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Theoretical simulation of the electronic circular dichroism spectrum of calicheamicin

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Abstract—The aglycon, or so-called 'warhead' portion, of several potent 10-membered ring enediyne antitumor antibiotics contain dienonecarbamate and enediyne chromophores in an unusual bicyclic ring structure in which these two subunits are essentially orthogonal to each other. The circular dichroism (CD) spectra of the calicheamicin, esperamicin, and shisijimicin A families, all of which contain this bicyclic ring system, exhibit a characteristic negative exciton coupled CD at about 310 and 270 nm. This signature CD feature suggested the absolute stereochemical relationship between these chromophores as originally assigned and which was later confirmed by stereospecific total synthesis. Because of the unique nature of this chromophoric interaction and the importance of using this CD spectral feature in the assignment of the absolute stereochemistry of other related enediynes, we report here simulations of the CD spectra of the calicheamicin aglycon A, and of two other truncated models, B and C, by using density functional theory (DFT) and the DeVoe coupled oscillator approach. The DFT calculations provide a strong theoretical basis that the planar enediyne chromophore alone gives a negligible CD contribution, while that coming from the twisted dienonecarbamate is much more substantial. However, the shape and the largest part of the intensity of experimental CD spectrum can only be reproduced when the two unsaturated moieties are simultaneously present. Thus, the exciton coupling between the two chromophores provides the most important contribution to the experimental CD spectrum of calicheamicin. This conclusion is in full agreement with the results from the DeVoe calculation.

1. Introduction

The extremely potent enediyne-containing antitumor antibiotics, isolated and characterized from a variety of microbial and marine sources, are some of the most unusual natural products isolated to date.[1] It is believed that the extreme toxicity of these agents is a result of their ability to bind and cleave double-stranded DNA. Their unique structures and novel bioreductive activation and DNA cleavage chemistry, mediated by carbon-centered diradical intermediates, have provoked widespread interest among scientists around the world. Over 20 members of this class have now been identified and contain both 9- and 10-membered ring enediyne subunits. Those containing a 10-membered 3-hexene-1,5-diyne subunit are relatively stable, whereas the 9-membered versions are more labile and are isolated complexed with an apoprotein to provide stability. Two 10-membered enediynes, namenamicin,[2] and shishijimicin[3] have been isolated from marine organisms (tunicates) although it appears that the true source is a microorganism growing symbiotically on the surface of the tunicate.

Calicheamicin γ_1^I(I) is the most studied member of the calicheamicin family of metabolites isolated from fermentation broths of *Microminspora echinospora* spp. *calichensis*, a bacterium obtained from a caliche or chalky soil sample near Kerrville, Texas.[1] Other members of this class include the corresponding brominated analogs along with variations in the carbohydrate domain and different alkyl residues on the amino sugar moiety. Strain improvement efforts, especially with media supplementation with sodium iodide, led to marked

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improvement in fermentation yields but provided iodinated analogs instead of the earlier obtained bromine-containing metabolites. These studies eventually led to the production of the γ_1^I(I) analog in yields sufficient for chemical characterization and subsequent commercial use. From now on, we will refer to this γ_1^I(I) analog as calicheamicin. Although individual members of the enediyne-containing antitumor agents by themselves are too toxic for clinical use, a calicheamicin γ_1^I(I)–monoclonal antibody conjugate, Mylotarg, is a first-in-class agent approved for the treatment of patients with relapsed myeloid leukemia.[4] The antibody part of the conjugate targets the toxin to the cancerous cell by recognition of a cell surface antigen thus limiting nonspecific toxicity.

Toward the end of the structural studies on calicheamicin, we speculated that the circular dichroism (CD) spectrum of this agent might provide the absolute stereochemical relationship between the enediyne and dienonecarbamate chromophores in the aglycon portion of the calicheamicins as well as the esperamicins.[1] The structures of calicheamicin, esperamicin C, a methanolysis product of esperamicin A1, and shishijimicin A are depicted in Chart 1. As shown, these chromophores exist in an unusual bicyclic ring structure in which the two chromophores are essentially orthogonal to each other. In the CD spectrum of calicheamicin, we observed what appeared to be a strong negative exciton split with a negative extremum at 312 nm and a positive extremum at 272 nm with $\Delta\varepsilon$s of −44 and +46, respectively—in other words, a left handed relationship between the dienone and enediyne electric transition moments.[5] This pointed to the stereochemistry as initially assigned and later confirmed by X-ray analysis of the totally synthetic and optically pure (−)-aglycon (calicheamicinone).[6] The CD of esperamicin C exhibited a spectrum almost identical to that of calicheamicin(I) indicating the identical absolute stereochemical relationship in the esperamicin family.[1] Shisijimicin A also exhibited a CD spectrum similar to that of calicheamicin, which was used to assign its absolute stereochemistry as identical to that of calicheamicin and esperamicin.[3]

