Conformational Changes in Cryptophane Having C_1-Symmetry Studied by Vibrational Circular Dichroism

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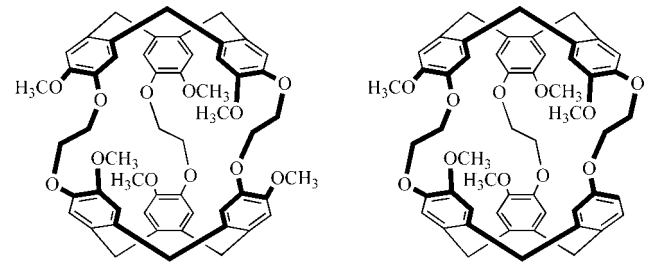
Vibrational circular dichroism (VCD) measurements and density functional theory (DFT) calculations were used to obtain the absolute configuration of a cryptophane molecule having C_1-symmetry (labeled cryptophane-H). This molecule exhibits chiroptical properties different from those published for cryptophane-A having D_3-symmetry [Brotin et al. *J. Am. Chem. Soc*. **2006**, *128*, 5533−5540]. In particular, we have shown that the conformation of the aliphatic linkers is very dependent on the solvent used and its ability to enter ($CDCl_3$ solution) or not ($C_2D_2Cl_4$ solution) in the cryptophane cavity. Calculations performed at the DFT (B3PW91/6-31G*) level establish, besides the absolute configuration, the preferential anti and gauche conformations of the aliphatic linkers of the chloroform@cryptophane-H complex and the empty cryptophane-H molecule, respectively. Polarimetric measurements performed in several solvents reflect also the change of conformation of the bridges upon guest encapsulation.

1. Introduction

Vibrational circular dichroism (VCD) has received much attention from chemists and has rapidly appeared as a powerful technique for the conformational analysis of chiral molecules.[1−3] The growing interest in this technique arises from the ability of VCD spectroscopy to predict the absolute configuration (AC) of molecules when density functional theory (DFT) calculations are done in parallel.[4] The determination of AC is thus made possible by comparison of the experimental spectrum with the predicted VCD spectrum calculated by using an arbitrarily chosen AC of the molecule. If the major bands of the measured and calculated VCD spectrum agree in relative magnitude and sign, then the AC chosen for the calculation is the same as that of the sample measured. With the computational power now available and the recent progress in computational methods, the determination of AC by VCD spectroscopy has no longer been restricted to the study of small chiral molecules. For instance, the mixed approach (DFT calculations/VCD experiments) has been used to elucidate larger, more complex structures, including supramolecular assemblies,[5−7] biopolymers (and oligomers), [8−11] foldamers,[12,13] and structural chiral complexes.[14−17] The last two studies concerned optically pure cryptophane derivatives, which are very interesting globular molecular objects.

Cryptophanes are nearly spherical cage molecules composed of two cyclotriveratrylene (CTV) bowls connected by three aliphatic linkers. The rigid bowl-shaped structure of the cavity of cryptophane makes these molecules very attractive for the investigation of host−guest interactions.[18−28] In a previous study,[16] we have performed VCD measurements and DFT calculations for cryptophane-A molecule (labeled **1** in Chart 1) and chloroform@cryptophane-A complex having D_3- and C_3-symmetry, respectively. This study represents an interesting and a challenging problem, because the cryptophane-A molecule

CHART 1



1 **2**

($C_{54}H_{54}O_{12}$) was one of the largest molecules ever investigated by ab initio calculations and VCD spectroscopy for the determination of its AC. Moreover, it is also interesting to determine if the encapsulation of an organic molecule by **1** could perturb the conformation of the host molecules (in particular, the ethoxy linkers) and is consequently able to change the VCD spectra with respect to the empty cryptophane. In this study, we have shown the potentiality of DFT calculations (B3PW91 functional and 6-31G* basis set) to predict both infrared (IR) and VCD spectra of cryptophane-A. A good agreement was observed between experimental and predicted spectra for the anti conformation of the aliphatic linkers, suggesting this preferential conformation for the empty cryptophane-A molecule and the chloroform@cryptophane-A complex. In contrast, no significant effect of the nature of the encapsulated solvent was observed in the experimental VCD spectra.

