysteine molecule is conformationally labile because of possible free rotation about the single bonds between the non-hydrogen atoms.^{11,12} On the other hand, intermolecular interactions of the cysteine molecule are manifold because each of the cysteine functional groups, OH, C=O, NH_2 , and SH, may operate as a hydrogen bond interacting center: either donor or acceptor or both. Moreover, because of the possibility to form a strong intramolecular hydrogen $\text{OH}\cdots\text{NH}_2$ bond (hereafter IHB), some of conformers are stabilized more than the others. The results on monomeric conformations have been reported before,^{12,13} yet for clear presentation of the current outcomes, here, we briefly summarize them.

Previously, more than fifty structures of cysteine were found by using the B3LYP and MP2 methods combined with the aug-cc-pVTZ basis set, and eight low-energy conformers were subject of further investigations.^{12,13} Among the most stable eight structures, five, **1**, **2**, **4**, **6**, and **8**, exhibit the presence of the IHB, whereas in the other three, **3**, **5**, and **7** no such bond is observed and they are referred to here as non-IHB conformers. The latter seem to be stabilized by both the $\text{NH}\cdots\text{O}$ and $\text{SH}\cdots\text{N}$ (or O) hydrogen-bond-like interactions. Similarities between the measured and the calculated IR matrix spectra, especially in the $\nu(\text{OH})$, $\nu(\text{SH})$, and $\nu(\text{C}=\text{O})$ stretching vibration regions, allowed us to prove the presence of at least three, yet possibly six, cysteine conformers with and without intramolecular hydrogen bonding.¹³

Here, our investigations are extended to intermolecular hydrogen bonds in the cysteine \cdots water (1:1) complexes. The interaction with water has been expected to affect the conformational stability of the cysteine molecule. Like other amino acids, the cysteine molecule occurs predominantly in its neutral form in the gas phase or in low-temperature inert matrixes, whereas in solution or in the solid state it exists in its zwitterionic form. Thus, a hydrogen bond interaction with solvent or crystal environment increases the stability of the cysteine zwitterionic forms. However, now, we restrict our consideration to the neutral cysteine form interacting with one water molecule because, as shown previously, to stabilize the zwitterion, either a few water molecules are needed or the environment must be modeled by the continuous polarization model.^{12,14}

In this study for each of the most stable eight cysteine conformers we considered a few different arrangements of interacting water molecule. Although the cysteine molecule has four sites amenable to form hydrogen bonds with water, i.e., OH, C=O, NH_2 , and SH groups, three of them may act as both proton donor and proton acceptor roles, and the carbonyl group can interact from at least two sides. Moreover, thanks to the flexibility of the cysteine skeleton, the complicated complex structure may be formed in which water can be inserted between two cysteine functional groups. As a result we considered more than forty (1:1) complex structures. However, the cyclic hydrogen bond of water with the whole COOH group seems to stabilize the complex in the largest extent.

As far as we are aware, no investigations have been reported on observations or calculations on the (1:1) cysteine–water complexes until now. In this study, we first analyze the conformational stability of the cysteine complexes with water.

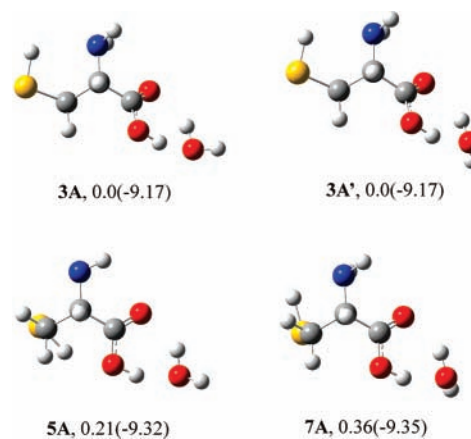


Figure 1. First group of considered forms of L-cysteine complexes with a water molecule: different cysteine conformers engaged in the same type of intermolecular hydrogen bond. Near the structure code the relative Gibbs free energy is given (kcal/mol) and binding energy ΔE_7 (kcal/mol) is shown in parentheses.

On this base we present the main objective of this paper: investigating the influence of the intermolecular hydrogen bonding on the VCD spectra. To this aim, we select some representants of the three groups of complexes to illustrate the effect of (i) the cysteine conformation on the VCD spectra of the same type of the intermolecular hydrogen bonding, (ii) the various types of the intermolecular hydrogen bonding on the VCD spectra of the non-IHB conformers with water, and (iii) the various types of the intermolecular hydrogen bonding on the VCD spectra of the IHB conformers with water. We hope that such an analysis will lead to a better understanding of the influence of intermolecular interactions on the VCD spectra and will contribute to the development of VCD spectroscopy as a tool for structural investigations of biologically active compounds.

The paper is structured as follows: Section 2 gives the description of the model and the computational details. Section 3.1 discusses the shape of the potential energy surface obtained for the (1:1) cysteine–water complex. Section 3.2 reports the influence of the complex structures on the VCD spectra. Conclusions are inferred in section 4.

2. Computational Details

2.1. Choice of the Systems. Eight low-energy structures of cysteine^{12,13} were the starting points in this investigation. Among them, five conformers (**1**, **2**, **4**, **6**, and **8**) exhibited the intramolecular $\text{OH}\cdots\text{NH}_2$ hydrogen bond (IHB) and three (**3**, **5**, and **7**) exhibited no such IHB. As the cysteine molecule has four sites potentially amenable to forming intermolecular hydrogen bonds with water, any of the conformers can form several (1:1) complexes with water. Scan of the full PES of the neutral (1:1) cysteine complexes with water is hardly possible, as we found as much as 51 conformers to be stable at the DFT and MP2 levels combined with the aug-cc-pVDZ basis set. Therefore, the (1:1) complexes were selected and segregated into three groups: first containing the lowest energy three cysteine conformers, **3**, **5**, and **7**, involved in the same type of intermolecular cyclic hydrogen bonding with water (Figure 1); second and third (Figures 2 and 3, respectively) containing the same cysteine conformer (without (**7**) and with (**1**) IHB, respectively) complexed with water at different interacting sites. Data for all complexes studied are included in the Supporting Information.

