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Simulating the Electronic Circular Dichroism Spectra of Photoreversible Peptide Conformations

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Abstract

Electronic circular dichroism (CD) spectroscopy of peptides is one of the most important experimental characterization tools to get insights regarding their structure. Nevertheless, even though highly useful, the reliable simulations of CD spectra result in a complex task. Here, we propose a combination of quantum mechanics/molecular mechanics (QM/MM) methods with a semiempirical Hamiltonian based on the Frenkel excitons theory to efficiently describe the behavior of a model 27-amino acid α-helical peptide in water. Especially, we show how the choice of the QM region, including different possible hydrogen-bonding patterns, can substantially change the final CD spectrum shape. Moreover, we prove that our approach can correctly explain the changes observed in the peptide conformation (from α-helix to α-hairpin) when covalently linked to a protonated retinal-like molecular switch and exposing the system to UVA light, as previously observed by experiment and extensive molecular dynamics. Hence our protocol may be straightforwardly exploited to characterize light-induced conformation changes in photoactive materials and more generally protein folding processes.

Introduction

The study of peptide conformation changes and protein folding processes are outstanding topics, as they are directly related to the biological activity and physiological response in living organisms. (1, 2) However, the study of protein folding processes is not an easy task due to the large number of degrees of freedom and the long time scale of the process. Hence, small model peptides are usually selected to study their conformational changes. In this regard, in the last decades

scientists have been focused on controlling the conformation of peptides as a way of modulating their biological function. (3, 4)

To this aim, an elegant and original strategy has been established: photoisomerization of a molecular switch attached to the peptide backbone, hence inducing controlled and reversible conformational changes of the peptide under study. (5, 6) In particular, α-helical peptides have been widely studied as the former is one of the most common secondary structure elements that can be found in native proteins. Moreover, this strategy has been applied to successfully control physiological processes, (7, 8) activate or modify enzymes expression, (9, 10) alter the biological activity of cells, (11-13) and activate ion transfer channels in neurons. (14, 15) Among all the possible families of molecular switches, light-driven switches are by far the most commonly used, (16) as light offers the main advantage of an extremely high spatial and temporal resolution. (17, 18) To date, numerous studies about fully reversible photoswitchable peptides have been reported, azobenzene being the most used photoswitch, (19-21) but considering as an alternative also other photoswitches. (22-28)

For all these reasons, we have aimed to study the light-triggered conformational change of an α-helical peptide of 27 amino acids with a retinal-like photoswitch covalently linked to the backbone (Figure 1) through two modified cysteine residues. In particular, the peptide presents a high content of alanine residues, favoring an α-helical structure. The peptide conformational changes induced by the switch photoisomerization have been previously studied from both an experimental and a computational point of view, (22, 29) therefore resulting in an optimal model to apply our methodology.

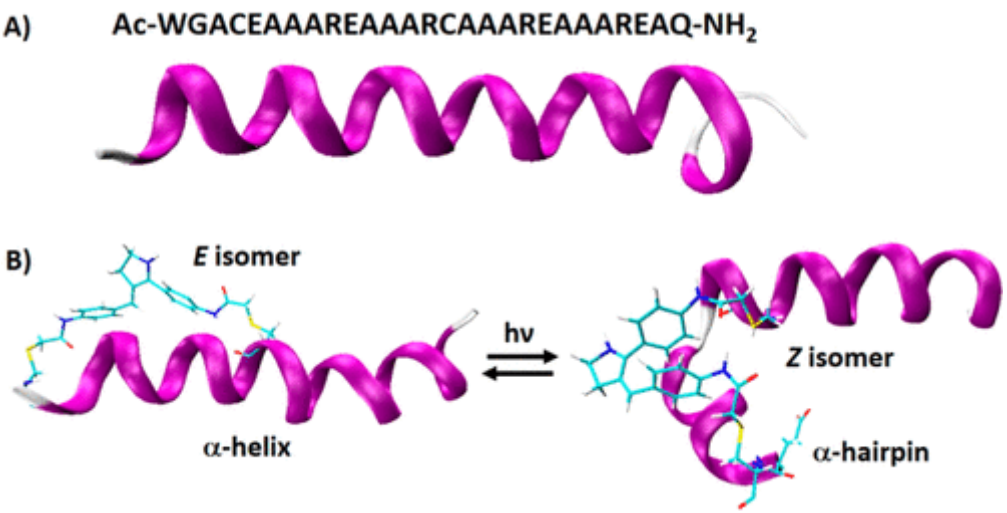

Figure 1. A) Primary and folded secondary α-helical structure of the proposed model peptide. B) Reversible α-helix to α-hairpin conformational change triggered by the