More recently, a synthetic route for the preparation of new chiral cryptophanes of C_1-symmetry with very high enantiomeric excess (close to 100%) has been given, and their chiroptical properties have been investigated.[17] We have shown that when one methoxy group is replaced with an electron-withdrawing group such as a hydrogen atom (labeled **2** in Chart 1), the chiroptical properties are significantly different from those of the highly symmetric cryptophane-A derivative. Moreover, we

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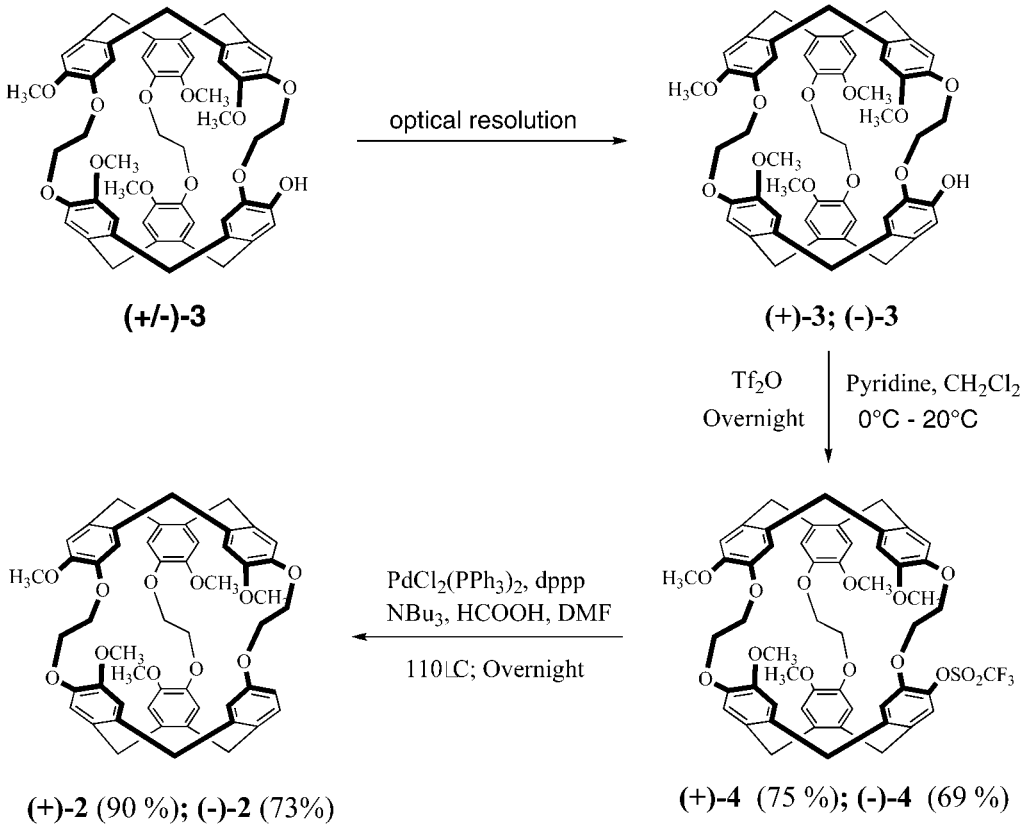

Figure 1. Preparation of enantiopure (+)-cryptophane-H [(+)-**2**] and (−)-cryptophane-H [(−)-**2**] from resolved cryptophanol (+)-**3** and (−)-**3**.

have found that the electronic circular dichroism (ECD) spectrum of this new cryptophane derivative (called also cryptophane-H) is very sensitive to the nature of the solvent. Thus, it appeared interesting to us to make further investigations of the chiroptical properties of **2** by VCD spectroscopy and DFT calculations to answer the following questions: (i) Is the conformation of the aliphatic linkers of empty cryptophane-H the same as that determined for the highly symmetric cryptophane-A derivative? (ii) Can the spectral modifications observed on ECD spectra for different solvents be associated with conformational changes of the bridges? (iii) Can the lack of symmetry and the presence of two different caps having different electronic densities induce a preferential orientation of the guest molecule in the cavity?