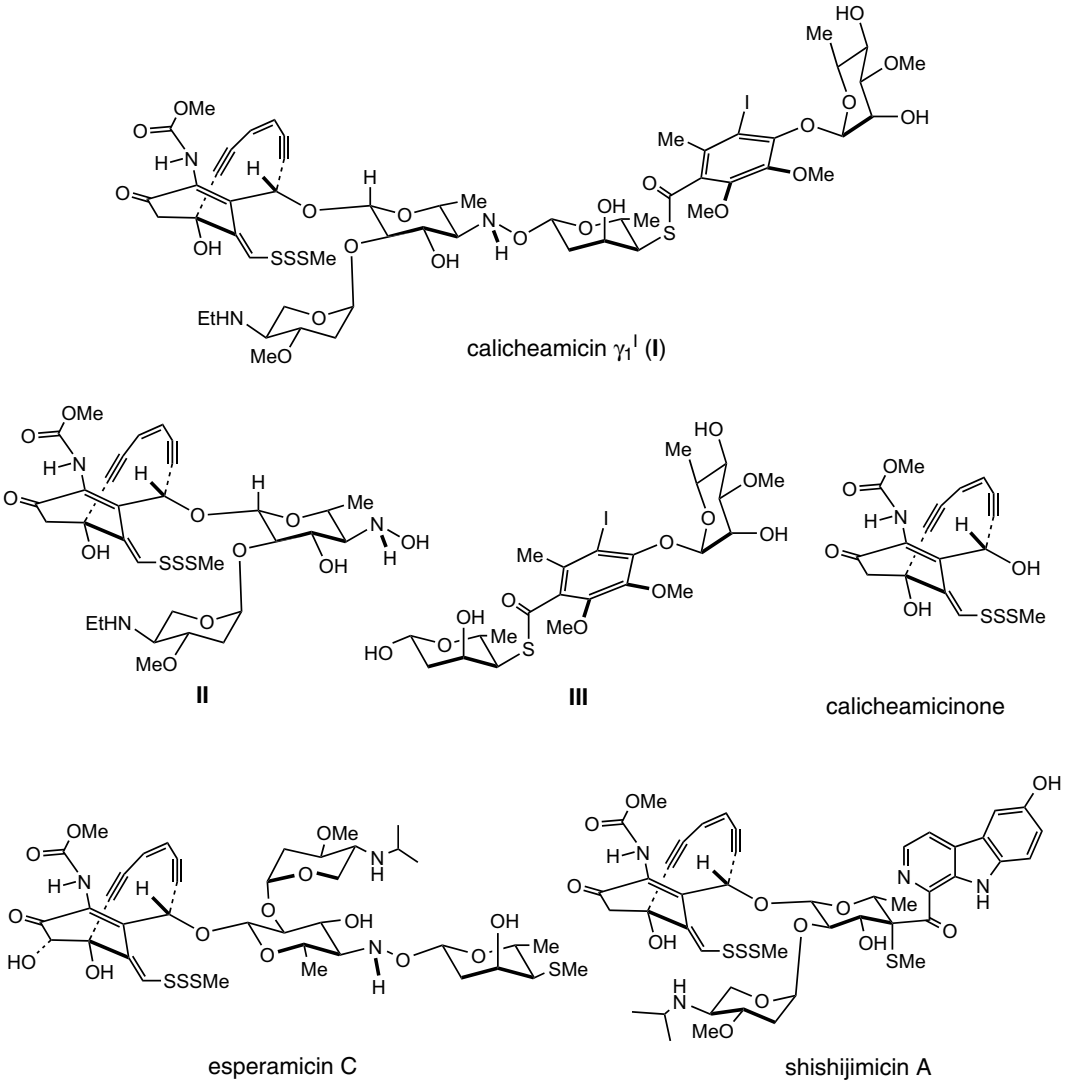

Chart 1.