photoisomerization of a switch covalently linked to the two cysteine residues. Representative snapshots from the MD simulations are shown.

In order to evaluate and monitor peptide conformational changes and secondary structure, electronic circular dichroism (CD) spectroscopy is widely used, as it is a fast, nondestructive, and quantitative technique. Moreover, thanks to the high sensitivity to the chromophore arrangement and to the eventual supramolecular organization, CD spectroscopy is used to monitor specific structural signatures in different complex arrangements such as soft materials, liquid crystals, nucleic acids, and peptides. (30-33) The simplest way to study the secondary structural organization of peptides is to follow the electronic transition due to the peptide −C(O)−N(H)− bond and the modifications induced by its supramolecular arrangement. For instance, α-helical peptides present a characteristic positive band at 193 nm and two negative bands at 208 and 222 nm. (34) Hence, their photoinduced conformational changes can be easily monitored by CD spectroscopy. However, even if rich and very sensitive, the information embedded in CD spectra is, in some cases, difficult to relate directly to an atomistic resolved picture of the molecular structure.

From a computational point of view, molecular dynamics (MD) are widely used to study the folding of peptides, as it gives additional information inaccessible to experiments. However, it is critical to validate the simulation results by a direct comparison with experimental data. In this regard, a straightforward procedure to check the theoretical results, and at the same time achieve the sought atomistic structure resolution, could be the simulation of the CD spectrum from the dynamical study and compare it with the experimental one. Nevertheless, the reliable simulation of CD spectra of large biomolecules represents a considerable challenge. Actually, if a single chromophore is responsible for the CD signal, one can resolve to the usual quantum chemistry (QM) methods to obtain electronic excited-states energy and properties. Moreover, by using hybrid quantum mechanics/molecular mechanics (QM/MM) calculations the environment effects can be taken into account and coupled to the chromophore excited-state properties. Nevertheless, usually the CD activity shown by biomolecules such as nucleic acids, peptides, and proteins is due to supramolecular-induced dichroism, constituting a more complex phenomenon to be described theoretically: the final spectrum results from the coupling and interaction of many different chromophores, i.e. the nucleotides or the amino acids. In these cases, the QM region to be considered would grow so much that it will result in an unfeasible calculation, especially when state-of-the-art multiconfigurational or TD-DFT (time dependent-density functional theory) methods are required. Hence two possible solutions do apply:

either treat the whole multichromophoric system by semiempirical methods or use appropriate effective Hamiltonians to couple the excited-state properties calculated for each chromophore separately. The former solution implies a careful calibration of the method to be chosen, and each modified or different system would require a new calibration procedure. As an attempt to automatize the calculation of CD spectra of protein structures, a semiempirical and *ab initio* parameters set was considered for use in the matrix method. Such parameters can in principle take into account backbone and aromatic side chain transitions, including charge transfer between neighboring peptide groups. (35, 36) Even though offering a rapid computational response that could be valuable to discriminate between different protein secondary structures, this method cannot reach the level of accuracy required to detect quantitative differences in the intensity and bands shape.

We therefore concentrate our attention on the latter solution, especially focusing on the Frenkel Hamiltonian to describe the excitonic coupling between independent chromophores. Hence the global phenomenological Frenkel Hamiltonian is built for the whole system after having calculated excited-states of peptide fragments, usually but not exclusively at the TD-DFT level. (37-42) The subsequent diagonalization of the effective Hamiltonian will hence give the excitation energies and the corresponding oscillation strengths or optical activities. Indeed, even though more complicated schemes do exist (mainly including the coupling between the fragments' excited-state density matrices), (41-45) the Frenkel Hamiltonian approach (46) simply relies on the coupling between the fragments' transition dipoles as well as their distances and orientations.