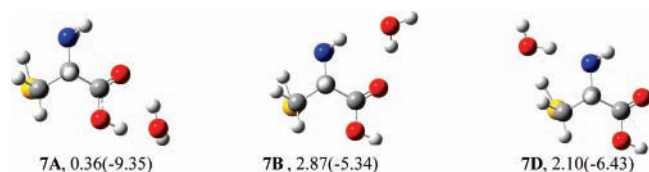


Figure 2. Second group of considered forms of L-cysteine complexes with a water molecule: cysteine conformer **7**, not stabilized by the intramolecular OH \cdots NH $_2$ hydrogen bond, engaged in different types of intermolecular hydrogen bond. Near the structure code the relative Gibbs free energy is given (kcal/mol) and binding energy ΔE_7 (kcal/mol) is shown in parentheses.

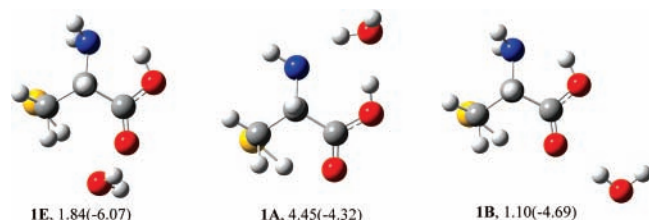


Figure 3. Third group of considered forms of L-cysteine complexes with a water molecule: cysteine conformer **1**, stabilized by the intramolecular OH \cdots NH $_2$ hydrogen bond, engaged in different types of intermolecular hydrogen bond. Near the structure code the relative Gibbs free energy is given (kcal/mol) and binding energy ΔE_7 (kcal/mol) is shown in parentheses.

2.2. Choice of the Computational Method. Recently, the DFT method has been accepted by the ab initio quantum chemistry community as a cost-effective approach to computations of molecular structures and spectra (vibrational and NMR) of molecules of chemical interest. Many studies have shown that vibrational frequencies calculated by means of DFT methods are more reliable than those obtained at the MP2 level.¹⁵

All the calculations were performed by using the hybrid Becke three-parameter Lee–Yang–Parr B3LYP functional,¹⁶ whose reliability in calculations of the ground-state geometries has been widely assessed.¹⁵ The aug-cc-pVDZ Dunning’s basis set,¹⁷ and for the most stable gas-phase conformers the aug-cc-pVTZ, were also employed.¹⁸ These basis sets are known to be adequate to describe both organic molecules and their hydrogen-bonded systems. The gas-phase structures were also calculated by using the MP2 method combined with the aug-cc-pVDZ basis set for all the structures and the aug-cc-pVTZ basis set for eight of the most stable conformers. The stationary structures are found by ascertaining that all the harmonic frequencies are real. The interaction energies were corrected by the counterpoise method¹⁹ and seven-point correction method for basis set superposition error.²⁰ The relative abundances of the most stable conformations were then estimated by using the Gibbs free energy ΔG relative to the most stable conformer. All the energy, geometry, and IR spectra calculations were obtained by using the Gaussian 03 suite of programs.²¹

For the VCD spectra calculations, implementation of direct analytical derivative methods for calculating HFFs, APTs, and AATs is the most important. Incorporation of gauge invariant atomic orbitals (GIAO) to the calculation of AATs makes it possible to predict the VCD spectra using the DFT method. The procedure for calculating the VCD rotational strength using DFT method is implemented in the Gaussian 03 program.²¹

3. Results and Discussion

3.1. Geometry and Energetics of the (1:1) Cysteine–Water Complexes. Table 1 summarizes the calculated total energies,

TABLE 1: B3LYP/aug-cc-pVDZ Calculated Interaction, Counterpoise-Corrected Interaction, Deformation-Corrected Interaction Energies (ΔE , ΔE_{CP} , ΔE_7 , kcal/mol), and Deformation and BSSE Terms for the Exemplary Water Complexes with Different Conformers of Cysteine^a

| complex | type of complex ^b | ΔE | ΔE_{CP} | ΔE_7 | ΔE_{def} | BSSE |
|---------|------------------------------|------------|-----------------|--------------|------------------|-------|
| 3-A | I | -9.65 | -9.86 | -9.17 | 0.69 | -0.48 |
| 5-A | I | -9.79 | -10.04 | -9.32 | 0.71 | -0.47 |
| 7-A | I and II | -9.83 | -10.08 | -9.35 | 0.73 | -0.48 |
| 7-B | II | -5.89 | -5.65 | -5.34 | 0.30 | -0.55 |
| 7-D | II | -7.15 | -7.05 | -6.43 | 0.62 | -0.71 |
| 1-A | III | -5.06 | -9.96 | -4.32 | 5.63 | -0.73 |
| 1-B | III | -4.97 | -4.79 | -4.69 | 0.09 | -0.28 |
| 1-E | III | -6.55 | -6.51 | -6.07 | 0.44 | -0.48 |

^a For total energies and Gibbs free enthalpies see Supporting Information Table ISI. ^b Type I: H $_2$ O plays both donor and acceptor roles in cyclic hydrogen bond with different cysteine conformations. Type II: The same cysteine non-IHB conformer but different water locations. Type III: The same cysteine IHB conformer but different water locations.

CP corrected binding energies,¹⁹ and binding energies corrected for deformation term, so-called seven-point CP correction,²⁰ for three groups of isomers selected out of more than forty complexes studied (Table IESI). The first group contains three, non-IHB conformers of cysteine (**3**, **5**, **7**) engaged in the same type of the cyclic intermolecular hydrogen bond (Figure 1). In this hydrogen bond the OH moiety of the carboxylic group is a proton donor to the water molecule and simultaneously the water OH group is a proton donor to the O=C moiety of the carboxylic group (Figure 1). The second and third group contain the same cysteine conformer without (**7**) and with (**1**) the intramolecular OH \cdots NH $_2$ hydrogen bond engaged in different types of intermolecular hydrogen bonds (Figures 2 and 3, respectively).

