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Calculation of the optical rotatory dispersion of solvated alanine by means of the perturbed matrix method

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Abstract

The zwitterionic form of aqueous L-alanine is chosen as a benchmark for the theoretical evaluation of the optical rotatory dispersion (ORD) in solution, as provided by a simple application of the perturbed matrix method (PMM). Results show the applicability of this procedure, suggesting that its use might provide a general theoretical-computational tool for describing, at atomic–molecular level, the optical activity of a molecule in a complex environment.

1. Introduction

The optical activity is a chemical–physical property of paramount fundamental and practical importance, originating from the interaction of light with chiral molecules. For many years this property has been extensively studied because of its key role in many areas of chemistry and biochemistry, such as enanthioselective synthesis and the determination of secondary structure of bio-macromolecules. More recently the deep understanding and modelling of this property is becoming of central importance as the recent advances in time-resolved circular dichroism (CD), able to follow folding kinetics, represent one of the most exciting perspective in protein folding area [1]. From a computational viewpoint the optical rotation as a function of the wavelength, optical rotatory dispersion (ORD), is typically the optical property modeled as it is simpler than CD to be calculated and provides equivalent information [2]. Modelling of ORD in vacuo can be carried out, nowadays, in a relatively straightforward way with a reasonable accuracy by using well established quantum chemical procedures [3,4]. On the other hand, the calculation of this property for a molecule embedded in a complex environment is much more problematic. At the best of our knowledge the only attempts in this direction have been performed both by mimicking the solvent with a homogeneous dielectric [5] and by a statistical sampling, via molecular dynamics (MD) simulations, of a predefined interaction Hamiltonian constructed in the unperturbed conditions [6], i.e., neglecting any electron density modification due to the environment. We have recently proposed a theoretical-computational method, the perturbed matrix method (PMM), which takes into account the atomic environment and is specifically designed for evaluating the electronic properties of a quantum center (QC) within a complex molecular system [7]. This method showed its reliability and accuracy in the calculation of absorption spectra of different molecular systems, ranging from small solutes [8] to chromophores in large biomacromolecules [9] in aqueous solution, as well as to describe chemical reactions [10]. In this work, we show how to obtain ORD spectra of solvated molecules as a

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straightforward application of PMM combined with MD, using the aqueous L-alanine in its zwitterionic state, as a test case.

2. Results

PMM is described in previous Letters [7,11,8] and in this Letter, we only show how to obtain ORD spectra. In this method, a portion of a complex molecular system, the quantum center, is treated quantum-mechanically with the rest of the system, e.g., the solvent and/or the protein, described as a semi-classical atomic environment and providing the perturbation. In practice, we calculate the unperturbed Hamiltonian matrix by ab initio calculations and, then, a molecular dynamics simulation is used to obtain a 'time-sequence' of the perturbing electric potential and field acting on the QC, to be used to construct the perturbed Hamiltonian matrix in time. Finally, diagonalisation of the perturbed Hamiltonian matrix $\tilde{H}$ at each MD frame, provides a 'trajectory' of QC perturbed eigenvalues (ϵ_i) and eigenvectors ($\boldsymbol{c}_i$) and, therefore, of whatever perturbed electronic property given by the generic operator $\hat{a}$ and expressed by the corresponding matrix $\tilde{a}$:

$$[\tilde{a}]_{i,j} = \boldsymbol{c}_i^{*T} \tilde{a}^0 \boldsymbol{c}_j, \tag{1}$$

$$[\tilde{a}^0]_{l,l'} = \langle \Phi_l^0 | \hat{a} | \Phi_{l'}^0 \rangle, \tag{2}$$

where $\tilde{a}^0$ represents the observable $\hat{a}$ in the unperturbed basis set defined by Φ_l^0 (the unperturbed Hamiltonian eigenfunctions). The theoretical quantity pertinent to optical activity is the light rotation angle per molecule (in the volume unit) and per unit of length of the medium passed by the incident light [12]