Recently, the CD spectra of short B-DNA double strands (15 base pairs) (46) and of DNA-G quadruplexes (47) have been obtained in the framework of the Frenkel excitons theory, while exploring the DNA conformational space by classical MD. In the present work, we propose to apply this methodology to the case of peptides. This constitutes an additional level of complexity compared to DNA, since the flexibility and hence the polymorphism of a peptide in water may be much higher than that of a DNA double strand. Indeed, in DNA although the backbone still experiences a large flexibility, two or three hydrogen bonds are produced between facing nucleotides and each base pair is π-stacked with the upper and lower base pair. On the other hand, in the case of an α-helix a single strand (the peptide backbone) is coiled in a spiral conformation only by C═O···H−N hydrogen bonds. As a matter of fact, α-helices are highly conservative secondary structure motifs when integrated in protein tertiary structures but maintain a high flexibility when alone in water solvent. This corresponds to a wide conformational space to be explored,

which constitutes the basis of the broadness of the CD spectra. Moreover, a high sensitivity to temperature should be considered. (22)

Methods

The systems under study are the peptide solely in water and covalently linked to a protonated retinal-like molecular switch in its *E* or *Z* configuration (Figure 1 and the Supporting Information).

The electronic ground-state conformational space has been explored by classical MD trajectories of the solvated systems at a temperature of 300 K, as previously reported by some of the authors: (29) the AMBER99SB force field (48) was applied to the peptide, the TIP3P model (49) was applied to water molecules, and GAFF (generalized AMBER force field) (50) parameters were applied to the molecular switch. A direct comparison with X-ray experimental data can be considered as a validation of the theoretical approach. Nevertheless, we do not dispose of a crystal structure for this specific system. Moreover, we would like to emphasize that the X-ray structure corresponds to a static picture, while by molecular dynamics different conformations can be accessed – including their relative stability – corresponding to the behavior of the molecule in its environment. (51-53)

The calculation of the CD spectra is performed as follows: (*i*) 80 snapshots are randomly selected from the MD; (*ii*) for each snapshot the peptide or covalently modified peptide is divided into *n* fragments; (*iii*) *n* QM/MM calculations – including mechanical, electrostatic, and polarizable embedding by electronic response of the surroundings (54) – are performed, including in the QM partition each of the fragments, while treating the QM/MM frontier by the hydrogen-link atom approach.

Depending on the number of amino acids included in each QM region, excited-states were obtained for each QM/MM calculation, by applying TD-DFT for the QM partition. In order to span an excited-states energy range wide enough to include all the required transitions, 10 of them were computed for QM regions composed of single amino acids, 30 for amino acids couples and triples, and 50 for quadruples (see Figure 2). In more detail, a benchmark was carried out for the *Z* model, including M06-2X, CAM-B3LYP, and B3LYP functionals (see the Supporting Information). The M06-2X functional was finally selected together with the 6-311+G(d,p) basis set, as it was also shown to successfully reproduce the absorption spectrum of the free peptide (55) (see the Supporting Information) and of the covalently modified peptide. (29)