Let us first consider a group of complexes stabilized by the cyclic hydrogen bond: i.e., **3-A**, **5-A**, and **7-A** (Figure 1). Remark that the cyclic hydrogen bond complexes display relatively large binding energies of -9.17, -9.32, and -9.35 kcal/mol, for **3-A**, **5-A**, and **7-A**, respectively. For the group of the considered structures such binding energies are the greatest (Figures 1 and IESI (Supporting Information), Tables 1 and IESI (Supporting Information)). Moreover, these complexes are the lowest Gibbs free energy minima found for the (1:1) cysteine–water complexes PES (Figures 1 and IESI, Tables 1 and IESI). The **3-A** structure is the global minimum; however, the structures **5-A** and **7-A** are local minima positioned above it by only 0.21 and 0.36 kcal/mol, respectively.

Next, as a second group, we compare the cyclic **7-A** complex with complexes of the same non-IHB cysteine conformer **7** type interacting differently with water (**7-B** and **7-D**, Figure 2). The first one, **7-A** with cyclic hydrogen bond, exhibits the largest binding energy (-9.35 kcal/mol) and is close to the global minimum on PES. The second complex, **7-B**, demonstrates the cyclic hydrogen bond as well. As for **7-A**, the water OH group is a proton donor to the O=C moiety of the carboxylic group; however, the water molecule O-atom is a proton acceptor of one of the NH $_2$ group H-atoms (Figure 2). The latter H-bond is much weaker than the analogous OH \cdots OH $_2$ bond in **7-A**, and therefore, the binding energy of **7-B** (-5.34 kcal/mol) is smaller than that of **7-A**. In comparison with **3-A**, this complex is also a higher local minimum on PES (2.87 kcal/mol with respect to global minimum **3-A**). The third complex, **7-D**, is stabilized by the HOH \cdots NH $_2$ intermolecular hydrogen bond and it is ad-

TABLE 2: Comparison between the B3LYP/aug-cc-pVDZ Calculated IR Frequencies (cm^{-1}) and Intensities ($\text{km}\cdot\text{mol}^{-1}$), and VCD Rotational Strengths ($10^{-44} \text{esu}^2 \text{cm}^2$) of the Selected Modes of the Water Complexes with the 3, 5, and 7 Cysteine Conformers Exhibiting a Cyclic Hydrogen Bond between Water and the Cysteine Carboxylic Group (A-Type Complexes)

| | 3-A | | 3'-A | | 5-A | | 7-A | | | | | |
|---|------|-------|--------|------|-------|-------|------|-------|--------|------|-------|-------|
| $\nu(\text{OH}_{\text{free}}^{\text{W}})$ | 3864 | 105.2 | -33.3 | 3863 | 101.8 | 29.8 | 3863 | 99.7 | -35.3 | 3860 | 92.8 | 25.3 |
| $\nu(\text{OH}_{\text{HB}}^{\text{W}})$ | 3616 | 369.8 | -45.6 | 3615 | 370.2 | -15.6 | 3606 | 372.5 | -79.2 | 3598 | 389.9 | -48.7 |
| $\nu^{\text{a}}(\text{NH}_2)$ | 3572 | 9.8 | 14.0 | 3572 | 10.2 | 14.4 | 3563 | 10.9 | 4.2 | 3566 | 7.1 | 9.0 |
| $\nu^{\text{s}}(\text{NH}_2)$ | 3488 | 3.9 | -5.1 | 3488 | 4.0 | -5.3 | 3480 | 3.5 | -3.1 | 3491 | 2.2 | 0.0 |
| $\nu(\text{OH}_{\text{HB}}^{\text{C}})$ | 3324 | 798.4 | 99.5 | 3324 | 795.6 | 33.8 | 3326 | 741.6 | 104.6 | 3322 | 731.9 | 37.0 |
| $\nu(\text{C}=\text{O}_{\text{HB}})$ | 1752 | 260.9 | 12.2 | 1752 | 263.7 | -73.2 | 1758 | 245.7 | 70.1 | 1759 | 249.6 | 3.1 |
| $\beta(\text{NH}_2)$ | 1654 | 28.5 | 15.6 | 1654 | 28.1 | 17.4 | 1644 | 35.1 | 23.6 | 1651 | 31.1 | 22.6 |
| $\beta(\text{H}_2\text{O})$ | 1608 | 140.1 | -126.3 | 1608 | 128.0 | 128.6 | 1609 | 134.1 | -111.3 | 1613 | 106.0 | 132.2 |

ditionally stabilized by the $\text{S}-\text{H}\cdots\text{OH}_2$ interaction. So, again, the geometry of the 7-D complex can be perceived as forming a cyclic hydrogen bond. The binding energy of 7-D is equal to -6.43 kcal/mol, and the relative Gibbs free energy equals 2.10 kcal/mol.

The third group contains different water complexes of the cysteine conformer **1** exhibiting the IHB (Figure 3). The most stable complex of this conformer, **1-E**, is stabilized by two intermolecular $\text{HOH}\cdots\text{O}=\text{C}$ and $\text{SH}\cdots\text{OH}_2$ bonds. Its binding energy is equal to -6.07 kcal/mol and the relative Gibbs free energy equals 1.84 kcal/mol. The other two selected complexes are characterized by slightly lower binding energies -4.32 and -4.69 kcal/mol for **1-A** and **1-B**, respectively. **1-A** is also quite highly positioned on PES because its relative Gibbs free energy is equal to 4.45 kcal/mol, whereas **1-B** is less stable than **3-A** only by 1.10 kcal/mol. In the **1-A** complex, the water molecule is inserted into IHB, destroying the very favorable $\text{OH}\cdots\text{NH}_2$ configuration (Figure 3). In such a way, the five-membered cyclic IHB is replaced by the seven-membered cyclic HB. Although two new H-bonds are formed, the complex is not very stable and does not have a large interaction energy, $+4.45$ and -4.32 , respectively. In the **1-B** structure, the water molecule acts as a proton donor to the OH moiety of the carboxylic group, which is just engaged in the IHB (Figure 3). Thus, unlike for **1-E** and **1-A**, in the **1-B** structure the water molecule is engaged in one H-bond only.

3.2. VCD Spectra. We have previously presented experimental IR and theoretical VCD spectra for cysteine monomer.¹³ We found that several VCD bands enable unequivocal differentiation between the conformers.¹³ Here we report the VCD spectra for the selected (1:1) cysteine–water complexes, especially interesting from the point of view of the main goal of this paper: to establish whether the interaction of different cysteine conformers with water molecules can be monitored selectively by the VCD spectra.

