Toward an Accurate Modeling of Optical Rotation for Solvated Systems: Anharmonic Vibrational Contributions Coupled to the Polarizable Continuum Model

Franco Egidi and Vincenzo Barone

Scuola Normale Superiore, Piazza dei Cavalieri, 7 I-56126 Pisa, Italy

Julien Bloino

CNR, Consiglio Nazionale delle Ricerche, Istituto di Chimica dei Composti Organometallici, UOS di Pisa, Via G. Moruzzi, 1 I-56124, Italy

Chiara Cappelli*

Scuola Normale Superiore, Piazza dei Cavalieri, 7 I-56126 Pisa, Italy and Dipartimento di Chimica e Chimica Industriale, Università di Pisa, via Risorgimento, 35 I-56126 Pisa, Italy

ABSTRACT: We present a newly implemented methodology to evaluate vibrational contributions (harmonic and anharmonic) to the optical rotation of solvated systems described by means of the polarizable continuum model (PCM). Proper account of an incomplete solvation regime in the treatment of both the electronic property and the molecular vibrations is considered, as well as the inclusion of cavity field effects. In order to assess the quality of our approach, test calculations on (*R*)-methyloxirane in various solvents and (*S*)-N-acetylproline amide in cyclohexane and aqueous solution are presented. The comparison with experimental findings is also shown.

I. INTRODUCTION

Chiroptical techniques, such as the measurement of optical activity (OR) or optical rotatory dispersion (ORD), have been around for several decades and have been used mainly by pharmaceutical or organic chemists to determine the enantiomeric purity of their synthesized samples by using empirical rules or heavy chemical derivatization in order to correlate the structure of the enantiomer to the sign of the measured properties.[1] The interest in the correct determination of enantiomeric purity is especially evident in the case of drugs, which in most cases are constituted by pure enantiomers, since only a particular configuration is biologically active, whereas the other may be inactive or even toxic. The use of OR to determine the absolute configuration and predominant conformation has been gaining renewed interest in recent years, due to the availability of quantum mechanical (QM) methods for predicting the OR. In this way, in fact, by comparing calculations and experiments, the assignment is done unequivocally, since the calculated value surely refers to only one of the enantiomerically pure structures.

From the point of view of the theoreticians, studying chiroptical properties and spectroscopies offers a unique chance of working in a field where the advancement of the theory opens the way to the investigation of new and more complex systems, and where the strict interplay between theory and experiment is often a real necessity. Also, from the purely theoretical and computational point of view, as chiroptical properties are formally mixed electric and magnetic responses,

the underlying QM theory is very challenging, as it requires the same accuracy for the evaluation not only of energetic parameters but also of the response of the molecular system to the electric and especially magnetic component of the radiation. For these reasons, the calculation of chiroptical properties has been viable only in recent years, following the tremendous progress of *ab initio* quantum chemistry in the recent decades.[2-8] The impact that quantum chemistry has had on the field has been so relevant that Polavarapu spoke of a "Renaissance in chiroptical spectroscopic methods for molecular structure determination" following the development of QM computational techniques.[9]

In the past decade, much effort has been devoted to develop methods for the accurate calculation of OR. The earliest works[10-14] employed the Hartree−Fock level of theory, but soon the importance of including in the model a treatment of the electron correlation was exposed.[15,16] To date, most of the computational studies on chiroptical properties have been based on response methods within density functional theory (DFT) and time-dependent DFT (TD-DFT), even though more accurate methods such as coupled cluster theory have also been used.[17-20]

The basis set dependence was first analyzed by Cheeseman et al.,[21] who pointed out the need to include diffuse basis functions in the model and suggested the basis sets aug-cc-

pVDZ and 6-311++G(2d,2p) to be the most cost-effective. Campos et al.[22] have shown that by increasing the size of the basis set there is a decrease in the agreement between the experimental and calculated OR using different DFT functionals (B3LYP, PBE1PBE, M06, M06-2X). They also showed that the B3LYP functional yields the least mean absolute deviation with respect to the experimental data for the systems they analyzed.[22]

At the same time, it has been reported that significant discrepancies may be observed when comparing experiments with calculated data that account for the sole electronic component of the OR. In fact, Ruud and co-workers[23,24] showed that vibrational corrections may contribute in a significant proportion to the total optical rotation and in fact may even cause it to change sign, as also observed by Kongsted et al.[25] Inclusion in the vibrational corrections of the effects due to the anharmonicity of the potential energy surface has also been shown to be quite significant in several cases.[24,26] Furthermore, by taking the Boltzmann average of the vibrational contribution over all vibrational states, it is possible to include in the calculations temperature effects other than those arising from the conformational weights of the different structures the molecule under study may possess, further refining the method.[27−29]

Therefore, in order to obtain a reliable method for modeling OR, both the electronic and nuclear parts of the system have to be treated accurately, because both can affect the phenomenon at the same level. This means extending the calculation to highly correlated QM methodologies when evaluating the electronic component of the OR, while resorting to anharmonic treatments for the nuclear component.

Yet, a highly correlated treatment of the electronic component of the OR with the inclusion of the temperature-dependent vibrational corrections (even at the anharmonic level) may still not lead to a satisfactory agreement with the experiment because chiroptical measurements are only seldom applied to isolated systems,[30−32] but more commonly they are performed in solutions. Solvent effects on the OR may be substantial,[33] since there is evidence that not only the absolute value but also the sign of the property can change when changing the polarity of the solvent. For a molecule that possesses many possible conformations, solvent effects may arise as a result of a change in the Boltzmann populations of the different conformers in the various solvents,[34] but even very rigid molecules can show a remarkably solvent-dependent optical rotation.[35] Therefore, accounting for the solvent effects in the calculations is crucial, and much effort has been devoted to this topic in recent years.[36]

The first QM theory of OR for molecules in solution is due to Rosenfeld[37] and is formulated in terms of a molecular solute, described at the QM level and characterized by its stationary states in the gas phase, and a surrounding solvent described as a dielectric medium, with given dielectric properties at the optical frequency of the electromagnetic field. Solvent effects are modeled by exploiting the Lorentz condition, which relates the local field acting on the molecular solute to its macroscopic counterpart. Therefore, a detailed description of the molecular aspects of the solute−solvent interaction is missing. A refined theory was then proposed by Onsager,[38] who introduced two new fundamental concepts, i.e., the reaction field to describe the mutual electrostatic interaction between the solute and the dielectric medium and the concept of the cavity field to describe the electromagnetic field actually experienced by the solute. The Rosenfeld theory of optical rotation was extended to the study of the ellipticity of optically active solutions by Moffit and Moscowitz,[39] and since then it has represented a main guide for an "a posteriori" analysis and rationalization of the observed chiroptical properties of solvated molecules, mainly in terms of qualitative structure−property relationships.[40]

In recent years, the development of QM continuum solvation models[41−46] has given a substantial contribution to the modeling of solvent effects on optical activity,[36,47,48] although such approaches are not able to account for any contribution to the optical rotation induced by the solute in the solvent. In the QM continuum solvation approach, solvent effects on the various properties, including the response properties determining optical activity, can be obtained directly without requiring any "a posteriori" correction as in the Lorentz field approach, which results in the ability to describe and analyze solvent effects in a detailed and more realistic way.

Mennucci et al.[47] coupled the DFT linear response method with the polarizable continuum model (PCM)[45] to calculate the OR of seven rigid molecules in seven different solvents. They included in their calculations the effects due to the electronic nonequilibrium (vide infra), and also proposed a method to account for the cavity field effect within the PCM formalism, but only applied it to one system. They did not however take into consideration the effects of the molecular vibrations and the vibrational nonequilibrium (vide infra). Continuum models have also been employed by Stephens et al.[15] and Kongsted et al.[49,50] to model the OR for solvated systems.

In some cases, the need to include explicit solvent molecules in the system arises, as in the case when there is a strong contribution from the solvent chiral imprint or from strong specific solute−solvent interactions, as shown by Mukhopadhyay et al.[51,52] and Losada et al.[53]

From the discussion reported above, it should be clear that computational works employing a continuum approach to model the effect of the solvent on optical rotation have so far neglected, for the most part, the additional solvation effects arising from the fact that the solvent alters the electric field acting on the molecule (the local field effect[54]) and those effects arising from the dynamical aspects of solvation (the nonequilibrium effect[55−57]). Special care also has to be taken when combining the vibrational corrections with solvent effects, for an additional nonequilibrium contribution arises from the molecular vibrations and must be taken into account for a complete description of both the vibrational and the solvation effects. In this work, we have extended previous work on this topic[47] with the aim of proposing a method able to calculate the optical rotation of solvated molecules by fully considering the "reaction" and "cavity" field effects (vide infra), as well as the anharmonic vibrational corrections within the PCM framework, with the additional account of the electronic and vibrational nonequilibrium effects. The methodology will be reported in the next section, whereas section 4 reports the application of the method to the calculation of the OR of (R)-methyloxirane in six different solvents, as well as the evaluation of the ORD of (S)-N-acetylproline amide (NAP) in a cyclohexane and water solution. The comparison with the relevant experimental findings is also proposed where applicable. Some concluding remarks end the presentation.