$$\frac{\Delta\theta}{\mathcal{N}d} = \frac{\mu_0}{3\hbar} \sum_{l=1}^{n} \frac{w^2}{w^2 - w_{0,l}^2} \mathrm{Im}\{\langle \Phi_0 \mid \hat{\boldsymbol{\mu}} \mid \Phi_l \rangle \cdot \langle \Phi_l \mid \hat{\boldsymbol{m}} \mid \Phi_0 \rangle\}, \tag{3}$$

where $\hat{\boldsymbol{\mu}}$ and $\hat{\mathbf{m}}$ are the electric and magnetic moment operators, Φ_l represents the lth (perturbed or unperturbed) electronic eigenfunction, $w_{0,l}$, w are the frequencies of lth excitation (from the ground state) and of the incident radiation, respectively, μ_0 is the vacuo magnetic permeability, $\mathcal{N}$ is the number of the optical active (solute) molecules in the volume unit, d is the length passed by the incident light and $\Delta\theta$ is the rotation angle of the polarized light due to the optical activity of the medium. Moreover n provides the total number of excited states used in the calculation, which should tend to infinity to obtain exact results; in practice such a number is finite and possibly small, according to the convergence of the sum in Eq. (3). From $\Delta\theta$ and the solute molecular mass M, it is straightforward to obtain the specific rotation $[\alpha] = \Delta\theta(\mathcal{N}dM)$ in deg/[dm(g/cm^3)], typically used to express the ORD data. We calculated $[\alpha]$ for both the isolated (unperturbed) and aqueous L-alanine in its zwitterionic form, using for the latter the perturbed energies and transition moments obtained, via Eqs. (1) and (2), by PMM and MD. The unperturbed properties (i.e., excitation energies, electric and magnetic moments) were obtained by DALTON [13] (CASSCF method, 10 electrons in 11 orbitals) and GAUSSIAN [14,15] (time dependent density functional theory, TD-DFT [16], method, B3-LYP [17,18] functional) software packages, using in both cases 6-311++G** atomic basis set. Such calculations were performed on the vacuo energy minimized structure which resulted, from molecular dynamics simulation, as very close to virtually all the accessible alanine configurations. Hence, unperturbed quantum chemical calculations on other alanine structures were disregarded. The classical molecular dynamics simulation was performed with the aid of GROMACS software package [19] in the NVT ensemble, using a box with 256 water molecules (SPC model [20]) plus an alanine molecule with roto-translational constraints [21], at the typical liquid water density (55.32 mol/l). Note that for the alanine molecule all the intramolecular degrees of freedom, except for the bond lengths constrained by LINCS [22], have been explicitly included in the simulation. The Gromos96 force field was used, the time length of the simulation was 25 ns with a time step of 2 fs and the temperature was kept fixed at 300 K by the isokinetic temperature coupling [23]. Finally, long range electrostatic interactions (beyond 0.9 nm radius) were treated by particle mesh Ewald (PME) method, as implemented in GROMACS. The possible gauge dependence of the magnetic moments was tested comparing the results obtained with London and non-London orbitals (the former should provide gauge independent results), and no relevant differences were observed. In Fig. 1, we show the unperturbed alanine ORD values (given by $[\alpha]$) at the sodium D-line wavelength (589 nm), as a function of the increasing number of excited states used in Eq. (3). We compare results obtained by both ab initio methods, CASSCF and TD-DFT, involving up to sixteen excited states. From the figure it is clear that only TD-DFT seems to converge, with a final value of $-34°$ rather close to the corresponding linear response theory [24] one ($-17°$) obtained by GAUSSIAN software package. This latter procedure, commonly employed for ORD calculations, circumvents the direct calculation of the sum of Eq. (3) and it is considered as a reasonably reliable method. CASSCF calculations provide $[\alpha]$ values which are clearly unstable and, when all the sixteen excited states are included, give a specific rotation (about $-660°$) which does not match the corresponding linear response theory value ($-28°$) obtained by DALTON software package. The unstable CASSCF ORD values are probably due to the limited active space (11 orbitals) used, which results in rather inaccurate