Recently[7] we re-examined the CD spectrum of calicheamicin and confirmed that this exciton split originates solely from the aglycon moiety by comparing the CD spectrum of fragments II and III obtained from calicheamicin by mild acid hydrolysis which cleaved the molecule at the labile glycosylated hydroxylamine linkage. Fragment II contains only the enediyne/dienonecarbamate chromophore whereas fragment III contains only the thiobenozoate chromophore. Fragment II exhibited essentially the identical CD as calicheamicin itself whereas that of III exhibited almost no CD. This ruled out any contribution from the thiobenzoate chromophore to the above-mentioned negative exciton split. Because of the unique nature of this chromophoric interaction, and the importance of using this signature CD in the assignment of the absolute stereochemistry of other related enediynes, it was decided to carry out a theoretical treatment of this apparent couplet with methods based on modern density functional theory (DFT) and DeVoe coupled oscillator approach. These calculations have now accurately predicted the experimental CD spectrum of calicheamicin and have thus provided a strong theoretical basis for the enediyne/dienone chromophoric interaction in 10-membered ring enediynes.

2. Results and discussion

2.1. Conformational aspects

Before simulation of the CD spectrum of the calicheamicin aglycon, the conformational aspects were evaluated. The conformation of calicheamicin aglycon (named as truncated model A, Fig. 1), derived from the X-ray crystallographic analysis of calicheamicinone[6c] was compared with that obtained after a full geometry optimization at the DFT/B3LYP/6-31G* level in vacuum. We found that both geometries of model A were very similar except for the carbamate moiety attached to C-10 (Fig. 1). Thus, the dihedral angle between C3–C6 and C14–C11 exhibited very close values, namely, −65.4° for the X-ray derived conformation and −66.8° for the optimized structure, respectively. Although we tried to obtain by NMR the solution conformation in various solvents, in particular regarding the carbamate group, no useful information could be obtained due to the rapid proton exchange of the amide proton. Therefore, we decided to use rather the X-ray derived structure throughout this study for the purpose of simulating the CD spectra, assuming that the solution and the solid-state geometry of calicheamicin aglycon may differ only slightly.

2.2. Simulated CD spectra of calicheamicin truncated models A–C

The UV and CD spectra of calicheamicin, measured in acetonitrile, are presented in Figure 2. The UV spectrum shows a clear shoulder at about 280 nm (ε ca. 10,000), followed by a second, more intense shoulder at 230 nm (ε ca. 30,000) and a maximum at 220 nm (ε ca. 55,000). The CD spectrum exhibits a clear, negative extremum at 310 nm with Δε −40, and a positive one at 270 nm with Δε +35, characteristic features of a CD exciton couplet. While only the shoulder corresponding to a UV band around 230 nm is observed, there is a clear UV max at 220 nm corresponding to a positive Cotton effect (Δε +30) at the same wavelength.

The spectroscopic analysis of this experimental CD spectrum, which will be carried out by calculations using the TDDFT approach as implemented in Gaussian03 and the DeVoe method (see computational details), began by taking into account the results of the investigation described by Ding et. al.[7] In this recent study, it was

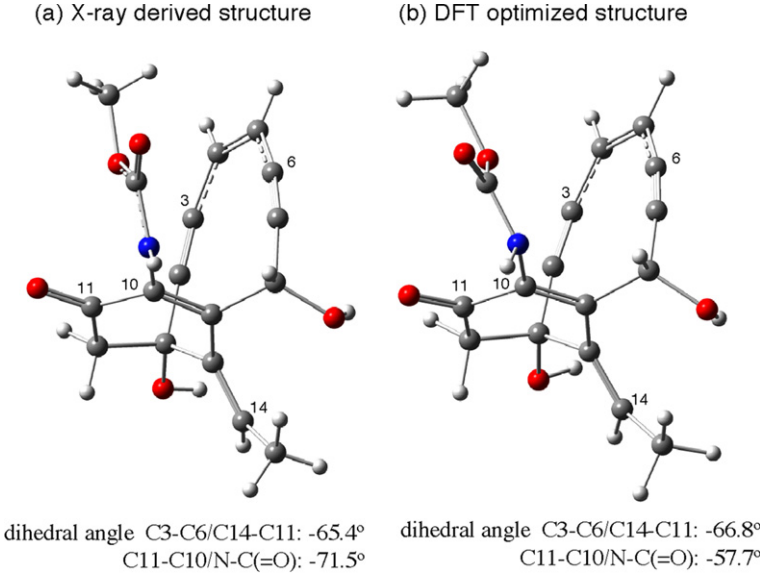

Figure 1. Conformation of truncated calicheamicin aglycon (Model A); (a) derived from X-ray crystallographic analysis of calicheamicinone and (b) obtained by geometrical calculation in vacuum at DFT/B3LYP/6-31G* level.