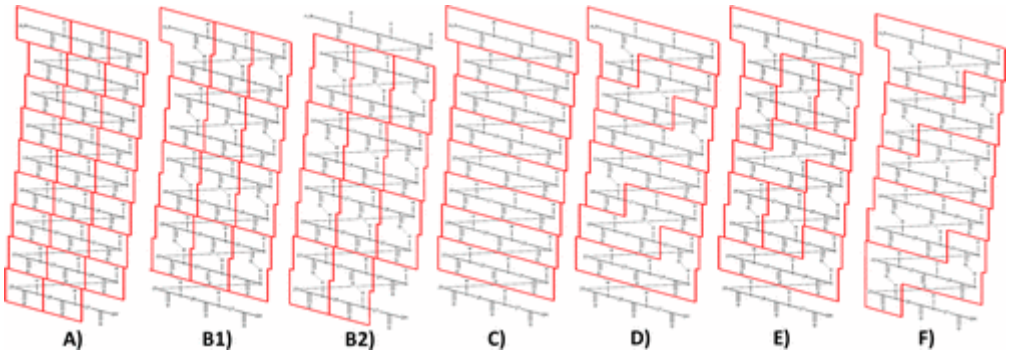

Figure 2. Different fragmentation schemes applied to calculate the CD spectrum of the model peptide: **A**) each amino acid separately; **B1**, **B2**) couples of amino acids, including the hydrogen bond between them; **C**) sequential sets of three amino acids; **D**) sequential sets of four amino acids, including one hydrogen bond per set; **E**) hybrid sets of four amino acids followed by three couples; **F**) sequential sets of five amino acids.

Once the excitation energies and the transitions dipole moments are known for all *n* fragments of a given snapshot, (*iv*) the effective Frenkel Hamiltonian is diagonalized in order to treat the *n* interacting chromophores and thus obtain the optical rotatory strengths, *r*, as described elsewhere by some of the authors. (56) (*v*) The *r* values of all 80 snapshots are then convoluted by a Gaussian function of fixed width at half-length (FWHL) of 0.4 eV, in order to obtain the final CD spectrum. To check the reliability of the method, a test CD spectrum was built including an increasing number of snapshots, hence showing the reached convergence (see the Supporting Information).

All QM/MM calculations were performed with a locally modified (57, 58) version of the Gaussian09 code, (59) coupled to Tinker. (60) The construction and diagonalization of the Frenkel Hamiltonian were locally implemented at the Université de Lorraine in Nancy.

Results and Discussion

Peptide in Water

As the peptide is formed by a covalently linked chain of 27 amino acids, a variety of fragmentation schemes can be in principle applied. Especially, we considered six fragmentation schemes (Figure 2), in order to check the performance of our method with respect to the QM partitioning. In all cases, side chains are included. It has to be noted here that the definition of the residues for each amino acid is different compared with the canonical one, since the O(═C)−N(−H)− peptide bond atoms have to be included in a unique residue, in order to obtain a reliable chemical description. The **A** scheme considers each amino acid separately; the **B** scheme is formed by couples of amino acids, so to include always a

–CO···HN– hydrogen bond between amino acids. The couples can be selected from the N-terminus (**B1**) or the C-terminus (**B2**) of the peptide; the **C** scheme includes three sequential amino acids per fragment (no hydrogen bonds included); the **D** scheme considers four sequential amino acids per fragment, hence including one hydrogen bond; the **E** scheme corresponds to a mixture of **D** and **B** schemes. This last scheme ought to obtain a better accuracy since it considers at the same time (*i*) one hydrogen bond for each – couple and quadruplet – unit, and (*ii*) a complete alpha helical turn is represented by a quadruplet followed by 3 consecutive amino acid couples. It therefore constitutes a repeatable pattern along an α-helix chain, and it is a good compromise between QM unit size and computational time. Finally, the **F** scheme includes five sequential amino acids per fragment, resulting in the largest proposed QM unit.

Hence, the CD spectrum of the model peptide has been calculated applying the different fragmentation schemes (Figure 3). Moreover, the calculated CD spectra have been compared with the experimental data obtained for the same peptide in the fingerprint region of an α-helix, i.e. from 200 to 250 nm. Indeed, in this energy window one finds two negative peaks arising from the amide π,π* (at 208 nm) and n,π* (at 222 nm) electronic transitions. It is usually the change of intensity of these two peaks (i.e., α-helix content) and also their relative intensity that is used to interpret and surmise the peptide conformational change.