2. THEORY

2.1. Optical Rotation: the Electronic Contribution. The specific rotation of an isotropic sample, which is usually expressed in deg dm^{-1} g^{-1} cm^3, can be calculated using the following formula:[58]

$$[\alpha] = -\frac{4\pi}{3}\frac{\omega}{c}\frac{N_A}{M_w}G_{aa}' \tag{1}$$

where ω is the angular frequency of the incident radiation, N_A is Avogadro's number, M_w is the molar mass of the chiral substance, and G'_{aa} is the trace of the electric dipole−magnetic dipole dynamic polarizability tensor:

$$G_{ab}' = -\frac{2}{\hbar}\sum_{j\neq 0}\frac{\omega}{\omega_{j0}^2 - \omega^2}\mathrm{Im}\langle 0|\mu_a|j\rangle\langle j|m_b|0\rangle \tag{2}$$

where μ denotes the electric dipole moment, m the magnetic dipole moment, and ω_{j0} the energy difference between state j and the ground state of the molecule. It can be seen that, as the frequency of the incident light approaches an absorption band of the molecule, the calculated specific rotation diverges. This formula can thus only be applied in the nonresonant regime.

The sum in eq 2 runs through all excited states of the molecule; therefore, its calculation is highly unpractical. As a result, methods based on linear response theory have been developed,[59] which calculate optical rotation using analytical derivative techniques that relate the G' tensor to the derivative of the wave function with respect to the dynamic electric and magnetic fields:

$$G_{ab}' = -2\hbar\omega\,\mathrm{Im}\left\langle \frac{\partial\Psi_0(\omega)}{\partial E_a}\middle|\frac{\partial\Psi_0(0)}{\partial B_b}\right\rangle \tag{3}$$

where Ψ_0 is the electronic ground state wave function and the derivative in the bra is evaluated with respect to the dynamic electric field, whereas the derivative in the ket is performed assuming a static magnetic field.[60]

2.2. Vibrational Corrections. As already pointed out in the Introduction, it has been shown[24] that molecular vibrations may be of the outmost importance in determining the correct sign and magnitude of optical rotation. In this work, we have included the effect of molecular vibrations by performing a vibrational averaging[26] of the property P using the nuclear wave function Φ:

$$P = \langle\Phi|P(Q)|\Phi\rangle = P(0) + \Delta_{\mathrm{vib}}P \tag{4}$$

where $P(0)$ is the specific rotation calculated at the equilibrium geometry and $\Delta_{\mathrm{vib}}P$ is the vibrational correction pertaining to the nuclear wave function Φ. We have also considered the effect of the anharmonicity of the potential energy surface by including anharmonic terms in the expansion of the electronic energy. The nuclear wave function depends on the vibrational quantum numbers associated with the normal modes of vibration; therefore, a Boltzmann average of all of the vibrational states can be performed to include the effect of temperature on the optical rotation of the molecule, yielding the following formula for the temperature dependent vibrational correction:[27,28]

$$\Delta_{\mathrm{VC}}P = -\frac{1}{4}\sum_a \frac{1}{\omega_a^2}\left(\frac{\partial P}{\partial Q_a}\right)_0 \sum_b \frac{K_{abb}}{\omega_b}$$
$$\coth\frac{\hbar\omega_b}{2k_BT} + \frac{1}{4}\sum_a \frac{1}{\omega_a}$$
$$\left(\frac{\partial^2 P}{\partial Q_a^2}\right)_0 \coth\frac{\hbar\omega_a}{2k_BT} \tag{5}$$

Equation 5 contains the first and diagonal second derivatives of the optical rotation calculated with respect to the mass weighted normal modes and evaluated at the equilibrium geometry, the angular frequencies of the normal modes ω_a, and the anharmonic semidiagonal third derivatives of the electronic energy K_{abb}, and it depends explicitly on the temperature T. The expression for the vibrational correction is the sum of two different contributions: the first one is a consequence of the anharmonicity of the potential energy surface while the second term would be present even if a harmonic description were employed.

In this study, we have implemented such formulas in a locally modified version of the Gaussian 09[61] computational chemistry program, which analytically calculates the first and second derivatives of the electronic energy with respect to the vibrational normal modes. Equation 5 requires the semi-diagonal third derivatives of the electronic energy, which were computed numerically using finite differences of the second derivatives along the normal modes.[62,63] Equation 5 also requires the derivatives of the optical rotation, which were calculated numerically as follows:

$$\left(\frac{\partial X}{\partial Q_a}\right) \simeq \frac{X(+\delta Q_a) - X(-\delta Q_a)}{2\delta Q_a};$$
$$\left(\frac{\partial^2 X}{\partial Q_a^2}\right) \simeq \frac{X(+\delta Q_a) - 2X(0) + X(-\delta Q_a)}{\delta Q_a^2} \tag{6}$$

where X denotes either the energy second derivatives or the optical rotation. In computational practice, the energy gradient, Hessian, and specific rotation are first evaluated analytically at the equilibrium geometry, thus giving $X(0)$. Then, the atoms are displaced along each normal coordinate a by a fixed length δ, first in the positive and then in the negative direction. At each step, the energy gradient, Hessian, and specific rotation are evaluated for the new geometry, collecting $X(+\delta Q_a)$ and $X(-\delta Q_a)$, which yield the required numerical derivatives.

2.3. Optical Rotation for Solvated Molecules: The PCM Approach. As already pointed out in the Introduction, the optical rotation of a molecule in solution can depend greatly upon the solvent, so that a change in solvent may even change the sign of the property.[35]

To include solvation effects into our model, we have used the polarizable continuum model (PCM),[41,45,64] which treats the solvent as a polarizable continuum with given dielectric properties. The molecule is placed inside of a molecule-shaped cavity within the polarizable continuum, and it induces on the cavity surface a charge density (represented by a set of point-like charges) which in turn modifies the electron density of the molecule and its equilibrium geometry. Therefore, in the calculations of molecular properties of solvated systems, both the "direct" solvent effect on the molecular wave function and

the "indirect" effect on the molecular geometry should be taken into account.

Nevertheless, in the case of molecular properties for solvated systems, additional solvation effects should be considered. The first one is the so-called *Local Field Effect*,[38,54] which stems from the fact that the electromagnetic field acting on the molecule is different than the Maxwell field acting on the sample: the external electromagnetic field is altered by the presence of the solvent, and the molecular property (in this case optical rotation) will be generated by the local field actually acting on the molecule in the cavity. Classically, the problem is solved via the Onsager–Lorentz model,[38] which treats the molecule as a point-like electric dipole at the center of a spherical cavity within a polarizable continuum representing the solvent. The local field is then related to the external field through a multiplicative factor which depends on the solvent static dielectric constant for static fields ($\vec{E}^{\text{loc}}$) and on the solvent optical dielectric constant for dynamic fields ($\vec{E}_\omega^{\text{loc}}$):

$$\vec{E}^{\text{loc}} = \frac{\varepsilon + 2}{3}\vec{E}^{\text{ext}}; \ \vec{E}_\omega^{\text{loc}} = \frac{\varepsilon_{\text{opt}} + 2}{3}\vec{E}_\omega^{\text{ext}} \tag{7}$$

This rather approximate treatment of the local field effect does not substantially improve the quality of the results with respect to the experimental values,[16] mostly because the solvent effect is seen as a multiplicative factor acting on the property calculated in vacuo; i.e., for a given solvent, the same factor is used for any molecule.

The key differences between the PCM and Onsager's model are that the PCM makes use of molecule-shaped cavities (and not spherical cavities) and that, in the PCM, the solvent–solute interaction is not simply reduced to the dipole term. PCM is also a quantum mechanical approach, and therefore the solute is described by means of its electronic wave function. Similarly to classical approaches, the basis of the PCM approach to the "local field" relies on the assumption that the "effective" field experienced by the molecule in the cavity can be seen as the sum of a reaction field term and a cavity field term. The reaction field is related to the polarization of the dielectric due to the solute charge distribution, whereas the cavity field term depends upon the polarization of the dielectric induced by the applied electromagnetic field. As previously reported in the literature,[48,54,65] in the PCM the cavity field effects are accounted for by introducing the concept of "effective" molecular response properties, which directly describe the response of the molecular solutes to the Maxwell field in the liquid.[48] By analogy with Onsager's theory, it is assumed that the response of the molecule to an external probing field can be expressed in terms of an "effective dipole moment", $\vec{\mu}^{\text{eff}}$, sum of the molecule dipole moment and the dipole moment arising from the molecule-induced dielectric polarization:[54]

$$\vec{\mu}^{\text{eff}} = \vec{\mu}^{\text{mol}} + \tilde{\mu} \tag{8}$$

where $\vec{\mu}^{\text{mol}}$ is the dipole moment of the molecule in solution (i.e., with the account of reaction field terms) and $\tilde{\mu}$ is the dipole moment that arises from the charge density induced by the molecule on the cavity surface. The latter is calculated with the following expression:[54]

$$\tilde{\mu} = -\sum_k V(\vec{s}_k) \frac{\partial q_k^{\text{ext}}}{\partial \vec{E}^{\text{ext}}} \tag{9}$$

where $V(\vec{s}_k)$ is the electric potential generated by the molecule and evaluated at the position of the polarization charges on the cavity surface and q_k^{ext} represents the external field-induced polarization charges. Contrary to the Onsager–Lorentz model, this treatment of the local field effects allows for a molecule-shaped cavity rather than a spherical cavity, and the molecule is modeled by its whole electron density obtained quantum mechanically rather than a point-like electric dipole. The results obtained with this method are therefore much more representative of the actual physics behind the phenomenon.