As we showed in our papers,^{8,9} the VCD spectrum reveals patterns characteristic and specific for types of intermolecular interactions especially through changes of the moieties engaged in hydrogen bonding but not only. In particular, we have shown that after complex formation with a chiral molecule, a nonchiral molecule becomes active in the VCD spectra. This is also the case for the system studied in this paper. As here we deal with 17 atom systems exhibiting 45 fundamental vibrations each; therefore we focus only on the most clearly interpretable spectral features, revealing the influence of the intermolecular complex type on the VCD spectra.

3.2.1. Different Cysteine Conformers Engaged in the Same Type of Intermolecular H-Bond. Out of over 40 studied complexes, the highest interaction energies exhibit those with the cyclic hydrogen bonding between water and the carboxylic cysteine group (Figure 1, Figure 1ESI). In such a complex, the water molecule as well as the acid carboxylic group both play the proton donor and proton acceptor roles: $\text{HOH}\cdots\text{O}=\text{C}$ bond

and $\text{COOH}\cdots\text{OH}_2$ bond, respectively. Additionally, the other OH moiety of water is not hydrogen bonded. From the vibrational spectroscopy point of view, all the above-mentioned groups are suspected to exhibit some interesting patterns or changes in both IR and VCD spectra. As vibrations of the NH_2 group occur in the same spectral ranges in Table 2 we list selected modes of the cyclic H_2O bond with the COOH group and the NH_2 vibrations.

Let us state again^{8,9} that first and foremost the nonchiral water molecule in complex with a chiral compound exhibits the VCD absorptions of the $\nu(\text{OH}_{\text{free}}^{\text{W}})$, $\nu(\text{OH}_{\text{HB}}^{\text{W}})$ (Figure 4a), and $\beta(\text{H}_2\text{O})$ modes (Figure 4b) at ca. 3700, 3500, and 1560 cm^{-1} . For **3-A**, **5-A**, and **7-A** all of these bands have meaningful VCD intensities (Table 2); moreover, the VCD intensities of the $\beta(\text{H}_2\text{O})$ bands in A-type complexes are one of the most prominent in the entire spectra (Figure 4b).

Table 2 illustrates also another very interesting feature: for the **3-A** and **5-A** complexes the $\nu(\text{OH}_{\text{free}}^{\text{W}})$ and $\beta(\text{H}_2\text{O})$ VCD bands display negative rotational strengths whereas the same vibration bands of the **3'-A** and **7-A** complexes show positive ones (Figure 4). This is connected with the arrangement of the OH_{free} moiety of the water molecule with respect to the plane defined by the O, C, and O atoms of the carboxylic group. If we agree that in the **3-A** and **5-A** complexes the H_{free} atom is arranged under the plane, the opposite is true for the **3'-A** and **7-A** complexes (Figure 1). (Note that **3'-A** differs from **3-A** just by the sign of the torsion angle of the water (non-H-bonded) H-atom with respect to the plane determined by the cyclic hydrogen bond.) Thus the sign of the rotational strengths of the $\nu(\text{OH}_{\text{free}}^{\text{W}})$ and $\beta(\text{H}_2\text{O})$ VCD bands indicates the subtle arrangement of the water molecule (Figure 4). However, this may not be true if the barrier between the two arrangements is too small and is overcome easily by the water wagging mode. The barrier between **3-A** and **3'-A** is equal to 1.265 and 1.243 kcal/mol, respectively, which means that to overcome the barrier the wagging mode must have a frequency exceeding 442.4 or 434.8 cm^{-1} , respectively. Yet the H_2O wagging modes, in **3-A** and **3'-A**, have frequencies 258.8 and 266.4 cm^{-1} , respectively. Thus, in temperatures low enough, the $\nu(\text{OH}_{\text{free}}^{\text{W}})$ and $\beta(\text{H}_2\text{O})$ intensive VCD bands may be sufficiently separated in frequencies to be split into a pair of oppositely directed bands.

Let us now remark that qualitatively the VCD intensity of the $\nu(\text{OH}_{\text{HB}}^{\text{W}})$ band for the whole set of A-type complexes shows the same character: it has the negative sign and is of medium to medium-strong VCD intensity (Figure 4a). The $\nu(\text{C}=\text{O}_{\text{HB}})$ VCD intensity varies rather erratically (Figure 4b). Finally, the $\beta(\text{NH}_2)$, $\nu^{\text{a}}(\text{NH}_2)$, and $\nu^{\text{s}}(\text{NH}_2)$ VCD bands preserve more or less the same character in the group of discussed spectra of the A-type complexes.