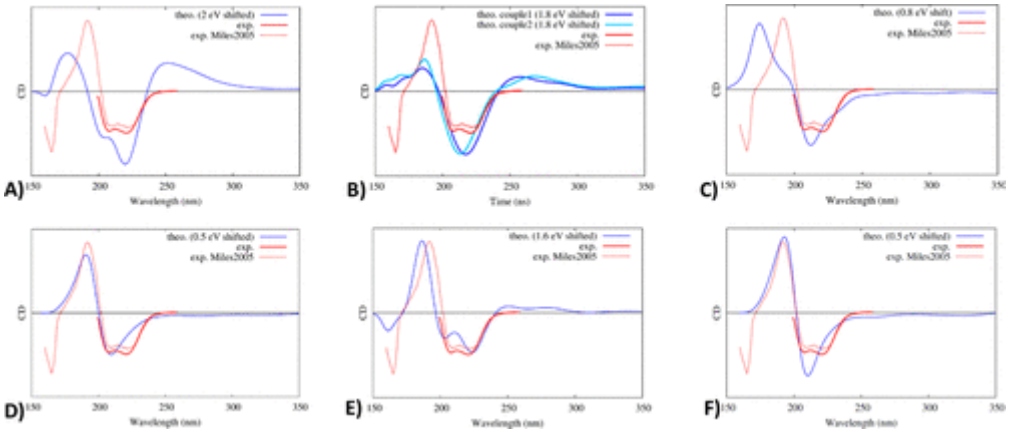

Figure 3. CD spectra calculated for the free peptide, including different fragmentation schemes (see Figure 2 for the letter notation). Each spectrum (blue) is compared with the available experimental data of the same peptide (red) and of a similar α helix (dashed line), concerning especially the positive peak at 190 nm. (61)

In more detail, the exciton splitting of the π,π* transitions in the amide groups that are held in a well-defined helical geometry generates interactions between the oriented transition dipole moments, leading to three absorbance bands: one, as aforementioned, at 208 nm, polarized parallel to the helix axis, and two overlapping bands at 190 nm, polarized

in the two directions perpendicular to the helix axis. For an α-helix, the parallel band is assigned to the negative CD peak at 208 nm, and the perpendicular bands are assigned to the positive (and hence more intense) CD peak at 190 nm. Since no experimental data at higher energy (i.e., before 200 nm) are available for the studied peptide, we compared our results with a similar amino acid sequence, giving rise to an α-helix too (Figure 3). (61)

At a first glance, we can see that all our results consist of blue-shifted peaks, even though the excitation energies of the proposed system are well described at the TD-DFT level (see Figure S4 in the Supporting Information). This is expected, considering the use of the semiempirical and extremely simple Frenkel Hamiltonian, as it was already reported for DNA. (46, 47) Even when applying more sophisticated methods to DNA, (41-45) such a limit still stands even if it can be reduced. At any rate, we do observe a relation between the selected fragmentation scheme and the shift in energy required to reproduce the experimental data: going from A to D, i.e. enlarging the selected partition from one to four amino acids, the energy shift decreased considerably: 2.0 eV for scheme **A**, 1.8 eV for scheme **B**, 0.8 eV for scheme **C**, 0.5 eV for scheme **D**. Being that **E** is a mixed scheme, the shift lies between its components: 1.6 eV. Scheme **F**, offering the largest partition (five amino acids), needs also a shift of 0.5 eV as scheme **D**, indicating that even larger partitions do not necessarily recover the shift from the experiment.

It is also interesting to check the intensity ratio between the positive peak at 190 nm and the negative one at 208 nm, that should ideally be 2:1. (62) Indeed, in this respect **A** and **B** schemes clearly fail, **C**, **D** and **F** schemes constitute an improvement, while only the **E** scheme outperforms the others.

Actually, concerning the (shifted) 200–250 nm range, **E** is the only scheme giving rise to a balanced description in terms of number of peaks – both π,π* and n,π* are present – and intensity, almost matching the experimental one. Moreover, it is also interesting to note that only **A** and **E** schemes show the two characteristic negative peaks. At a first glance, it would be expected to obtain the most accurate CD simulated spectrum for scheme **F**, since it includes sequentially the largest QM units. Nevertheless, we have to consider that the CD signal is built as the coupling of transition dipole moments, each placed on the barycenter of a QM unit. In scheme **F**, the sequential arrangement of each quintuplet unit does not give rise to an α-helical arrangement. Hence, after coupling all moment vectors, the CD bands (i.e., the CD spectrum shape) cannot be fully recovered. On the other hand, schemes **A** and **E** result in a reasonable description of the CD spectral signature.