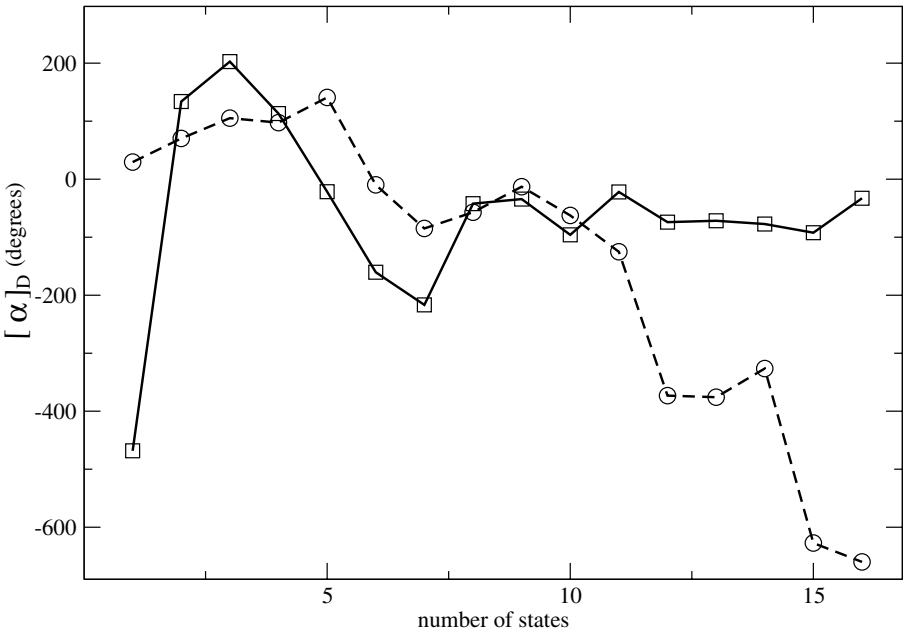

Fig. 1. The vacuum (unperturbed) values of the L-alanine optical activity at 589 nm ($[\alpha]_D$) as calculated using up to the first sixteen excited states. Dashed line and circles = CASSCF, solid line and squares = TD-DFT.

electric and (especially) magnetic transition moments for high electronic excitations necessary for $[\alpha]$ to converge. TD-DFT, on the other hand, although probably less accurate for the first excitations, can provide a rather stable and reliable procedure also for highly excited states, hence allowing for a possible convergence. The use of further TD-DFT excited states, although possible and for a few higher energy excitations tested still providing relatively stable ORD values (data not shown), it is very likely to introduce only noise because of the unreliability of the transition magnetic moments. Moreover, the (correct) higher energy terms (beyond the 16th excited state) in the sum of Eq. (3) should provide negligible (absolute) contributions when focusing on optical activity in the frequency range far lower than the first excitation energy. In Fig. 2, we show the perturbed