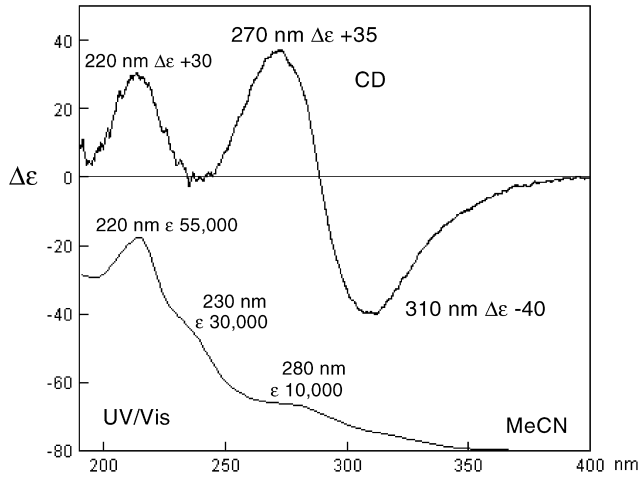

Figure 2. Experimental UV/vis and CD spectra of **I** in acetonitrile ($c = 1 \times 10^{-4}$ M).

concluded that the CD spectrum of calicheamicin is due mainly to the aglycon moiety that contains two chromophores, a complex dienonecarbamate and an ene-1,5-diyne group. Therefore, the present investigation started by creating a necessary input geometry. These data were obtained from the X-ray structure of (−)-calicheamicinone,[6c] and the structures of the corresponding three truncated models A (calicheamicin aglycon), B (dienonecarbamate group), and C (enediyne chromophore), that are shown in Figure 3a–c. The sugar part has been completely disregarded and substituted by a hydrogen atom. In addition, in order to simplify the calculations, the $-CH_2SSSCH_3$ group has been substituted with a methyl group. This substitution can be justified by taking into account that the absorption of the trisulfide chromophore[8] is quite small, ε_{max} ca. 1000. These three basic models were employed to carry out the calculations.

Figure 4 depicts the experimental CD spectrum of the calicheamicin molecule and the predicted CD spectra (calculated at the TDDFT/B3LYP/aug-cc-pVDZ level) of model A, for example, calicheamicin aglycon, and those of the truncated models B and C as isolated chromophores, but with the same geometries as in the aglycon model A.

The comparison clearly reveals that none of the spectra of B and C alone can give rise to the experimental spectrum of I. In fact, while the enediyne chromophore C alone gives only a negligible contribution, that of the dienonecarbamate B is much more significant, even though it does not match the experimental $\Delta\varepsilon$ values of I of ca. −40/+40, since the Cotton effects within 250–350 nm are of order of +5/−5. Yet, it is noteworthy that the molecular fragment B provides an important contribution to the CD spectrum in the entire range; in fact we are dealing here with a highly unsaturated, intrinsically twisted chromophore. It is well known that such structures can give rise to very strong Cotton effects. It is also worth mentioning that the very weak absorption band at long wavelengths (i.e., between 330 and 400 nm) of this group provides a clear contribution to the CD spectrum. The calculated CD spectrum of the calicheamicin aglycon A, however, provided a CD spectrum of an exciton-split pattern due to the presence of the two interacting chromophores. There is a first intense negative Cotton effect at ca. 340 nm, and second positive effect at ca. 290 nm, followed by a few other positive Cotton effects between 240 and 200 nm in good agreement with the experimental spectrum in the same region. This clearly indicates that the CD spectrum of calicheamicin is as a result of the dominant contribution of two interacting chromophores as in model A.[5]

In order to understand the real contribution of this interaction in the predicted CD spectrum of the caliche-