All in all, we can conclude that the **E** scheme is the most appropriate to study CD spectra of the proposed α-helix. In general, such a scheme could be applied to each sequence of amino acids resulting in an α-helical secondary structure. In this particular case, it will be applied to calculate also the spectrum of the peptide covalently linked to the photoswitch in its *Z* conformation (Figure 4A).

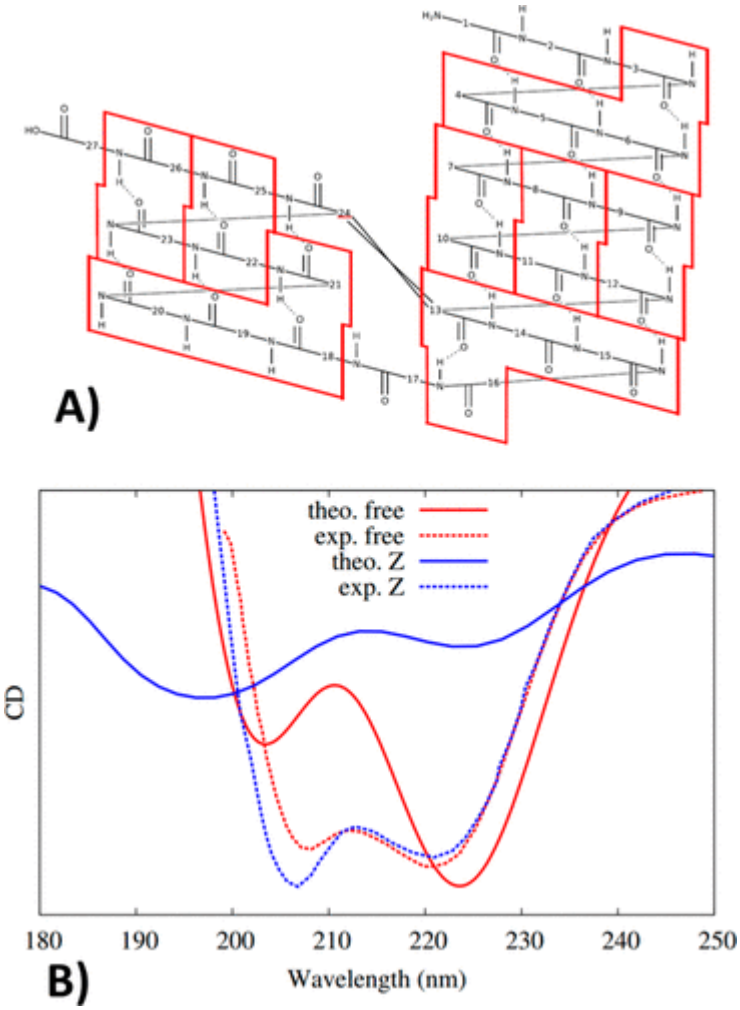

Figure 4. A) Sketch of the peptide in its α-hairpin conformation, due to *E*-to-*Z* photoisomerization. The applied fragmentation scheme (**E**) is shown in red. B) CD spectrum of the computed *Z*-derived peptide (solid blue line) as compared to the computed free peptide (solid red line), when applying the same fragmentation scheme. The respective experimental spectra are added (dashed lines). (22)

Effect of Photoswitching

The *E*-linked peptide presents an α-helix conformation, similarly to the free peptide, as the sulfur–sulfur distance of the two cysteine residues is close to the end-to-end distance of the photoswitch (see Figure 1). Indeed, the CD spectra of the free and the *E*-linked peptides are quite similar. Actually, it is expected – both experimentally and theoretically –

that the helicity content slightly increases (from 65 to 69%) when a linkage to the *E*-switch is present, due to the rigidification of the secondary structure. (29) Nevertheless, such subtle CD spectra changes are also highly dependent on the temperature and anyway should lie below the error admitted by our approach.