On the basis of such a treatment, eq 2 then becomes:

$$G'^{\text{eff}}_{ab} = -\frac{2}{\hbar} \sum_{j\neq0} \frac{\omega}{\omega_{j0}^2 - \omega^2} \text{Im}\langle0|\mu_a^{\text{eff}}|j\rangle\langle j|m_b|0\rangle \tag{10}$$

where the effective electric dipole moment replaces the molecule electric dipole moment. In principle, a local field contribution should be included in the expression of the magnetic dipole moment as well; however, if the response of the solvent to magnetic perturbations is described via the relative magnetic permeability, which is usually very close to unity, this effect is expected to be rather small and can be neglected,[34] at least to a first approximation.

The second additional effect that we included in the model pertains to the dynamical aspects of solvation.[55−57] The motions associated with the different degrees of freedom of the solvent molecules involve different time scales. During a spectroscopic experiment, the electron density of the solute will evolve in time, and depending on the characteristic time scale of the perturbation, some degrees of freedom of the solvent will be able to rearrange to the new solute electron density while others will remain static, entering a nonequilibrium configuration. In an electronic absorption experiment, for instance, the excitation takes place in a time on the order of femtoseconds, and it is therefore reasonable to assume that only the electrons of the solvent molecules will be able to rearrange themselves to the new solute electron density, while the nuclei will remain fixed. This effect is included in the calculation of the electronic component of optical rotation within the PCM framework by separating the solvent polarization into two different contributions:[55]

$$\mathbf{P}(t) = \mathbf{P}_{\text{fast}} + \mathbf{P}_{\text{slow}} \tag{11}$$

where $\mathbf{P}_{\text{fast}}$ is the polarization due to the degrees of freedom that can be considered fast with respect to the spectroscopic phenomenon at hand and, therefore, is able to remain at equilibrium with the solute, and $\mathbf{P}_{\text{slow}}$ is the slow contribution of the solvent polarization which remains static during the perturbation. When calculating the electronic component of optical rotation, $\mathbf{P}_{\text{fast}}$ accounts for the electronic degrees of freedom of the solvent, while $\mathbf{P}_{\text{slow}}$ accounts for the nuclear degrees of freedom. Computationally, this effect is treated by splitting the cavity surface charges in two different sets, one connected to the fast contribution and the other connected to the slow contribution, which are treated separately.

When extending the method beyond the simple electronic treatment of optical rotation, a vibrational correction is included. The vibrational correction arises from the vibrational motion of the molecule, which is characterized by a much different time scale than that associated with the electronic component. The response of the solvent to the vibrational motion of the solute will involve a nonequilibrium contribution associated with the translational and rotational degrees of

freedom of the solvent molecules, which reasonably cannot rearrange themselves fast enough to remain at equilibrium with the solute during the vibration. To take this effect into account with the PCM, the solvent polarization is again split into a fast and a slow component, which are represented by two respective sets of point-like charges on the cavity surface, but this time the fast component will include the contribution due to the electronic and vibrational degrees of freedom, while the slow component will treat the effect of translations and rotations.[56,57] The nonequilibrium free energy obtained with this method is twice differentiated to generate the molecule's normal modes of vibration, which are used to define the vibrational correction under the nonequilibrium condition, and as an additional nonequilibrium effect, the PCM cavity is assumed to remain fixed during molecular vibrations. Therefore, when computing the numerical derivatives of the energy Hessian and of the calculated specific rotation, the program only moves the atoms, while the cavity remains immobile. Such a model has recently been extended to evaluate anharmonic effects[57] and will be exploited in the present work.

In summary, the temperature-dependent vibrational correction calculated under the nonequilibrium regime can be rewritten as

$$
\Delta_{VC}\overline{P}^{eff} = -\frac{1}{4}\sum_a \frac{1}{\overline{\omega}_a^2}\left(\frac{\partial \overline{P}^{eff}}{\partial Q_a}\right)_0 \sum_b \frac{\overline{K}_{abb}}{\overline{\omega}_b}
$$
$$
\coth\frac{\hbar\overline{\omega}_b}{2k_B T} + \frac{1}{4}\sum_a \frac{1}{\overline{\omega}_a}\left(\frac{\partial^2 \overline{P}^{eff}}{\partial Q_a^2}\right)_0
$$
$$
\coth\frac{\hbar\overline{\omega}_a}{2k_B T} \tag{12}
$$

where P^{eff} is the specific rotation obtained by including in the calculation both the cavity field effect using eq 10 and the electronic nonequilibrium. The further presence of an overline above the quantities in the formula indicates that they are calculated with the inclusion of the vibrational nonequilibrium.

To end this section, it is worth remarking the advances with respect to previous works, which are here discussed. Essentially, the most refined method available so far is the one of Mennucci et al.,[47] who included a treatment of the electronic non-equilibrium in addition to the direct and indirect solvent effect and who also proposed a method for the treatment of the cavity field effect but only applied it to a single system, while resorting to the Onsager−Lorentz model for the bulk of the results. That study, however, lacked a treatment of the effects due to the molecular vibrations and also of the associated nonequilibrium contribution. Therefore, this paper further develops ref 47 by also including temperature-dependent anharmonic vibrational corrections within a vibrational nonequilibrium framework and a full account of cavity field effects. Using our method, the solvent and vibrational effects are efficiently coupled together, and therefore a more accurate representation of the physical system is gained.

3. COMPUTATIONAL DETAILS

All DFT calculations were carried out with a locally modified version of the Gaussian 09 program[61] using the popular B3LYP exchange-correlation functional.[66−68] Equilibrium geometries and the respective specific rotations were calculated using the aug-cc-pVDZ basis set for methyloxirane and the 6-311+

+G(d,p) basis set for N-acetylproline amide (NAP). The B3LYP/aug-cc-pVDZ level of theory has been extensively used to calculate specific rotations of methyloxirane in the past,[24,26,29] while B3LYP/6-311++G(d,p) has been successfully used to model the solvation and chiroptical properties of NAP in apolar as well as polar solvents.[69−71] Note however that, as previously reported in the literature,[72,73] some inaccuracies in the calculated absolute values for some gaseous systems can arise from the lack of diffuse polarization functions for hydrogen. Origin independence of the calculated optical rotations was ensured by employing *Gauge Including Atomic Orbitals* (GIAOs).[74]

Solvation effects were accounted for using the polarizable continuum model (PCM).[45] Molecular cavities were built by intersecting spheres centered on the atoms. The spheres' radii, measured in Ångströms, were defined as follows: $R(C) = 1.926$, $R(H) = 1.443$, $R(O) = 1.750$, and $R(N) = 1.830$, each multiplied by a factor of 1.1. The solvents' static and optical dielectric constants were, respectively, $\varepsilon = 78.36$ and $\varepsilon_{opt} = 1.78$ for water, $\varepsilon = 35.69$ and $\varepsilon_{opt} = 1.81$ for acetonitrile, $\varepsilon = 20.49$ and $\varepsilon_{opt} = 1.85$ for acetone, $\varepsilon = 2.27$ and $\varepsilon_{opt} = 2.25$ for benzene, $\varepsilon = 2.23$ and $\varepsilon_{opt} = 2.13$ for CCl$_4$, and $\varepsilon = 2.02$ and $\varepsilon_{opt} = 2.04$ for cyclohexane. All calculations in solution were preceded by a reoptimization of the molecular geometry in the presence of the polarizable continuum. Local field effects[54] and electronic and vibrational nonequilibrium effects[55−57] were included in the calculation, and solvent effects were included in the calculation of vibrational corrections as well. The evaluation of numerical derivatives required in eq 5 was performed by setting the displacement equal to 1 pm for the calculation of both OR derivatives and cubic force field components. All of the OR data reported in the tables and figures are given in deg dm^{-1}g^{-1}cm^3, unless otherwise stated.

4. RESULTS AND DISCUSSION

In order to evaluate the relevance of the various effects constituting the physical model described above, its application to two test cases, i.e., the OR of (R)-methyloxirane in various solvents and the ORD of NAP in cyclohexane and water solution, is presented in this section. The comparison with previous calculations is also discussed for methyloxirane, and in both cases a comparison with experimental findings is proposed.

We chose to begin our investigation with methyloxirane because there is a vast amount of literature concerning the calculation of the OR of this molecule. Also, the availability of experimental data for the OR of methyloxirane in many different solvents allows for an extended evaluation of the performances of the model.

4.1. (R)-Methyloxirane. Before focusing on solvent effects on the OR of (R)-methyloxirane, the specific rotation of (R)-methyloxirane at the sodium D line wavelength (589.3 nm) and the vibrational corrections at $T = 0$ K (ZPVC) and $T = 298$ K are reported for the isolated molecular system in Table 1. The choice of such a wavelength follows previous studies on this system (see, e.g., refs 20 and 25), showing that the use of the B3LYP functional becomes problematic for the calculation of the OR at lower wavelengths, e.g. 355 nm. This is due to the specific pole-structure related to the B3LYP linear response function.[20,25]

As is shown in the third column of Table 1, the vibrational correction calculated by considering the contribution of all of the molecular normal modes is substantial with respect to the

**Table 1. Specific Rotation of (R)-Methyloxirane in Vacuo at Two Different Temperatures[a]**

T/K	$[\alpha]_D^{el}$	$\Delta_{VC}[\alpha]_D$	$\Delta'_{VC}[\alpha]_D$	$[\alpha]_D^{tot}$
0	15.07	−8.27	−3.47	11.60
298.15	15.07	−12.51	−2.34	12.73

[a] $\Delta_{VC}[\alpha]_D$ is the total vibrational correction, whereas $\Delta'_{VC}[\alpha]_D$ is the vibrational correction obtained by subtracting the lowest normal mode contribution (see text). $[\alpha]_D^{tot}$ is the total specific rotation at the given temperature.

purely electronic values at both temperatures. In order to get more insight into this issue, the contribution arising from each normal mode is given in Table 2, at both the harmonic and anharmonic levels.