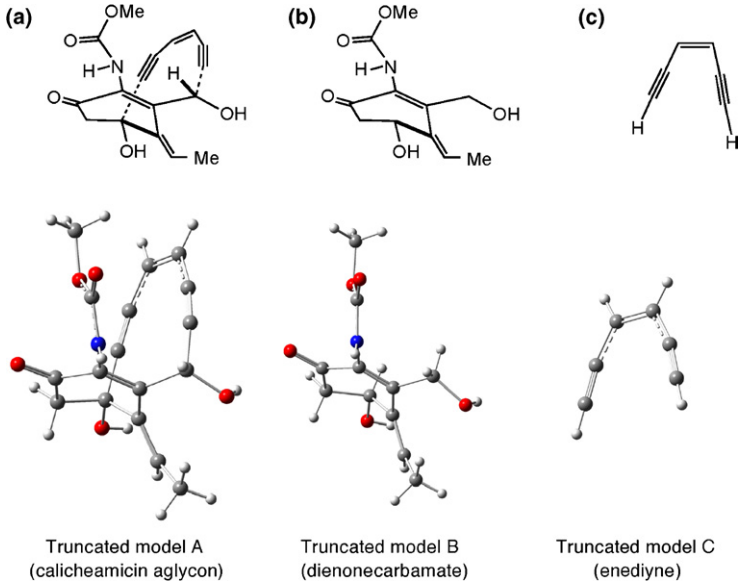

Figure 3. Truncated models of calicheamicin and input geometries for TDDFT calculation. (a) Model A (calicheamicin aglycon); (b) Model B (dienonecarbamate); (c) Model C (enediyne).

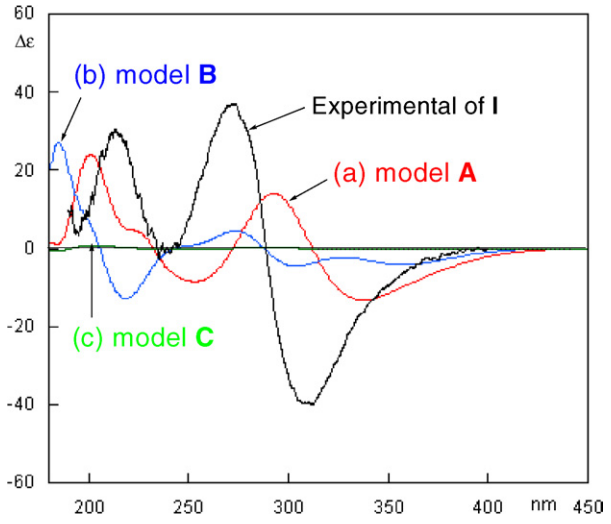

Figure 4. Comparison between experimental CD of calicheamicin **I** and calculated CD of three truncated models by TDDFT/B3LYP/aug-cc-pVDZ level: (a) truncated model A (calicheamicin aglycon); (b) truncated model B (dienonecarbamate); (c) truncated model C (enediyne).

amicin aglycon, the spectral region 250–370 nm has been analyzed regarding the exciton couplet-like features (see Figs. 5 and 6). Five main transitions are found at 370, 335, 310, 300 and 290 nm in the calculated UV spectrum of the dienonecarbamate chromophore (truncated model B) (not shown), where the maximum at ca. 300 nm is of the highest intensity. These transitions give rise to non-negligible Cotton effects (see Fig. 5a) but their intensity become significant only when the enediyne chromophore is present as well, that is, when the calculations are carried out on the entire structure of the calicheamicin aglycon, model A (Fig. 5b).

This figure shows that the bisignate Cotton effects centered around 300 nm in the CD of aglycon A arise from two main effects: the first from the chirality of the distorted model B (see Fig. 5a) and, the second and most important, from an exciton coupling interaction between the dienonecarbamate and enediyne chromophores. In fact, the calculated CD spectrum of dienonecarbamate between 270 and 370 nm shows three transitions with reduced rotational strengths of −27, −40, +38, going from long to short wavelengths (see Fig. 5). In the calculated CD spectrum of model A are found, approximately at the same wavelengths, three transitions with very similar reduced rotational strengths (−29, −34, +34). Clearly, these transitions are located in the dienone chromophore and result from the chirality of the distorted dienonecarbamate moiety in model A (Fig. 5b). They are also responsible for the tailing of the Cotton effect at about 340 nm (transition with $R_{red} = -29$), and only to a small extent for the two strong opposite Cotton effects centered at ca. 300 nm. These latter transitions, shown in Figure 5b with $R_{red} = -64$ and +61, are the most important contributions associated with a couplet effect between dienonecarbamate/enediyne moieties, since they are not found