3.2.2. Same Cysteine Conformer Engaged in Different Types of Intermolecular H-Bond. (A) Cysteine Conformer without the

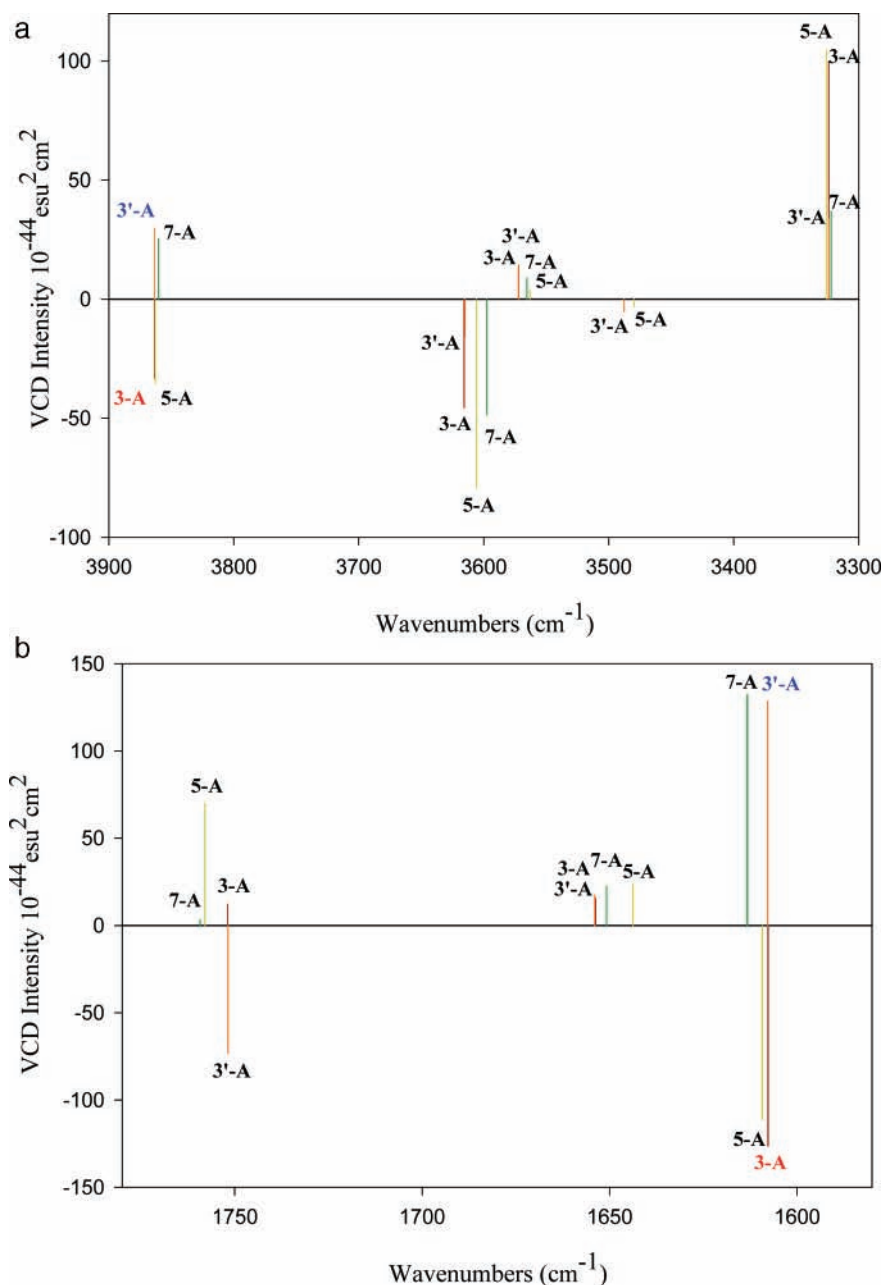


Figure 4. Harmonic B3LYP/aug-cc-pVDZ VCD spectra of L-cysteine complexes with a water molecule. Different cysteine conformers engaged in the same type of cyclic intermolecular hydrogen bond: (a) region of the $\nu(\text{OH})$ and $\nu(\text{NH}_2)$ stretching vibrations bands; (b) region of the $\beta(\text{H}_2\text{O})$ and $\beta(\text{NH}_2)$ bending vibrations.

TABLE 3: Comparison between the B3LYP/aug-cc-pVDZ Calculated IR Frequencies (cm^{-1}) and Intensities ($\text{km}\cdot\text{mol}^{-1}$), and VCD Rotational Strengths ($10^{-44} \text{esu}^2 \text{cm}^2$) of the Selected Modes of the Water Complexes with the 7 Cysteine Non-IHB Conformer Exhibiting Various Types of Hydrogen Bonding between Water and the Cysteine Molecule

| | 7-A (cyclic) | | | 7-B ($\text{HOH}\cdots\text{O}=\text{C}$); ($\text{NH}_2\cdots\text{OH}_2$) | | | 7-D ($\text{HOH}\cdots\text{NH}_2$); $\text{C}=\text{O}$ free | | |
|---|--------------|-------|-------|---|-------|-------|---|-------|-------|
| $\nu(\text{OH}_{\text{free}}^{\text{W}})$ | 3860 | 92.8 | 25.3 | 3881 | 101.7 | 13.5 | 3870 | 67.3 | -1.6 |
| $\nu(\text{OH}_{\text{free}}^{\text{C}})$ | | | | 3731 | 62.8 | 13.1 | 3737 | 71.5 | 3.1 |
| $\nu(\text{OH}_{\text{HB}}^{\text{W}})$ | 3598 | 389.9 | -48.7 | 3674 | 318.4 | 46.9 | | | |
| $\nu^{\text{a}}(\text{NH}_2)$ | 3566 | 7.1 | 9.0 | 3567 | 37.3 | -17.6 | 3552 | 11.3 | 6.6 |
| $\nu(\text{NH}_2-\text{OH}_{\text{HB}}^{\text{W}})$ | | | | | | | 3475 | 128.2 | 47.7 |
| $\nu(\text{NH}_2+\text{OH}_{\text{HB}}^{\text{W}})$ | | | | | | | 3461 | 504.1 | 21.5 |
| $\nu^{\text{s}}(\text{NH}_2)$ | 3491 | 2.2 | 0.0 | 3494 | 22.5 | 12.2 | | | |
| $\nu(\text{OH}_{\text{HB}}^{\text{C}})$ | 3322 | 731.9 | 37.0 | | | | | | |
| $\nu(\text{C}=\text{O}_{\text{free}})$ | | | | 1780 | 341.8 | 63.5 | 1804 | 279.5 | 50.7 |
| $\nu(\text{C}=\text{O}_{\text{HB}})$ | 1759 | 249.6 | 3.1 | | | | | | |
| $\beta(\text{NH}_2)$ | 1651 | 31.1 | 22.6 | 1656 | 29.5 | 12.5 | 1634 | 27.6 | 11.5 |
| $\beta(\text{H}_2\text{O})$ | 1613 | 106.0 | 132.2 | 1626 | 110.8 | 34.7 | 1647 | 69.6 | -17.2 |

Intramolecular H-Bond. Consider now the non-IHB cysteine **7** conformer in various (1:1) intermolecular complexes with water molecules (Figure 2, Table 3). The **7-A** complex is stabilized

by the cyclic hydrogen bond, as described above, and is the most stable in the whole group of the studied structures. The **7-B** structure is stabilized by a kind of linear $\text{HOH}\cdots\text{O}=\text{C}$