As is shown, 58% of the ZPVC comes from the lowest energy mode, which corresponds to the torsional movement of the methyl group around the C−C bond. This type of molecular vibration (see Figure 1) is poorly described by a normal mode picture, which employs Cartesian coordinates, and is intrinsically highly anharmonic.[25] A proper description of this normal mode would make use of the torsional angle as a curvilinear coordinate, as previously reported by Mort and Autschbach,[29] who performed a rotational averaging over the hindered rotations of a few test molecules, including methyloxirane. However, since the focus in this work is to couple solvent effects to vibrational corrections, it is unclear whether in this case the presence of the solvent would further generate a frictional force, thus impeding the rotational motion of the methyl group. Therefore, the application of the method by Mort and Autschbach[29] is not straightforward in our case, since it should in principle be reformulated to account for such effects. For these reasons, in the following, we will simply subtract the contribution of the first normal mode from the total vibrational correction, in vacuo as well as in the subsequent calculations in solution. The data obtained in this manner are reported in the rightmost column of Table 1. Notice that such an approach, if surely approximated, has already been exploited by Wiberg et al.[75] In addition, our values are also in agreement with the values obtained by Ruud and Zanasi,[24] who exploited a different approach to vibrational corrections, based on the definition of an effective geometry.

Further inspection of Table 2 also shows that the harmonic and anharmonic contributions to the ZPVC are of similar magnitude; therefore, forsaking the anharmonic treatment of vibrations could lead to a large error in the evaluation of the vibrational correction.
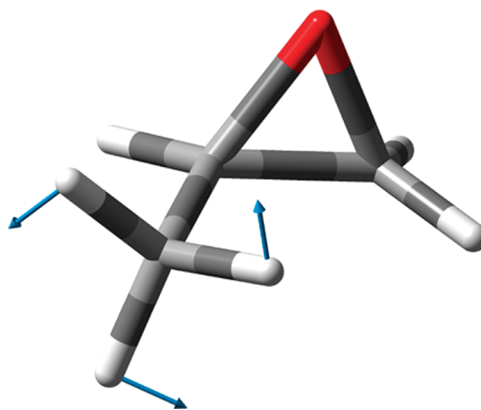
Figure 1. The first normal mode of methyloxirane, corresponding to the 202 cm^{-1} vibration.

Moving to solvent effects, the values calculated for (R)-methyloxirane in water, acetonitrile, acetone, benzene, carbon tetrachloride, and cyclohexane are reported in Table 3. These solvents were chosen because of their wide range of polarity and because of the available experimental data. In particular, the row labeled "PCM" shows the electronic component of the specific rotation, including the electronic nonequilibrium effect but devoid of the local field effect. Compared to the property calculated in vacuo ($[\alpha]_D^{vac}$ = 15.07, see Table 1), a significant change is noted, especially for polar solvents. The further inclusion of the local field effect ("PCM+loc") causes the electronic component of the specific rotation to rise by almost 20% for all solvents. This shows that the local field effect cannot be neglected if an accurate calculation is to be performed.

The $\Delta'_{VC}[\alpha]_D^{Eq}$ and $\Delta'_{VC}[\alpha]_D^{NEq}$ rows refer to the vibrational corrections, calculated at T = 298 K. In particular, $\Delta'_{VC}[\alpha]_D^{Eq}$ is obtained without the inclusion of the vibrational non-equilibrium effect, which is instead included in the data reported as $\Delta'_{VC}[\alpha]_D^{NEq}$. The inclusion of the vibrational nonequilibrium effect is especially relevant for the three polar solvents, as expected from the large difference between their respective static and optical dielectric constants. The data shown in Table 3 confirm the fact that the vibrational corrections represent a large part of the observed specific rotation, and neglecting them would introduce a substantial error in its prediction.

Finally, $[\alpha]_D^{tot}$ is the total calculated specific rotation, obtained by summing the electronic and nonequilibrium

Table 2. Harmonic and Anharmonic Contributions of Each Normal Mode to the ZPVC of (R)-Methyloxirane in Vacuo

normal mode	1	2	3	4	5	6	7	8
wavenumber (cm^{-1})	202	365	410	761	837	895	965	1027
$\Delta_{VC}[\alpha]_D^{anh}$	−0.40	0.02	−0.65	1.04	−0.27	0.38	1.05	1.41
$\Delta_{VC}[\alpha]_D^{harm}$	−4.40	0.49	−0.56	−0.15	0.33	−1.02	−0.15	−1.11
normal mode	9	10	11	12	13	14	15	16
wavenumber (cm^{-1})	1111	1142	1152	1175	1284	1382	1428	1455
$\Delta_{VC}[\alpha]_D^{anh}$	−0.57	−0.04	−0.34	0.61	−0.71	−0.06	−0.58	0.08
$\Delta_{VC}[\alpha]_D^{harm}$	−0.17	−1.34	−0.45	−0.19	1.12	0.00	0.10	−0.47
normal mode	17	18	19	20	21	22	23	24
wavenumber (cm^{-1})	1471	1517	3030	3086	3097	3100	3122	3179
$\Delta_{VC}[\alpha]_D^{anh}$	−0.44	−0.25	0.33	0.91	0.34	−1.52	−0.73	0.31
$\Delta_{VC}[\alpha]_D^{harm}$	0.61	−0.64	−0.20	−0.20	0.01	−0.23	−0.80	1.21

Table 3. Specific Rotation of (R)-Methyloxirane in Various Solvents, with the Successive Inclusion of the Different Effects (See Text)

	H_2O	CH_3CN	acetone	benzene	CCl_4	cyclohexane
PCM	8.09	8.32	8.63	12.75	12.73	12.98
PCM+loc	9.57	9.87	10.26	14.92	14.75	14.87
$\Delta'_{VC}[\alpha]_D^{Eq}$	−3.34	−3.53	−3.48	−3.92	−3.87	−3.82
$\Delta'_{VC}[\alpha]_D^{NEq}$	−2.64	−2.72	−2.84	−4.03	−3.85	−3.76
$[\alpha]_D^{tot}$	6.93	7.15	7.42	10.89	10.91	11.11
$[\alpha]_D^{exp}$ (Ref. 35)	−4.3	6.0	8.2	30.6	18.7	11.9

vibrational components, while the bottom row contains the experimental data measured by Kumata et al.[35]

By looking in more detail at the data reported in Table 3, we first note that an excellent agreement between calculated and experimental data is obtained for acetonitrile, acetone, and cyclohexane, which actually have very different polarity. For these solvents, the PCM formalism, enriched by the inclusion of local field and nonequilibrium effects, provides a good description of the solvation of methyloxirane. Therefore, our purely electrostatic model is in such a case able to reproduce the dominating contributions to the solute−solvent interaction. A larger deviation is observed instead in the case of carbon tetrachloride; such findings are not unexpected due to the fact that we are using a purely electrostatic approach. In fact, in this case, the presence of the chlorine atoms generates a larger solvent polarizability, thus making dispersion and repulsion effects, utterly discarded in our model, more significant.

The agreement in the case of water and benzene is less satisfactory, but again such behavior is not unexpected. In fact, as has already been shown in refs 51 and 53, in the case of the OR of methyloxirane in water, most of the observed optical rotation arises from the solute−solvent clustering pattern that is formed thanks to the directional component of the hydrogen bonds. Therefore, in order to get quantitative agreement between calculations and experiments, an explicit treatment of the solvent molecules would be required. Mukhopadhyay et al.[52] have also shown that in the case of methyloxirane in benzene solution, most of the observed optical rotation is the result of the so-called chiral imprint, i.e., the chiral solute causes the solvation shell to arrange into a chiral configuration, which in turn sensitively contributes to the observed optical rotation. Similarly to water, the inclusion of explicit solvent molecules would be appropriate in this case.

To end the discussion on methyloxirane, in order to evaluate the performance of our method with respect to other approaches, we will compare our data with previously reported data. Notice that, among the many papers reporting the calculated specific rotation of methyloxirane, only a few include a treatment of solvation effects, and to the best of our knowledge, none of them include all of the solvation effects considered here. For the sake of comparison, two works have been chosen,[49,50] both exploiting continuum solvation approaches.

In Table 4, our calculated data (only the purely electronic contribution is reported) are compared with coupled cluster data[49] obtained by using a continuum solvation approach exploiting a spherical cavity. The geometry calculated for the isolated molecule is considered, and vibrational effects are discarded. CC2 data also neglect local field effects, whereas a Lorentz model is used for CCSD data.