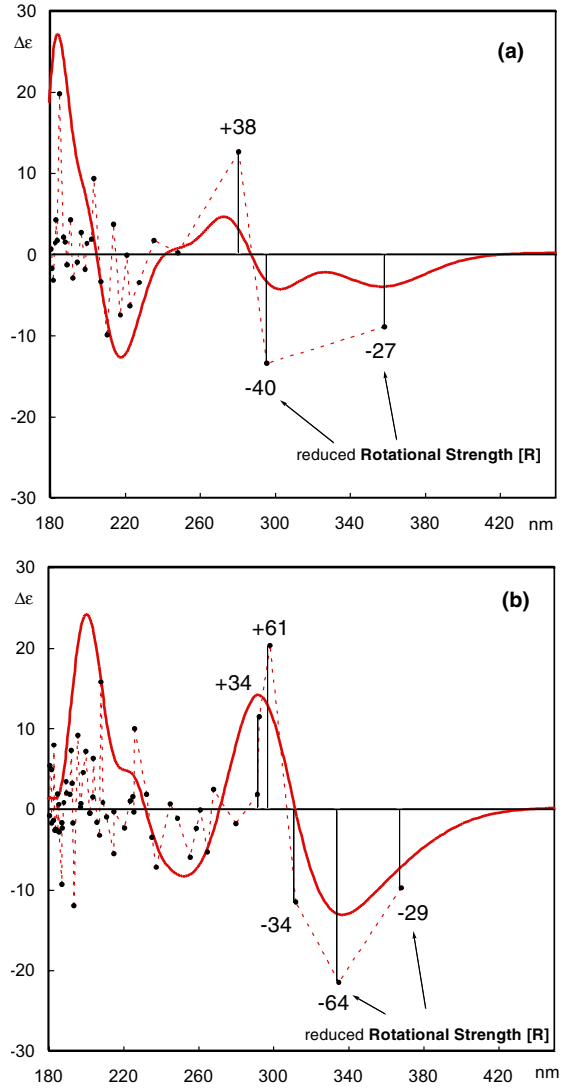

Figure 5. Calculated CD of (a) truncated model B (dienonecarbamate); (b) truncated model A (calicheamicin aglycon); [R] = R(cgs) × 10^{40} according to Ref. 5d.

in the calculated spectrum of the dienonecarbamate moiety itself.

2.3. Calculated CD spectrum of calicheamicin aglycon (model A) by DeVoe method

In order to provide another independent evaluation of the role played by the exciton coupled interactions in calicheamicin aglycon A, in addition to TDDFT calculations, we also carried out calculations by the DeVoe coupled-oscillator method.[9] According to this method, the molecule is considered as composed of a set of sub-systems, that is, chromophores polarized by the external electromagnetic radiation and coupled with each other by their own dipolar oscillating fields. The optical properties (absorption, refraction, optical rotatory dispersion, and circular dichroism) of the molecule under study can be calculated by taking into account the interaction of such subsystems. Therefore, this treatment required a division of the molecule into a set of

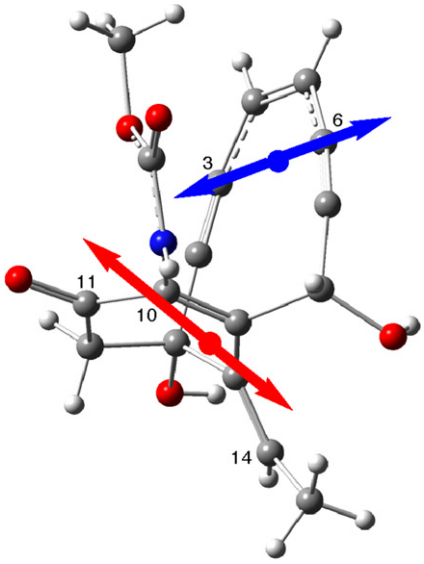

Figure 6. Dipole transition moments used for DeVoe CD calculation of truncated model A (calicheamicin aglycon): red oscillator; dienonecarbamate transition at 295 nm with oscillator strength of $8D^2$. Blue oscillator; enediyne transition at 263 nm with oscillator strength of $30D^2$.

subsystems that have to be suitably characterized. Typically, the application of the DeVoe method requires (a) a knowledge of the molecular conformation (structure of the single conformer and its population) in order to obtain the necessary geometrical parameters ($\mathbf{e}_1$, $\mathbf{e}_2$, $\mathbf{R}_{12}$, G_{12}); (b) a knowledge of the electrically allowed transitions involved (i.e., polarization direction, location, allied dipole strength) for obtaining the $I_i(v)$ and $R_i(v)$ values.[10]