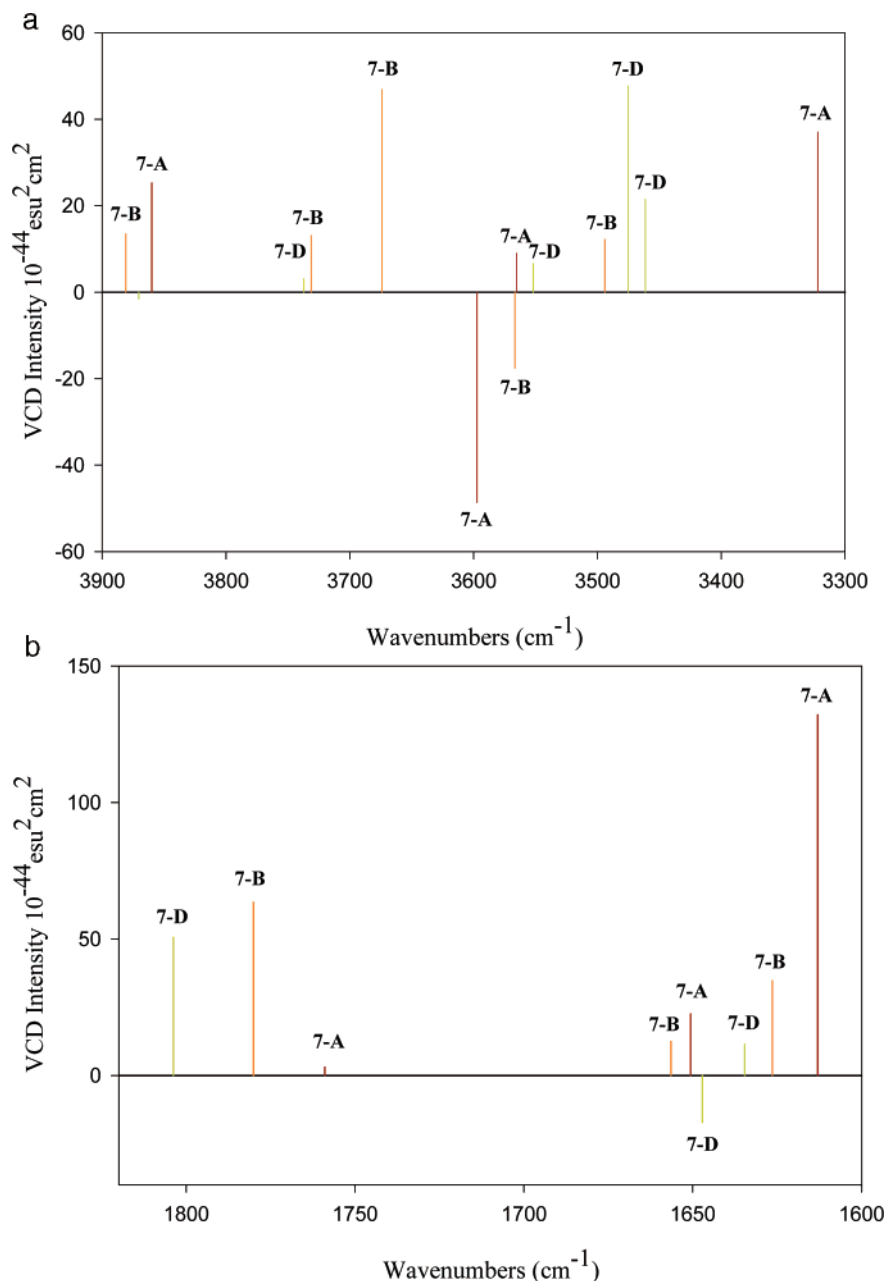


Figure 5. Harmonic B3LYP/aug-cc-pVDZ VCD spectra of L-cysteine complexes with a water molecule. Cysteine conformer **7**, not-stabilized by the intramolecular OH \cdots NH $_2$ hydrogen bond, engaged in different types of intermolecular hydrogen bond: (a) region of the ν (OH) and ν (NH $_2$) stretching vibrations bands; (b) region of the β (H $_2$ O) and β (NH $_2$) bending vibrations.

TABLE 4: Comparison between the B3LYP/aug-cc-pVDZ Calculated IR Frequencies (cm $^{-1}$) and Intensities (km \cdot mol $^{-1}$), and VCD Rotational Strengths (10 $^{-44}$ esu 2 cm 2) of the Selected Modes of the Water Complexes with the 1 Cysteine IHB Conformer Exhibiting Various Types of Hydrogen Bonding between Water and the Cysteine Molecule

| | 1-E | | | 1-A | | | 1-B | | |
|---|------|-------|-------|------|--------|-------|------|-------|-------|
| ν (OH $^W_{\text{free}}$) | 3870 | 98.5 | 41.0 | 3860 | 83.3 | -20.1 | 3874 | 96.7 | 16.6 |
| ν (OH $^W_{\text{HB}}$) | 3674 | 231.2 | -62.4 | | | | 3686 | 418.0 | 4.8 |
| ν^{a} (NH $_2$) | 3579 | 19.1 | -21.9 | 3525 | 10.7 | -20.2 | 3582 | 20.0 | -20.7 |
| ν^{s} (NH $_2$) | 3456 | 19.2 | 16.5 | 3448 | 8.0 | -5.7 | 3467 | 13.9 | 16.6 |
| ν (OH $^W_{\text{HB}}$ -OH $^{\text{C}}_{\text{IHB}}$) | | | | 3414 | 1458.8 | 23.3 | | | |
| ν (OH $^W_{\text{HB}}$ +OH $^{\text{C}}_{\text{IHB}}$) | | | | 3304 | 290.0 | 3.6 | | | |
| ν (OH $^{\text{C}}_{\text{IHB}}$) | 3373 | 300.4 | 26.2 | | | | 3402 | 302.5 | -7.3 |
| ν (C=O $_{\text{HB}}$) | | | | | | | 1806 | 357.6 | -93.0 |
| ν (C=O) | 1798 | 333.2 | -99.5 | 1785 | 248.3 | -71.8 | | | |
| β (NH $_2$) | 1630 | 41.0 | -53.0 | 1643 | 23.5 | -8.3 | 1634 | 32.9 | -61.9 |
| β (H $_2$ O) | 1627 | 50.1 | 68.2 | 1616 | 66.4 | -44.1 | 1645 | 56.6 | 8.3 |

hydrogen bond and an additional HNH \cdots OH $_2$ intermolecular interaction. The **7-D** complex exhibits a linear HOH \cdots NH $_2$ hydrogen bond and, unlike in the two former cases, displays the free C=O group. Thus, in the first two complexes water

plays both proton donor and proton acceptor roles, but for different proton donors, OH and NH in **7-A** and **7-B**, respectively, whereas in **7-D** it plays exclusively the proton donor role.