Despite the indubitable quality of coupled cluster methods to describe electron correlation, the use of a less refined approach

Table 4. Comparison between Our OR Calculated Values (Purely Electronic Contribution) and Those Found by Kongsted et al.[49a]

method	water	acetone	benzene	CCl_4	cyclohexane	vacuo
CC2[49]	26.7	27.2	30.6	30.2	30.1	25.9
CCSD[49]	24.2	24.6	27.2	26.4	25.2	19.2
this work	9.57	10.26	14.92	14.75	14.87	15.07

[a]CC2 and CCSD values were obtained by using the aug-cc-pVDZ basis set for carbon, the aug-cc-pVTZ basis set for oxygen, and the d-aug-cc-pVDZ basis set for hydrogen. CCSD values were also corrected for the Lorentz local field effects.

for solvation effects does not improve the quality of the results with respect to their experimental counterparts (see Table 3). In particular, only a small solvent effect was predicted at the CCSD level while moving from one solvent to another. Larger solvent effects are reported at the CC2 level, although the calculated CC2 absolute values are generally significantly overestimated. Therefore, even increasing the quality of the description of the electronic Hamiltonian seems to be ineffective if solvent effects are not described by a sufficiently refined model. Still in the same context, our data are also generally in better agreement with experiments than the B3LYP/aug-cc-pVTZ/PCM data of Kongsted and Ruud[50] (see Table 5) obtained by exploiting a different definition of the

Table 5. Comparison between Our Calculated OR Values and Those Found by Kongsted et al.[50] at the B3LYP/aug-cc-PVTZ Level

	cyclohexane	CH_3CN	water	vacuo
ref 50	−3.8	−8.4	−8.5	−6.5
this work	11.1	7.2	6.9	12.7
exptl.[35]	11.9	6.0	−4.3	

PCM cavity in terms of shape and size. Also, local field effects and vibrational nonequilibria were not considered, and ZPVC was included through the effective geometry method. We note that the huge difference in terms of both magnitude and sign between our data and those of Kongsted and Ruud[50] is not simply due to a different choice of the basis set. In fact, if solvent−vacuum shifts are considered (see Table 6), a completely different estimation of solvent effects is reported.

Table 6. Comparison between Our Calculated Solvent Induced Shifts on OR (Solvent−Vacuum) and Those Found by Kongsted et al.[50] at the B3LYP/aug-cc-PVTZ Level

	cyclohexane	CH_3CN	water
ref 50	2.7	−1.9	−2.0
this work	−1.6	−5.5	−5.8

5. (S)-N-ACETYLPROLINE AMIDE

We have so far focused on a small rigid molecular system, i.e., a molecular system basically consisting of a single conformation. More often, chiroptical properties are measured for larger and conformationally flexible molecules[76] in the condensed phase. In these cases, the application of the method that we have presented in section 2 implies the evaluation of the properties, i.e., of the electronic and vibrational terms, on all of the accessible conformations for the system at the given temperature. Therefore, any spectroscopic study should be preceded by a conformational search on the potential energy surface of the solvated system. Such a conformational search is often not trivial, especially as the number of structural degrees of freedom increases. Even when the conformational search is completed, additional calculations of the property for each conformer are required, and the final property to be compared with the experiments is obtained by averaging the single values for each conformation weighted by the relevant Boltzmann populations for a given temperature.

In the case of solvated systems, the definition of the Boltzmann weights is not univocal. First, the definition of the conformer may not be straightforward, especially in the case of strongly interacting solute–solvent (or solute–solute) couples.[34,77] In this case, in fact, aggregation effects can apply, so that the problem is to decide where the solute ends and the solvent begins (or even which is the correct material system to be exploited to define the solute, i.e., a monomeric, dimeric, etc. moiety).[34,77−81] In addition, the evaluation of the Boltzmann weights requires the calculation of the (free) energies of the various conformations, which in the case of a solvated system should include not only terms related to the electrostatic solute–solvent interaction, but also nonelectrostatic contributions, such as dispersion, repulsion, and in the case of cavity-based continuum solvation models, cavitation effects: all of them can affect the final energy in different ways and can even be sensitively different for the various conformations.

In the line of such considerations, in this section, we will apply the method presented in section 2 to N-acetylproline amide (NAP; Figure 2), for which previous computational
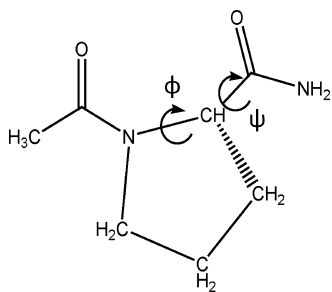
Figure 2. Schematic view of NAP with the indication of the φ and ψ conformational angles.

works have shown PCM to be able to correctly describe its spectroscopic properties both in water and in apolar solvents.[69,71,82]

As has been previously reported in the literature,[43,69,83−85] NAP can exist in three different conformations, named C_7, 3_{10}, and PII (see Figure 3), whose relative Boltzmann populations can radically differ depending on the nature of the surrounding environment, the level of treatment of nonelectrostatic interactions, and the size of the PCM molecular cavity.[69,71,82]
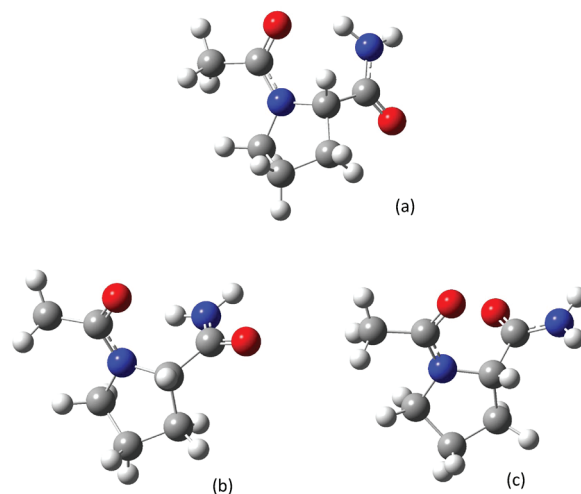
Figure 3. NAP in the three conformations considered here. (a) C_7 (ϕ = −82°, ψ = 75°); (b) 3_{10} helix I (ϕ = −71°, ψ = −27°); (c) PII (ϕ = −63°, ψ = 146°).

In our calculations, we weighted the different conformations by using the Boltzmann weights employed by Cappelli and Mennucci[69] for their calculations: 99% C_7 and 1% 3_{10} in cyclohexane and 4% C_7, 28% 3_{10}, and 68% PII in water.

In Table 7, we report the calculated specific rotation of NAP in water and cyclohexane, divided into its electronic and vibrational components, for every conformation that is stable in each solvent. The total, harmonic, and anharmonic vibrational corrections are shown, and all are evaluated at T = 300 K. It can be seen from the table that, contrary to the case of methyloxirane, the electronic component of the specific rotation does not significantly change with the solvent for the C_7 conformation, going from −4735.0 in water to −4735.7 in cyclohexane, whereas we witness a more significant change for the 3_{10} conformation, going from −1613.3 in water to −1786.9 in cyclohexane (the PII conformation is not stable in cyclohexane). There is however a very pronounced difference between the electronic component of the OR evaluated for the C_7 conformation and that calculated for the remaining two conformers.

The total vibrational corrections (VC) depend strongly on the respective conformation: for NAP in water, the VC is 2.6% of the electronic component for the C_7 conformation, 6.6% for the 3_{10} conformation, and 12.7% for the PII conformation. These findings reinforce the idea that the VC must be calculated for every conformer when dealing with conformationally flexible molecules, for their importance with respect to the electronic component may change significantly, while still remaining a relevant component of the total calculated specific rotation. Table 7 also reveals that in the case of NAP it is particularly significant to include both the harmonic and anharmonic components in the calculation of the vibrational corrections: for the C_7 conformation in cyclohexane, the harmonic component is −738.5, while the anharmonic component is +664.1. Thus, they are similar in magnitude but opposite in sign; therefore keeping only the harmonic part would cause a huge error in the evaluation of the VC.

The total calculated specific rotation of NAP at 280 nm is −1976.1 in water and −4781.9 in cyclohexane. The very large difference between the two values is mainly the result of the conformational effect: in cyclohexane, the C_7 conformation,

Table 7. Calculated Specific Rotation for NAP in Water and Cyclohexane at λ = 280 nm[a]

	C$_7$		3$_{10}$		PII		tot
	El	VC	El	VC	El	VC	$[\alpha]$
water	−4735.0	−120.5	−1613.3	−106.6	−1698.1	−214.0	−1976.1
(a)		−496.9		−128.5		−153.0	
(b)		376.4		21.8		−61.1	
Cyc	−4735.7	−74.4	−1786.9	−211.7			−4781.9
(a)		−738.5		−305.7			
(b)		664.1		94.0			