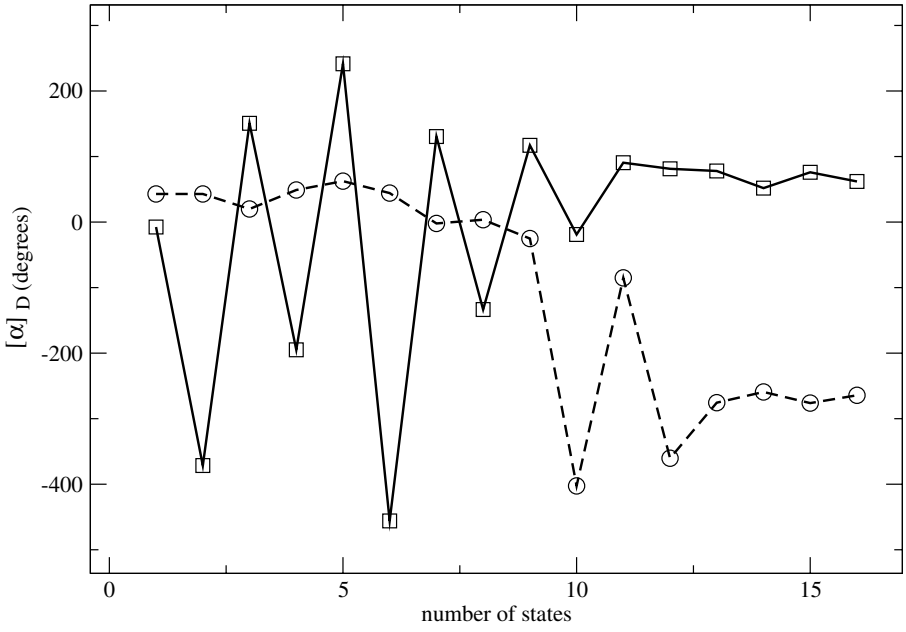

Fig. 2. The aqueous (perturbed) values of the L-alanine optical activity at 589 nm ($[\alpha]_D$) as calculated using up to the first sixteen excited states. Dashed line and circles = CASSCF/PMM, solid line and squares = TD-DFT/PMM.

alanine [α] values (obtained by PMM based on the previous ab initio methods) at the sodium D-line wavelength (589 nm), as a function of the increasing number of (perturbed) excited states (again up to the 16th). Such ORD values have been evaluated averaging the (perturbed) rotation angle over the whole MD trajectory and PMM results were obtained diagonalising at each MD frame a perturbed Hamiltonian matrix constructed using the ground and first 20 excited (electronic) states. In this way, we obtained a reliable evaluation of the first sixteen perturbed excited states (note that the perturbed Hamiltonian matrix we use does not involve magnetic moments). Also in this figure, only the [α] values obtained by PMM calculations based on TD-DFT (TD-DFT/PMM) seem to converge, reaching a value of about +60° when sixteen perturbed excited states are used. Interestingly such a value is reasonably in agreement with the experimental one (+1°), and

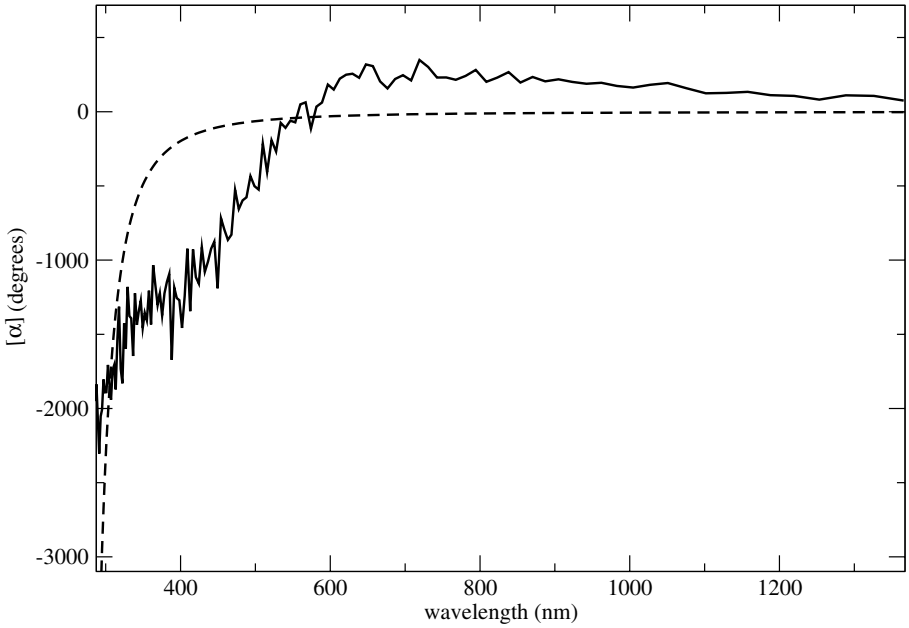

Fig. 3. Acqueous (perturbed, solid line) and vacuum (unperturbed, dashed line) ORD spectra of L-alanine, as obtained by TD-DFT and TD-DFT/PMM calculations using sixteen excited states.