Regarding the conformational aspects of model A, we took the same approach used by the TDDFT calculations by considering the geometries derived from the X-ray structure of calicheamicinone. The extended dienonecarbamate group has been described by a single oscillator polarized along the line connecting the carbon atom of the C=O group with the terminal C-14 atom of the unsaturated system, with the center located in the middle point of the line between C-10 and C-14 (see Fig. 6), with a dipolar strength of $8D^2$ and maximum at 295 nm. These parameters derive from our TDDFT/B3LYP/aug-cc-pVDZ calculations on the dienonecarbamate chromophore where the most intense transition (electric allowed transition) has been calculated at 295 nm with the oscillator strength of 0.12. The choice of the location is justified considering that this excitation involves mainly the two C=C double bonds. Using the experimental UV spectrum of calicheamicin, a dipolar strength of $8D^2$ has been inserted in the DeVoe calculations in order to obtain a good overlap between experimental and calculated UV spectra.

The enediyne chromophore was described by a single oscillator polarized along the internal double bond centered in the middle of the line joining the two sp carbons, C-3 and C-6. To this oscillator, we assigned the dipolar strength of $30D^2$ with a maximum at 263 nm. Based on the TDDFT/B3LYP/aug-cc-pVDZ calculations of model C, only one very strong and electrically allowed transition has been found in the spectral range down to 200 nm. This transition at 263 nm has an oscillator strength of 0.26, and is polarized as depicted in Figure 6. It is located in the middle of the conjugated system because all the unsaturated carbon atoms have similar contributions in the description of this transition. The position of this transition at 263 nm is in good agreement with that reported by Okamura and Sondheimer for a synthetic *cis*-acyclic enediyne.[11] The dipolar strength of $30D^2$ and ε value of about 27,000 in the calculated spectra has been obtained after adjustment to the UV spectrum of calicheamicin in MeCN. The DeVoe predicted CD spectrum is reported in Figure 7 together with the experimental one.

Even though the calculated negative couplet ($\Delta\varepsilon$ – 13; +13), centered at about 280 nm, is much less intense than the experimental one (only about one third of it), there is a full agreement between the sign and the

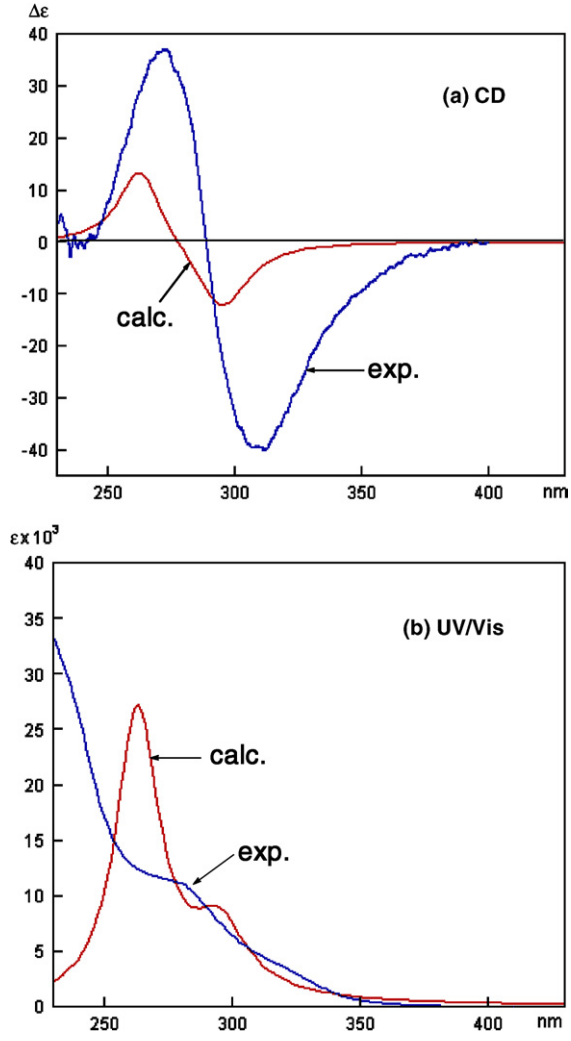

Figure 7. Experimental spectra in blue: CD (a) and UV (b) of calicheamicin (**I**) in acetonitrile ($c = 1 \times 10^{-4}$ M). DeVoe calculated spectra in red: CD (a) and UV (b) of the truncated model A (calicheamicin aglycon).

position of the calculated exciton couplet with that of the observed one.