[a]Electronic and vibrational contributions are given. (a) harmonic VC; (b) anharmonic VC.
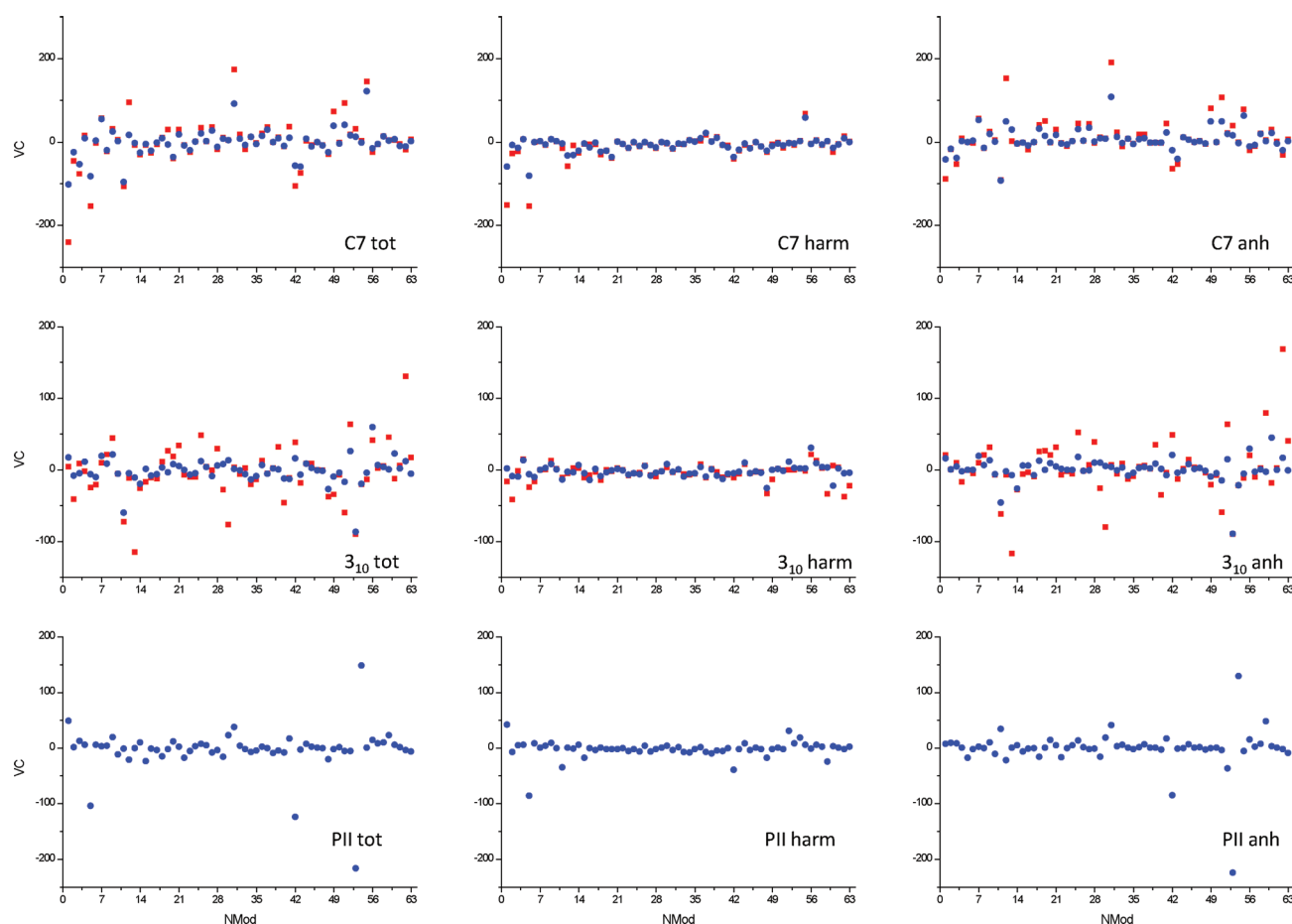

Figure 4. Total, harmonic, and anharmonic vibrational correction to the three NAP conformations in cyclohexane (red, square) and water (blue, circle).

with its intramolecular hydrogen bond, is by far the most populated, and as already stated, its calculated optical rotation is very much different from that arising from the other two conformations. In water, the situation is reversed, and the 3$_{10}$ and PII conformations become the most populated, thus causing the OR to change.

The three conformations also have very different vibrational corrections, but by looking at the vibrational contribution from each normal mode, some common features appear. In Figure 4, we report the vibrational correction pertaining to each of the 63 normal modes of NAP, split into its harmonic and anharmonic components, for the three conformers. All modes appear to give a substantial contribution to the total VC; therefore, it would be inappropriate to include only some of them in the calculation. Moreover, the relative magnitude of the VC for the

different modes changes when changing conformations, and so does the total VC as well.

Some normal modes give rise to a much more substantial contribution than others. The low energy torsional movements of the amide group bound to the stereogenic center and the methyl group (normal modes 1 and 5 for the C$_7$ and PII conformations and 2 and 5 for the 3$_{10}$ conformation) generally give rise to a strong harmonic contribution to the VC, while the normal modes that give a stronger anharmonic contribution are those involving the stretching and bending of the amidic hydrogen atoms and the hydrogen atom bound to the stereogenic center (normal modes 11, 31, 42, and 55 for the C$_7$ conformation; 11, 30, 42, and 51 for the 3$_{10}$ conformation; and 11, 31, 42, and 53 for the PII conformation). When changing the solvent from cyclohexane to water, the vibrational

corrections for each normal mode become smaller, even though the total vibrational correction rises.

To end the discussion on NAP, it is worth comparing our findings with the data of Madison and Schellman,[86] who have measured the ORD of NAP in water and cyclohexane between 190 and 290 nm at 300 K. We apply our method to the calculation of the ORD of NAP in those same solvents and in the same frequency interval. The ORD calculation has been performed point-wise, with an interval of 10 nm, and the vibrational corrections are calculated at a temperature $T = 300$ K to reflect the experimental conditions.

Our analysis reveals the presence of numerous resonant frequencies between 190 and 220 nm for NAP in water and between 190 and 230 nm for NAP in cyclohexane, which lead to a diverging specific rotation; therefore, we will only consider the results obtained in the interval between 240 and 290 nm (see Figure 5).
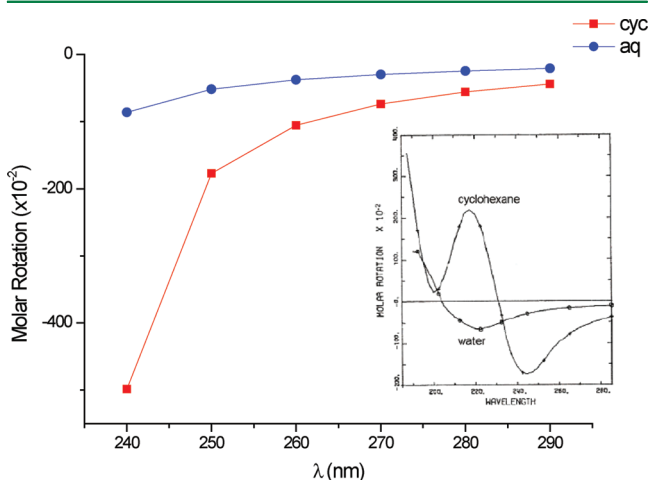

Figure 5. Calculated molar rotation as a function of the frequency of NAP in cyclohexane and water solution. Experimental findings taken from ref 86 are shown in the inset.

The calculations in cyclohexane exhibit excellent agreement with the experimental data from 290 to 250 nm; then, the calculated values start to drop as they approach the vertical asymptote, whereas the experimental curve shows a change of sign due to the Cotton effect. Computations in water also show very good agreement with the experimental data, even though they seem to be slightly overestimating the ORD. In the case of water, the resonant frequency is further away, so the graph does not seem to tend to $-\infty$ in the shown frequency interval. It is evident that the PCM performs very well, even though it does not treat the directional component of the hydrogen bonds that are surely present in the NAP−water system and, as already mentioned above, that is mainly due to the fact that here the solvent effects are dominated by conformational changes induced by the solvent. Therefore, the very good agreement between calculated and experimental values in this case is to be ascribed to the fact that the PCM describes very well the electrostatic component of solvation, which seems to be the dominant contribution in determining the relative weights of the different conformations in both solvents.

6. SUMMARY, CONCLUSIONS, AND FUTURE DIRECTIONS

In this paper, we have presented a newly implemented methodology to evaluate the vibrational contributions (harmonic and anharmonic) to the OR of solvated systems described by means of the PCM. In particular, we have focused on the development of a method to properly account for an incomplete solvation regime in the treatment of both the electronic property and the molecular vibrations, as well as on the inclusion of cavity field effects. These features substantially increase the quality of the models for the OR of solvated systems available so far in the literature, giving rise to a better description of the physics behind the phenomenon.

The results reported for both (R)-methyloxirane and (S)-N-acetylproline amide confirm that the vibrational correction constitutes a substantial part of the total OR and that it cannot be neglected if accurate values are to be obtained. In particular, the harmonic and anharmonic contributions are comparable in magnitude, and in some cases they are of different sign, so that limitation to the first one seems to be arbitrary. Furthermore, although some modes give huge VCs, it may be inappropriate to limit the calculation to these modes only, because the combination of the VCs arising from the other vibrational modes may still be very significant and give a total contribution comparable to that of the dominating modes. This is a relevant computational issue in the case of large molecules: in fact, in this case, the anharmonic calculations can be very cumbersome, so that the possibility of limiting the anharmonic analysis to a few modes only would be beneficial. From the data we have reported, that seems to not be viable.

Another conclusion which can be drawn is that, by keeping as a reference the calculation in vacuo, solvent effects can be as large as the OR itself, and therefore they cannot be discarded in the modeling. Such solvent effects can arise from various sources, also depending on the nature of the solute−solvent couple. In fact, not only purely direct and indirect effects are relevant, but also a considerable contribution (about 20−30% of the total calculated OR) originates from cavity field and vibrational nonequilibrium effects. The solvent-induced changes in the conformational preference of flexible molecules can even be more relevant, and totally different OR values can originate from the various conformations. In such cases, not only a physically meaningful description of the OR of each conformation in solution is to be achieved but also a correct quantitative description of the PES minima is necessary.

It is also worth noting that from our study it appears clearly that vibrational and solvent effects are not additive; i.e., that in order to reach a more physical description of the phenomenon and to better reproduce experimental values in solution, it is not sufficient to account for the solvent effects on the electronic component of the OR but, because of their nonlinear nature, it is necessary to include them in the evaluation of the vibrational corrections as well.

Two issues have not been considered in this work but would surely deserve a close investigation in future works, i.e., the extension of our model to cases where aggregation effects dominate the solvation phenomenon and, in addition, in this work nonelectrostatic contributions have only been taken into account in the evaluation of conformational preferences, whereas a coherent physical modeling would also call for them in the evaluation of the response properties.

■ **AUTHOR INFORMATION**

Corresponding Author

*E-mail: chiara.cappelli@sns.it.

Notes

The authors declare no competing financial interest.

■ **REFERENCES**

(1) Djerassi, C. *Optical Rotatory Dispersion*; McGraw-Hill Book Company: New York, 1960.