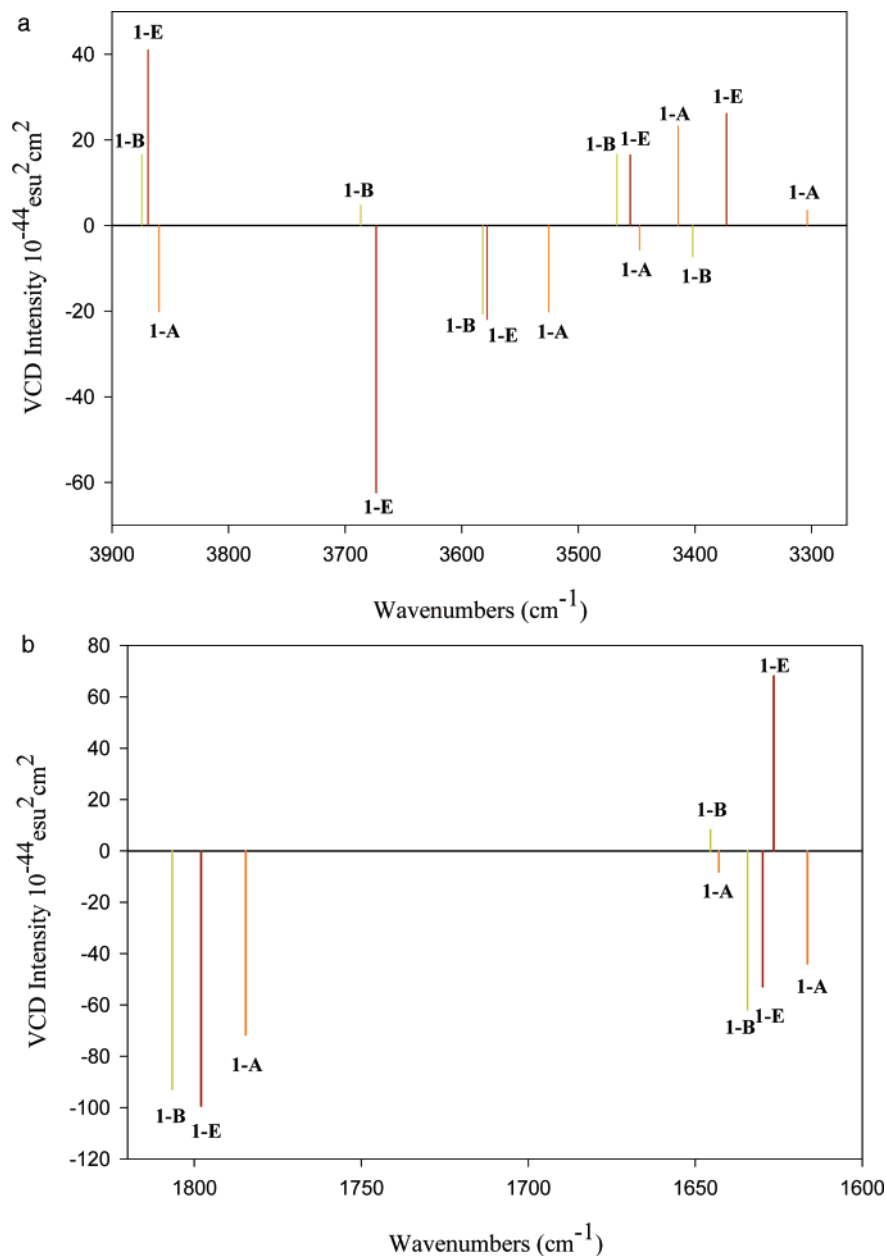


Figure 6. Harmonic B3LYP/aug-cc-pVDZ VCD spectra of L-cysteine complexes with a water molecule. Cysteine conformer **1**, stabilized by the intramolecular OH \cdots NH $_2$ hydrogen bond, engaged in different types of intermolecular hydrogen bond: (a) region of the $\nu(\text{OH})$ and $\nu(\text{NH}_2)$ stretching vibrations bands; (b) region of the $\beta(\text{H}_2\text{O})$ and $\beta(\text{NH}_2)$ bending vibrations.

Obviously, for such different complexes even the IR absorption reveals a lot of patterns enabling differentiation of the conformers. However, the VCD spectra seem to be much more selective. For example (Figure 5), the three complexes show similar IR intensity of $\nu(\text{OH}_{\text{free}}^{\text{W}})$ and $\beta(\text{H}_2\text{O})$, whereas the VCD intensities decrease from **7-A**, through **7-B**, to **7-D**, from ca. 25.3, through 13.5, to -1.6 and from ca. 132.2, through 34.7, to $-17.2 \times 10^{-44} \text{ esu}^2 \text{ cm}^2$, respectively.

An interesting pattern can be detected in the range 3700–3550 cm^{-1} VCD (harmonic) spectra (Figure 5a, Table 3). For the sequence of **7-A**, **7-B**, and **7-D** structures, the two VCD bands, $\nu(\text{OH}_{\text{HB}}^{\text{W}})$ and $\nu^{\text{a}}(\text{NH}_2)$, have signs $-$ and $+$; $+$ and $-$; and none and $+$. Thus, if one could have certainty that only these three complexes can be observed in the system, one would distinguish equivocally its components based solely on this range of the VCD spectrum.

Similarly, the other selective pattern can be observed in the range 3500–3300 cm^{-1} (Figure 5a, Table 3). For the sequence

of **7-A**, **7-B**, and **7-D** structures, the first exhibits one medium-strong positive band near the low limit of the range (37.0), the second shows one medium positive band at the high limit of the range (12.2), and the third one shows two medium-strong positive bands located at the high limit of the range (47.7 and $21.5 \times 10^{-44} \text{ esu}^2 \text{ cm}^2$, respectively). However, in this case the IR spectrum seems to be more selective because the bands are more differentiated by the IR intensities.