3. Conclusions

The optical activity of the calicheamicin-like molecules results from the simultaneous presence of the dienonecarbamate and the enediyne chromophores. The theoretical CD simulations by TDDFT/B3LYP/aug-cc-pVDZ reported here show that the dienonecarbamate chromophore gives an important contribution, because three transitions that determine the CD spectrum in the 400–240 nm range are actually located in this fragment. However, the overall CD intensity can be reproduced by only taking into account the simultaneous presence of the planar enediyne chromophore. This conclusion was also supported by DeVoe coupled-oscillator calculations. In summary, the CD spectrum of calicheamicin (at least between 240 and 400 nm) is a result of the intrinsic CD of the distorted dienonecarbamate chromophore (broad CD band within 340–400 nm) as well as of the strong exciton coupled CD contribution of its allowed transitions with those of the enediyne chromophore.

4. Computational details

The geometry optimization of the truncated model A has been carried out at the DFT/B3LYP/6-31G* level by means of Gaussian03 software.[12] All the UV/CD computations have been carried out by means of the Gaussian03 software[12] employing the TDDFT approach, the B3LYP functional and the aug-cc-pVDZ basis set. The rotational strength calculations have been carried out both in velocity and length formalism; the results in the two formalisms are almost identical. The calculated CD spectra in $\Delta\varepsilon$ units have been obtained by using overlapping Gaussian functions according to:[13]

$$\Delta\varepsilon(E) = \frac{1}{2.297\times10^{-39}} \times \frac{1}{\sqrt{2\pi}\sigma}\sum_a \Delta E_{0a} R_{0a} \exp -[(E-\Delta E_{0a})/2\sigma]^2$$

where σ is the width of the band at 1/e height and ΔE_{0a} and R_{0a} are the excitation energies and rotational strengths for the transition from 0 to a, respectively. The σ value is an empirical parameter, and we used the value of 0.15 eV because this gives a good fitting with the experimental width of the bands. The DeVoe calculations were performed by means of a program written by Hug et al.[14] This program is available, free of charge, from the authors of the present article.

Acknowledgments

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Supplementary data

DFT/B3LYP/6-31G* full optimized geometries of model A including the Cartesian coordinates of the truncated model A-C using Gaussian03 software package. This material is available free of charge via the journal website. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.bmc.2005.04.007.

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10. Once the molecule is divided into groups, each group is represented in terms of one (or more) classical oscillator(s). Each oscillator represents an electric-dipole-allowed transition, defined by the polarization direction $\mathbf{e}_i$ and the complex polarizability $\alpha_i(v) = R_i(v) + iI_i(v)$. The $(I_i v)$ value is obtainable from the experiment, that is, from the absorption spectra of the compounds that can be considered good models of the subsystems, and $R_i(v)$ can be calculated from $I_i(v)$ by means of a Kronig–Kramers transform. More often, to simplify the calculation, a

Lorentzian shape is assumed for an absorption band, so $I_i(v)$ and $R_i(v)$ can be obtained by simple analytical formulae, which require (see Cech, C. L.; Hug, W.; Tinoco, I. Jr., *Biopolymers* 1976, *15*, 131) the dipole strength, λ_{max} and the bandwidth. From the general formulation of the DeVoe model, retaining only the terms to first order in G_{12} (physically, this means considering that the electric dipole on the i chromophore is caused by the external e.m. field plus the dipolar fields of the other dipole polarized by the external field only) the following expression can be deduced (for two different chromophores having only one electrically allowed transition each), which provides CD as a frequency function: $\Delta\varepsilon(v) = 0.014\pi^2 N\mathbf{e}_1 X\mathbf{e}_2 \boldsymbol{R}_{12} G_{12} v^2 [I_1(v)R_2(v) + I_2(v)R_1(v)]$; $G_{12} = (1/r_{12})^3 [\mathbf{e}_1.\mathbf{e}_2 - 3(\mathbf{e}_1\mathbf{e}_{12})(\mathbf{e}_2\mathbf{e}_{12})]$. Here $\mathbf{e}_1$, $\mathbf{e}_2$ are the unit direction vectors of the transition dipole moments of the first and second chromophore, respectively, $\boldsymbol{R}_{12}$ is the distance vector between them and r_{12} its modulus, G_{12} is the point–dipole–point–dipole interaction term and v is the frequency expressed in cm^{-1}. This expression gives rise to a couplet-like feature if the absorption maxima of the chromophore 1 and 2 are near in frequency ('quasidegenerate' coupled oscillator system).

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