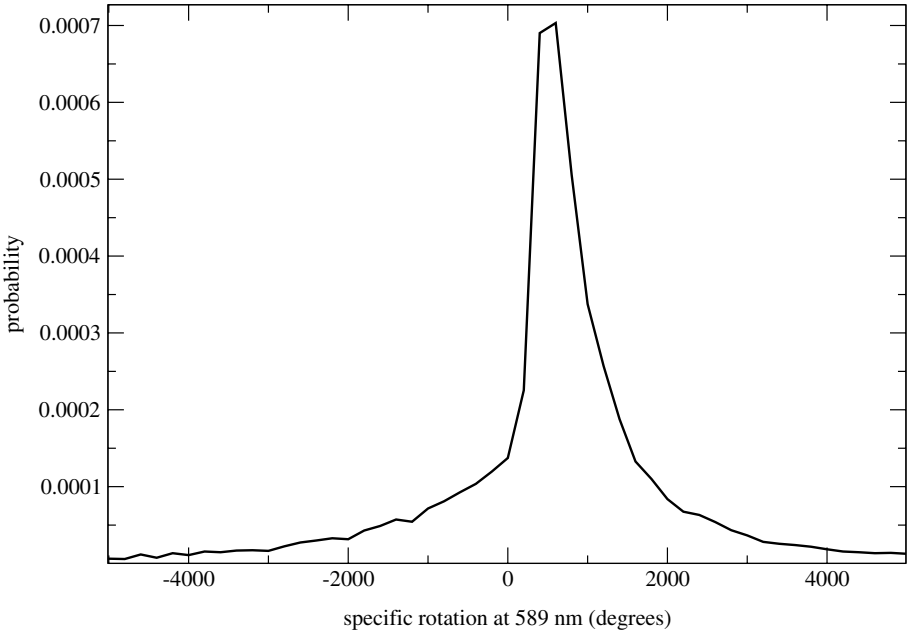

Fig. 4. Specific rotation distribution (at 589 nm) of L-alanine in water as obtained by TD-DFT/PMM and MD sampling.

shows the relevant effect of the perturbation on the rotation angle. As expected the [α] values obtained by PMM calculations based on CASSCF (CASSCF/PMM) are again not well converging, confirming the unperturbed data (see Fig. 1). In Fig. 3, we present the unperturbed and perturbed [α] spectra, using sixteen excited states, for TD-DFT and TD-DFT/PMM, respectively (given the previous results we omit CASSCF and CASSCF/PMM data). From this figure, it is evident the relevant effect of the solvent at virtually all the wavelength investigated, which is further evidenced by Fig. 4, where we show the distribution of the specific rotation at a single system configuration (at 589 nm), as obtained by the MD trajectory.

3. Conclusions

In this Letter, we showed how to obtain ORD spectra of a solvated molecule as a simple application of PMM combined with molecular dynamics simulations. Results for aqueous L-alanine clearly showed the applicability of the proposed procedure which, in principle, could be used for any kind of quantum center once a reliable set of unperturbed electric and magnetic moments are available. However, a special care is required for the choice of the number of excited states to be used in Eq. (3) and for the ab initio method providing the unperturbed electric and magnetic moments. The former must guarantee a reasonable convergence and the latter should provide reliable transition moments up to the excitations needed to achieve such a convergence. For the molecule investigated in this Letter, L-alanine in its zwitterionic form, the CASSCF procedure we used is clearly unable to provide a reliable perturbed or unperturbed ORD, probably because of its active space limitation (11 orbitals). TD-DFT on the other hand, seems to be a rather stable methodology providing reasonably accurate unperturbed properties even when highly excited states are concerned as in the present case where high energy excitations are necessary to obtain convergence of the specific rotation. These results suggest that the proposed PMM method for ORD calculation may open the way to the investigation of the optical activity of solute molecules within a complex molecular environment and, given the fast improvement of the computational power, promises an atomic-molecular interpretation of experimental optical activity data.

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