The *E*-to-*Z* photoisomerization of the switch induces a conformational change of the peptide, *i.e*. from α-helix to α-hairpin (Figure 4A). We are therefore interested in looking at the changes of the calculated CD spectrum of free and *Z*-linked peptides. In Figure 4B we compare the calculated CD spectra for the free and *Z*-linked peptide (both by the **E** fragmentation scheme) with the available experimental data. (22) By analyzing the CD spectrum of the *Z*-linked peptide, we observe a decrease in intensity of all positive and negative peaks compared to the free peptide. Moreover, the band shapes are kept, so such photoinduced change is not sufficient to unfold considerably the helical secondary structure. This can be explained in terms of a decrease in the helicity content (by almost 20%, as experimentally measured (22)) when converting an α-helix into an α-hairpin. By MD studies it was shown that such a helicity decrease is concentrated especially in the turn region, in order to bend the α-helix. (29)

Even more interestingly, an intensity inversion between the negative peaks at 208 and 222 nm is observed, as also detected and discussed experimentally. The physical explanation lying behind such spectral phenomenon is still under debate, even though the most reliable suggestions point toward the length of the α-helices and their interaction. (63-65) In our case, a single α-helix is modeled in water, nevertheless the conformational change in an α-hairpin makes possible for two helical strands to be in close side-to-side contact, along various orientations (see Figure 1B). We can therefore suggest that this intensity inversion could be due to a particular case of interaction between helices, caused specifically by the photoinduced rearrangement of the whole peptide and/or by the decrease of the α-helix length due to the bend.

The former is even more sounding considering that α-helices are known to produce strong collective dipole moments oriented toward the helical axis whose interaction can strongly alter the excitonic coupling, inducing supramolecular CD signals. (66) Note also that this interaction is implicitly taken into account by our protocol via the electrostatic embedding to which each QM partition is submitted.

The shown proficiency in simulating the fine structure of the CD spectrum, in close relationship with the observed geometrical rearrangements, is definitively a step forward in the complex task of CD simulation. Especially in the point of view of the spectrum shape, our

method was demonstrated to outperform in the description of α-helical peptides, compared to previous approaches. (40)

Conclusions

In the present study, we have shown a feasible method to afford a computationally challenging task: the simulation of the electronic circular dichroism spectra of peptides in water solvent. Especially, we have shown that the accuracy of the results changes systematically depending on the fragmentation scheme used to split the peptide into different interacting units. Indeed, the shift in energy with respect to the expected experimental values and the fine shape of the peaks was presented and discussed, highlighting positive sides and limits of the proposed method. Once established the best scheme representing the CD spectral features of the modeled α-helical peptide, the effects on its overall conformation due to covalent linkage of a photoswitch were calculated. This made it possible to explain the changes experimentally observed in the CD spectrum on the basis of the modeled macromolecular rearrangements, that is usually the missing information from experiments.

Such a successful application of the Frenkel Hamiltonian method – coupled with QM/MM modeling of a statistically relevant ensemble of structures given by MD dynamics – paves the way not only to a possible application to different secondary structure elements, as β-sheets, but also to full proteins and proteins assemblies (i.e., tertiary and quaternary structures). Also, the investigated α-hairpin pattern constitutes the basis of interacting parallel α-helices found in most proteins. Hence, the capability demonstrated by our method to predict its CD spectrum is encouraging for possible future applications, to e.g. G protein-coupled receptors.

Moreover, being that the fragmentation of the structure is an essential feature of the method, it offers the possibility to highly parallelize the necessary calculations, shifting the problem from the size of the system to the available computational resources. Also, the relative small size of the QM partition allows for imagining the further design and implementation of Web server, or even grid, based approaches allowing for the *ab initio* determination of supramolecular CD spectra. This would definitely assist and improve the structural resolution of biological or artificial polymers.

Finally, another source of required improvements in the field is constituted by the development and application of alternative approaches to the Frenkel excitons theory, since its semiempirical basis makes possible computationally highly feasible tasks, but at the same time it gives rise to blue-shifts in the CD spectra, as compared to experiments.

We should note that this problem affects also more sophisticated approaches, (41-45) hence demanding the development of alternative strategies.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jctc.7b00163.

- Benchmark of different DFT functionals; convergence of the CD spectrum over a range of snapshots; chemical structure of the retinal-like molecular switch; free peptide UV spectrum (PDF)

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Notes
The authors declare no competing financial interest.

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