(2) Polavarapu, P. L. Optical Rotation: Recent Advances in Determining the Absolute Configuration. *Chirality* **2002**, *14*, 768−781.

(3) Stephens, P. J.; McCann, D. M.; Cheeseman, J. R.; Frish, M. J. Determination of Absolute Configurations of Chiral Molecules Using Ab Initio Time-Dependent Density Functional Theory Calculations of Optical Rotation: How Reliable Are Absolute Configurations Obtained for Molecules With Small Rotations? *Chirality* **2005**, *17*, S52−S64.

(4) Pecul, M.; Ruud, K. The Ab Initio Calculation of Optical Rotation and Electronic Circular Dichroism. *Adv. Quantum Chem.* **2005**, *50*, 185−212.

(5) Crawford, D. T.; Tam, M. C.; Abrams, M. L. The Current State of Ab Initio Calculations of Optical Rotation and Electronic Circular Dichroism Spectra. *J. Phys. Chem. A* **2007**, *111*, 12057−12078.

(6) Ruud, K.; Thorvaldsen, A. J. Theoretical Approaches to the Calculation of Raman Optical Activity Spectra. *Chirality* **2009**, *21*, E54−E57.

(7) Autschbach, J. Computing Chiroptical Properties with First-Principles Theoretical Methods: Background and Illustrative Examples. *Chirality* **2009**, *21*, E116−E152.

(8) Barron, L. D.; Buckingham, D. A. Vibrational Optical Activity. *Chem. Phys. Lett.* **2010**, *492*, 199−213.

(9) Polavarapu, P. L. Renaissance in Chiroptical Spectroscopic Methods for Molecular Structure Determination. *Chem. Rec.* **2007**, *7*, 125−136.

(10) Hansen, A. E.; Bouman, T. D. Natural Chiroptical Spectroscopy: Theory and Computations. *Adv. Chem. Phys.* **1980**, *44*, 545−644.

(11) Jørgensen, P.; Simons, J. *Second quantization-based methods in quantum chemistry*; Academic: New York, 1981.

(12) Polavarapu, P. L. Ab initio molecular optical rotations and absolute configurations. *Mol. Phys.* **1997**, *91*, 551−554.

(13) Polavarapu, P. L.; Chakraborty, D. K. Absolute Stereochemistry of Chiral Molecules from ab Initio Theoretical and Experimental Molecular Optical Rotations. *J. Am. Chem. Soc.* **1998**, *120*, 6160−6164.

(14) Polavarapu, P. L.; Chakraborty, D. K. Ab initio molecular theoretical optical rotations of small molecules. *Chem. Phys.* **1999**, *240*, 1−8.

(15) Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J.; Mennucci, B.; Tomasi, J. Prediction of optical rotation using density functional theory. *Tetrahedron: Asymmetry* **2000**, *11*, 2443−2448.

(16) Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J. Calculation of Optical Rotation Using Density Functional Theory. *J. Phys. Chem. A* **2001**, *105*, 5356−5371.

(17) Ruud, K.; Helgaker, T. Optical rotation studied by density-functional and coupled-cluster methods. *Chem. Phys. Lett.* **2002**, *352*, 533−539.

(18) Pedersen, T. B.; Koch, H.; Boman, L.; de Merás, A. M. S. Origin invariant calculation of optical rotation without recourse to London orbitals. *Chem. Phys. Lett.* **2004**, *393*, 319−326.

(19) Norman, P.; Ruud, K.; Helgaker, T. Density-functional theory calculations of optical rotatory dispersion in the nonresonant and resonant frequency regions. *J. Chem. Phys.* **2004**, *120*, 5027−5035.

(20) Tam, M. C.; Russ, N. J.; Crawford, D. T. Coupled Cluster Calculations of optical rotatory dispersion of (S)-methyloxirane. *J. Chem. Phys.* **2004**, *121*, 3550−3557.

(21) Cheeseman, J. R.; Frisch, M. J.; Devlin, F. J.; Stephens, P. J. Hartree-Fock and Density Functional Theory ab Initio Calculation of Optical Rotation Using GIAOs: Basis Set Dependence. *J. Phys. Chem. A* **2000**, *104*, 1039−1046.

(22) Campos, C. T.; Jorge, F. E.; Silva, T. P.; Coppo, M. Basis set convergence on optical rotation DFT calculations. *Chem. Phys. Lett.* **2010**, *494*, 170−173.

(23) Ruud, K.; Taylor, P. R.; Astrand, P.-O. Zero-point vibrational effects on optical rotation. *Chem. Phys. Lett.* **2001**, *337*, 217−223.

(24) Ruud, K.; Zanasi, R. The Importance of Molecular Vibrations: The Sign Change of the Optical Rotation of Methyloxirane. *Angew. Chem., Int. Ed.* **2005**, *44*, 3594−3596.

(25) Kongsted, J.; Pedersen, T. B.; Jensen, L.; Hansen, A. E.; Mikkelsen, K. V. Coupled Cluster and Density Functional Theory Studies of the Vibrational Contribution to the Optical Rotation of (S)-Propylene Oxide. *J. Am. Chem. Soc.* **2006**, *128*, 976−982.

(26) Mort, B. C.; Autschbach, J. Magnitude of Zero-Point Vibrational Corrections of Optical Rotation in Rigid Organic Molecules. *J. Phys. Chem. A* **2005**, *109*, 8617−8623.

(27) Mort, B. C.; Autschbach, J. Temperature Dependence of the Optical Rotation of Fenchone Calculated by Vibrational Averaging. *J. Phys. Chem. A* **2006**, *110*, 11381−11383.

(28) Mort, B. C.; Autschbach, J. Temperature Dependence of HD Spin-Spin Coupling Constants of Heavy Metal Hydride and Dihydrogen Complexes Calculated by Vibrational Averaging. *J. Am. Chem. Soc.* **2006**, *128*, 10060−10072.

(29) Mort, B. C.; Autschbach, J. A Pragmatic Recipe for the Treatment of Hindered Rotations in the Vibrational Averaging of Molecular Properties. *ChemPhysChem* **2008**, *9*, 159−170.

(30) Šebestík, J.; Bouř, P. Raman Optical Activity of Methyloxirane Gas and Liquid. *J. Phys. Chem. Lett.* **2011**, *2*, 498−502.

(31) Müller, T.; Wiberg, K. B.; Vaccaro, P. H. Cavity Ring-Down Polarimetry (CRDP): A New Scheme for Probing Circular Birefringence and Circular Dichroism in the Gas Phase. *J. Phys. Chem. A* **2000**, *104*, 5959−5968.

(32) Wilson, S. M.; Wiberg, K. B.; Murphy, M. J.; Vaccaro, P. H. The Effects of Conformation and Solvation on Optical Rotation: Substituted Epoxides. *Chirality* **2008**, *20*, 357−369.

(33) Eliel, E. L.; Wilen, S. H.; Doyle, M. P. *Basic Organic Stereochemistry*; Wiley Interscience: New York, 2001.

(34) Cappelli, C.; Corni, S.; Mennucci, B.; Cammi, R.; Tomasi, J. Vibrational Circular Dichroism within the Polarizable Continuum Model. *J. Phys. Chem. A* **2002**, *106*, 12331−12339.

(35) Kumata, Y.; Furukawa, J.; Fueno, T. The Effect of Solvents on the Optical Rotation of Propylene Oxide. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3920−3921.

(36) Mennucci, B.; Cappelli, C.; Cammi, R.; Tomasi, J. Modeling Solvent Effects on Chiroptical Properties. *Chirality* **2011**, *23*, 717−729.

(37) Rosenfeld, L. Quantenmechanische Theorie der natürlichen optischen Aktivität von Flüssigkeiten und Gasen. *Z. Phys.* **1928**, *52*, 161−174.

(38) Onsager, L. Electric Moments of Molecules in Liquids. *J. Am. Chem. Soc.* **1936**, *58*, 1486−1493.

(39) Moffitt, W.; Moscowitz, A. Optical Activity in Absorbing Media. *J. Chem. Phys.* **1959**, *30*, 648−660.

(40) Moscowitz, A.; Charney, E.; Weiss, U.; Ziffer, H. Optical Activity in Absorbing Media. *J. Am. Chem. Soc.* **1961**, *83*, 4661−4663.

(41) Tomasi, J.; Persico, M. Molecular Interactions in Solution: An Overview of Methods Based on Continuous Distributions of the Solvent. *Chem. Rev.* **1994**, *94*, 2027−2094.

(42) Cramer, C. J.; Truhlar, D. G. Implicit Solvation Models: Equilibria, Structure, Spectra, and Dynamics. *Chem. Rev.* **1999**, *99*, 2161−2200.

(43) Cossi, M.; Scalmani, G.; Rega, N.; Barone, V. New developments in the polarizable continuum model for quantum mechanical and classical calculations on molecules in solution. *J. Chem. Phys.* **2002**, *117*, 43−54.

(44) Scalmani, G.; Barone, V.; Kudin, K. N.; Pomelli, C. S.; Scuseria, G. E.; Frisch, M. J. Achieving linear-scaling computational cost for the polarizable continuum model of solvation. *Theor. Chem. Acc.* **2004**, *111*, 90−100.

(45) Tomasi, J.; Mennucci, B.; Cammi, R. Quantum Mechanical Continuum Solvation Models. *Chem. Rev.* **2005**, *105*, 2999−3093.

(46) Scalmani, G.; Frisch, M. J. Continuous surface charge polarizable continuum models of solvation. I. General formalism. *J. Chem. Phys.* **2010**, *132*, 114110−114114.