Another interesting feature can be found in the region of the $\nu(\text{C}=\text{O})$ absorptions (Figure 5b). The strong $\nu(\text{C}=\text{O})$ bands in the IR spectra of **7-A**, **7-B**, and **7-D** structures are placed every 20 cm^{-1} starting from 1760 and ending at 1800 cm^{-1} , whereas in the VCD spectra the first one is almost absent and the two other have similar intensities (63 and $51 \times 10^{-44} \text{ esu}^2 \text{ cm}^2$, respectively).

The most important feature for the $\beta(\text{NH}_2)$ band is its location ca. 20 cm^{-1} lower for the **7-D** complex than in

the 7-A and 7-B complexes. Its IR intensity is practically not selective at all, and the VCD intensity is medium (Figure 5b).

(B) *Cysteine Conformer Stabilized by the Intramolecular H-Bond*. Consider now the IHB cysteine **1** conformer in various (1:1) intermolecular complexes with water molecule (Figure 3). Among the (1:1) complexes of the **1** cysteine conformer with water, the **1-E** complex has the largest interaction energy (Table 1). It is stabilized by a cyclic hydrogen bond in which water plays both proton donor and proton acceptor role: $\text{HOH}\cdots\text{O}=\text{C}$ and $\text{SH}\cdots\text{OH}_2$, respectively. In the **1-A** complex, the water molecule is inserted between the $\text{OH}\cdots\text{NH}_2$ IHB of cysteine and the $\text{OH}\cdots\text{O}(\text{H})-\text{H}\cdots\text{NH}_2$ hydrogen bond is formed. The third chosen complex, **1-B**, is the most stable in the group of the **1** conformer complexes; however it is stabilized by a simple, linear, $\text{OH}\cdots\text{O}=\text{C}$ hydrogen bond. On the other hand, its interaction energy equals -4.69 kcal/mol, only.

As for the **7** non-IHB conformer, for such a different water configurations in the complexes with the **1** IHB conformer, it can be expected that the IR spectrum would be selective enough to distinguish between the complex structures (Table 4). However again, the VCD spectrum is much more discriminating. For example, the $\nu(\text{OH}^{\text{W}_{\text{free}}})$ bands, located at ca. 3875 cm^{-1} in the (harmonic) spectra, for the three complexes **1-E**, **1-A**, and **1-B**, have very similar IR intensities, but quite different VCD intensities (Figure 6a): for **1-A** it has a negative sign ($-20 \times 10^{-44}\text{ esu}^2\text{ cm}^2$) and for **1-E** and **1-B** the positive one. The same holds true for the $\beta(\text{H}_2\text{O})$ and $\nu^s(\text{NH}_2)$ modes. However, the $\nu(\text{OH}^{\text{W}_{\text{HB}}})$ VCD band at ca. 3680 cm^{-1} is present only for **1-E** and **1-B**, for the former it is middle-strong whereas for the latter it is weak and positive (Figure 6a). Because of participation of the OH^{W} moiety of **1-A** in the seven-membered $\text{OH}\cdots\text{O}(\text{H})-\text{H}\cdots\text{NH}_2$ hydrogen bond, the $\nu(\text{OH}^{\text{W}_{\text{HB}}})$ mode of **1-A** is coupled with the $\nu(\text{OH}^{\text{C}_{\text{HB}}})$ mode. The two modes split into in-phase and in-counterphase $\nu(\text{NH}_2+\text{OH}^{\text{W}_{\text{HB}}})$ and $\nu(\text{NH}_2-\text{OH}^{\text{W}_{\text{HB}}})$ vibrations that are red-shifted by ca. 370 and 250 cm^{-1} . These two bands form a specific pattern in both IR and VCD spectra (Figure 6a, Table 4). However, distinguishing **1-E** from **1-B** in the range $3470\text{--}3370\text{ cm}^{-1}$ does not seem to be difficult because the former exhibits two positive, middle-intensity bands at the limits of the range, whereas the latter has one positive and one negative.

Finally, the $\nu^s(\text{NH}_2)$, $\nu(\text{C}=\text{O})$, and $\beta(\text{NH}_2)$, IR, and VCD bands do not seem to be very specific for the kind of complex (Table 4, Figure 6b). However, it is noticeable that the $\nu(\text{C}=\text{O})$ stretching vibration VCD bands have negative rotational strengths (Figure 6b).

4. Conclusions

In this paper we have presented the results of DFT(B3LYP)/aug-cc-pVDZ calculations of interaction energies and vibrational circular dichroism (VCD) spectra for selected chiral L-cysteine conformers with a water molecule. Out of more than forty complexes studied, three small groups of complexes have been selected to illustrate interrelations between intermolecular hydrogen bond arrangement and pattern observed in the VCD spectra. The first group contains different cysteine conformers engaged in the same type of intermolecular hydrogen bond. The second and third group contains a selected cysteine conformer engaged in different types of intermolecular hydrogen bond, but in the former group the cysteine conformer is not, whereas in the latter it is stabilized by the intramolecular $\text{OH}\cdots\text{NH}_2$ hydrogen bond.

The $\nu(\text{OH})$ and $\nu(\text{NH})$ and $\beta(\text{OH}_2)$ and $\beta(\text{NH}_2)$ ranges of the theoretical VCD spectra were the subject of a detailed

analysis. On this basis, the VCD spectra were found to be sensitive to conformational changes and water arrangement in cysteine complexes. The VCD spectra seem to be especially useful for discriminating between different chiral forms of intermolecular hydrogen-bonding complexes. In particular, we show that the VCD modes of an achiral water molecule after complex formation acquire significant rotational strengths whose signs change in line with the geometry of the complex. Moreover, for some water arrangements the VCD spectra can be sensitive to water-wagging-conformers and, in temperatures low enough, the intensive $\nu(\text{OH}^{\text{W}_{\text{free}}})$ and $\beta(\text{H}_2\text{O})$ VCD bands may be sufficiently separated in frequencies to be split into pairs of oppositely directed bands.

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Supporting Information Available: Figure of the considered forms of L-cysteine complexes with water. Table of Gibbs free energies; interaction, counterpoise-corrected interaction, deformation-corrected interaction energies; and deformation and BSSE terms. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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