(47) Mennucci, B.; Tomasi, J.; Cammi, R.; Cheeseman, J. R.; Frisch, M. J.; Devlin, F. J.; Gabriel, S.; Stephens, P. J. Polarizable Continuum Model (PCM): Calculations of Solvent Effects on Optical Rotations of Chiral Molecules. *J. Phys. Chem. A* **2002**, *106*, 6102−6113.

(48) Cappelli, C. Continuum Solvation Approaches to Vibrational Properties In *Continuum Solvation Models inChemical Physics: Theory and Applications*; Mennucci, B., Cammi, R., Eds.; Wiley: Chichester, U. K., 2007; pp 167−179.

(49) Kongsted, J.; Pedersen, T. B.; Strange, M.; Osted, A.; Hansen, A. E.; Mikkelsen, K. V.; Pawlowski, P.; Jørgensen, P.; Hättig, C. Coupled Cluster Calculations of the optical rotation of *S*-propylene oxide in gas phase and solution. *Chem. Phys. Lett.* **2005**, *401*, 976−982.

(50) Kongsted, J.; Ruud, K. Solvent effects on zero-point vibrational corrections to optical rotations and nuclear magnetic resonance shielding constants. *Chem. Phys. Lett.* **2008**, *451*, 226−232.

(51) Mukhopadhyay, P.; Zuber, G.; Goldsmith, M.-R.; Wipf, P.; Beratan, D. N. Solvent Effect on Optical Rotation: A Case Study of Methyloxirane in Water. *ChemPhysChem.* **2006**, *7*, 2483−2486.

(52) Mukhopadhyay, P.; Zuber, G.; Wipf, P.; Beratan, D. N. Contribution of a Solute's Chiral Solvent Imprint to Optical Rotation. *Angew. Chem., Int. Ed.* **2007**, *46*, 6450−6452.

(53) Losada, M.; Nguyen, P.; Xu, Y. Solvation of Propylene Oxide in Water: Vibrational Circular Dichroism, Optical Rotation, and Computer Simulation Studies. *J. Phys. Chem. A* **2008**, *112*, 5621−5627.

(54) Cammi, R.; Cappelli, C.; Corni, S.; Tomasi, J. On the Calculation of Infrared Intensities in Solution within the Polarizable Continuum Model. *J. Phys. Chem. A* **2000**, *104*, 9874−9879.

(55) Mennucci, B.; Cammi, R.; Tomasi, J. Excited states and solvatochromic shifts within a nonequilibrium solvation approach. *J. Chem. Phys.* **1998**, *109*, 2798−2807.

(56) Cappelli, C.; Corni, S.; Cammi, R.; Mennucci, B.; Tomasi, J. Nonequilibrium formulation of infrared frequencies and intensities in solution. *J. Chem. Phys.* **2000**, *113*, 11270−11279.

(57) Cappelli, C.; Lipparini, F.; Bloino, J.; Barone, V. Towards an accurate description of anharmonic infrared spectra in solution within the polarizable continuum model: Reaction field, cavity field and nonequilibrium effects. *J. Chem. Phys.* **2011**, *135*, 104505−104514.

(58) Barron, L. *Molecular Light Scattering and Optical Activity*, 2nd ed.; Cambridge University Press: New York, 2004; pp 123−169.

(59) McWeeny, R. *Methods of Molecular Quantum Mechanics*, 2nd ed.; Academic Press: New York, 1992.

(60) Autschbach, J. Time-Dependent Density Functional Theory for Calculating Origin-Independent Optical Rotation and Rotatory Strength Tensors. *ChemPhysChem.* **2011**, *12*, 3224−3235.

(61) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.;Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.;Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision A.02; Gaussian, Inc.: Wallingford, CT, 2009.

(62) Barone, V. Accurate Vibrational Spectra of Large Molecules by Density Functional Computations beyond the Harmonic Approximation: The Case of Azabenzenes. *J. Phys. Chem. A* **2004**, *108*, 4146−4150.

(63) Barone, V. Anharmonic vibrational properties by a fully automated second-order perturbative approach. *J. Chem. Phys.* **2005**, *122*, 014108−014117.

(64) Miertus, Š.; Scrocco, E.; Tomasi, J. Electrostatic interaction of a solute with a continuum. *Chem. Phys.* **1981**, *55*, 117−129.

(65) Pipolo, S.; Cammi, R.; Rizzo, A.; Cappelli, C.; Mennucci, B.; Tomasi, J. Cavity field effects within a polarizable continuum model of solvation: application to the calculation of electronic circular dichroism spectra of R-(+)-3-Methyl-cyclopentanone. *Int. J. Quantum Chem.* **2011**, *111*, 826−838.

(66) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B* **1988**, *37*, 785−789.

(67) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. Results obtained with the correlation energy density functionals of Becke and Lee, Yang, Parr. *Chem. Phys. Lett.* **1989**, *157*, 200−206.

(68) Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys.* **1993**, *98*, 5648−5652.

(69) Cappelli, C.; Mennucci, B. Modeling the Solvation of Peptides. The Case of (*S*)-N-Acetylproline Amide in Liquid Water. *J. Phys. Chem. B* **2008**, *112*, 3441−3450.

(70) Cappelli, C.; Monti, S.; Scalmani, G.; Barone, V. On the Calculation of Vibrational Frequencies for Molecules in Solution Beyond the Harmonic Approximation. *J. Chem. Theory Comput.* **2010**, *6*, 1660−1669.

(71) Biancardi, A.; Cappelli, C.; Mennucci, B.; Cammi, R. Toward a Quantum-Mechanical Description of 2D-IR Spectra of Solvated Systems. *J. Phys. Chem. B* **2010**, *114*, 4924−4930.

(72) Wiberg, K. B.; gui Wang, Y.; Vaccaro, P. H.; Cheeseman, J. R.; Trucks, G.; Frisch, M. J. Optical Activity of 1-Butene, Butane, and Related Hydrocarbons. *J. Phys. Chem. A* **2004**, *108*, 32−38.

(73) Srebro, M.; Govind, N.; de Jong, W. A.; Autschbach, J. Optical Rotation Calculated with Time-Dependent Density Functional Theory: The OR45 Benchmark. *J. Phys. Chem. A* **2011**, *115*, 10930−10949.

(74) Ditchfield, R. Self-consistent perturbation theory of diamagnetism. *Mol. Phys.* **1974**, *27*, 789−807.

(75) Wiberg, K. B.; Vaccaro, P. H.; Cheeseman, J. R. Conformational Effects on Optical Rotation. 3-Substituted 1-Butenes. *J. Am. Chem. Soc.* **2003**, *125*, 1888−1896.

(76) Crawford, D. T.; Allen, W. D. Optical activity in conformationally flexible molecules: a theoretical study of large-amplitude vibrational averaging in (R)-3-chloro-1-butene. *Mol. Phys.* **2009**, *107*, 1041−1057.

(77) Cappelli, C.; Mennucci, B.; da Silva, C. O.; Tomasi, J. Refinements on solvation continuum models: Hydrogen-bond effects on the OH stretch in liquid water and methanol. *J. Chem. Phys.* **2000**, *112*, 5382−5392.

(78) Rega, N.; Cossi, M.; Barone, V. Intrinsic and Environmental Effects in the Structure and Magnetic Properties of Glycine Radical in Aqueous Solution. *J. Am. Chem. Soc.* **1997**, *119*, 12962−12967.

(79) Rega, N.; Cossi, M.; Barone, V. Structure and Magnetic Properties of Glycine Radical in Aqueous Solution at Different pH Values. *J. Am. Chem. Soc.* **1998**, *120*, 5723−5732.

(80) Cappelli, C.; Mennucci, B.; Monti, S. Environmental Effects on the Spectroscopic Properties of Gallic Acid: A Combined Classical and Quantum Mechanical Study. *J. Phys. Chem. A* **2005**, *109*, 1933−1943.

(81) Barone, V.; Improta, R.; Rega, N. Quantum Mechanical Computations and Spectroscopy: From Small Rigid Molecules in the Gas Phase to Large Flexible Molecules in Solution. *Acc. Chem. Res.* **2008**, *41*, 605−616.

(82) Cappelli, C.; Monti, S.; Scalmani, G.; Barone, V. On the Calculation of Vibrational Frequencies for Molecules in Solution Beyond the Harmonic Approximation. *J. Chem. Theory Comput.* **2010**, *6*, 1660−1669.

(83) Hahn, S.; Lee, H.; Cho, M. Theoretical calculations of infrared absorption, vibrational circular dichroism, and two-dimensional vibrational spectra of acetylproline in liquids water and chloroform. *J. Chem. Phys.* **2004**, *121*, 1849−1865.

(84) Lee, K.-K.; Hahn, S.; Oh, K.-I.; Choi, J. S.; Joo, C.; Lee, H.; Han, H.; Cho, M. Structure of N-Acetylproline Amide in Liquid Water: Experimentally Measured and Numerically Simulated Infrared and Vibrational Circular Dichroism Spectra. *J. Phys. Chem. B* **2006**, *110*, 18834−18843.

(85) Hahn, S.; Lee, H.; Cho, M. Site-Specific Hydrogen-Bonding Interaction between N-Acetylproline Amide and Protic Solvent Molecules: Comparisons of IR and VCD Measurements with MD Simulations. *J. Phys. Chem. B* **2006**, *110*, 13355−13365.

(86) Madison, V.; Schellman, J. Location of proline derivatives in conformational space. *Biopolymers* **1970**, *9*, 511−588.