In this study, IR and VCD measurements and theoretical ab initio quantum calculations were used to determine the conformation of **2** with empty cavities (in $C_2D_2Cl_4$ solution) or with guest entities (in the $CDCl_3$ and CD_2Cl_2 solutions). The calculations of the IR and VCD intensities of this very large molecule with C_1-symmetry have been made at the DFT level, using B3PW91 functional and 6-31G* basis set. Even though these calculations were time-demanding due to the lack of symmetry of this cryptophane molecule, we have considered either anti or gauche conformation for the three ethoxy linkers or a mixture of these two conformations.

2. Experimental Section

Synthesis of Resolved Cryptophane-H (+)-2 and (−)-2. Optically pure cryptophane-H (+)-**2** and (−)-**2** were prepared from a multistep synthesis from racemic cryptophanol (±)-**3**.[29−31] The latter in turn provided the two isomers cryptophanol (+)-**3** and (−)-**3** (see Figure 1), according to a previously published procedure.[32] A subsequent reaction of (+)-**3** and (−)-**3** with anhydride triflic in a mixture of pyridine and CH_2Cl_2 at 0 °C gave rise to the two isomers (+)-**4** and (−)-**4** with good yields. Next, reduction of the triflic moiety was performed with a catalytic amount of $PdCl_2(PPh_3)_2$ in the presence of formic acid and 1,3-bis(diphenylphosphino)propane (dppp) in a mixture of DMF and tri-*n*-butylamine (NBu_3) at 110 °C to provide the two cryptophane isomers (+)-**2** and (−)-**2** in good yields.[17]

TABLE 1: Optical Rotations $[\alpha]^{25}_{\lambda}$ (10^{-1} deg cm^2 g^{-1}) of (+)-2 and (−)-2 at 25 °C[a]

	conc.[b]	[α] 589	[α] 577	[α] 546	[α] 436	[α] 365
(+)-**2**[c]	0.15	+255.5	+270.6	+315.0	+600.5	+1126.6
(−)-**2**[c]	0.18	−254.9	−267.3	−310.0	−583.0	−1097.4
(+)-**2**[d]	0.15	+203.3	+214.5	+248.8	+478.7	+918.4
(−)-**2**[d]	0.15	−205.4	−214.6	−248.2	−475.2	−916.0
(+)-**2**[e]	0.17	+147.3	+159.6	+183.5	+352.6	+704.3
(−)-**2**[e]	0.17	−148.3	−163.5	−184.7	−359.4	−708.8
(+)-**1**[c]	0.17	+269.0	+284.0	+326.5	+626.5	+1152.0
(−)-**1**[c]	0.13	−274.0	−288.0	−332.0	−623.4	−1154.0
(−)-**1**[d]	0.20	−233.9	−245.5	−282.6	−536.2	−1013.5
(−)-**1**[e]	0.17	−207.0	−221.3	−258.6	−485.9	−917.9

[a] Experimental errors on [α] values are estimated to ±5%. [b] Concentration is given in grams per 100 mL. [c] Performed in chloroform. [d] Performed in dichloromethane. [e] Performed in 1,1,2,2-tetrachloroethane.

Optical rotations of (+)-**2** and (−)-**2** were measured at several wavelengths on a Jasco P-1010 polarimeter with a 100 mm cell thermostatted at 25 °C and are reported in Table 1. These optical rotations recorded in various solvents ($CHCl_3$, CH_2Cl_2, and $C_2H_2Cl_4$) have the same magnitudes with opposite signs (within the range of the experimental error) as expected for a pair of enantiomers.

FTIR Measurements. The infrared and VCD spectra were recorded with a ThermoNicolet Nexus 670 FTIR spectrometer equipped with a VCD optical bench.[33] In this optical bench,

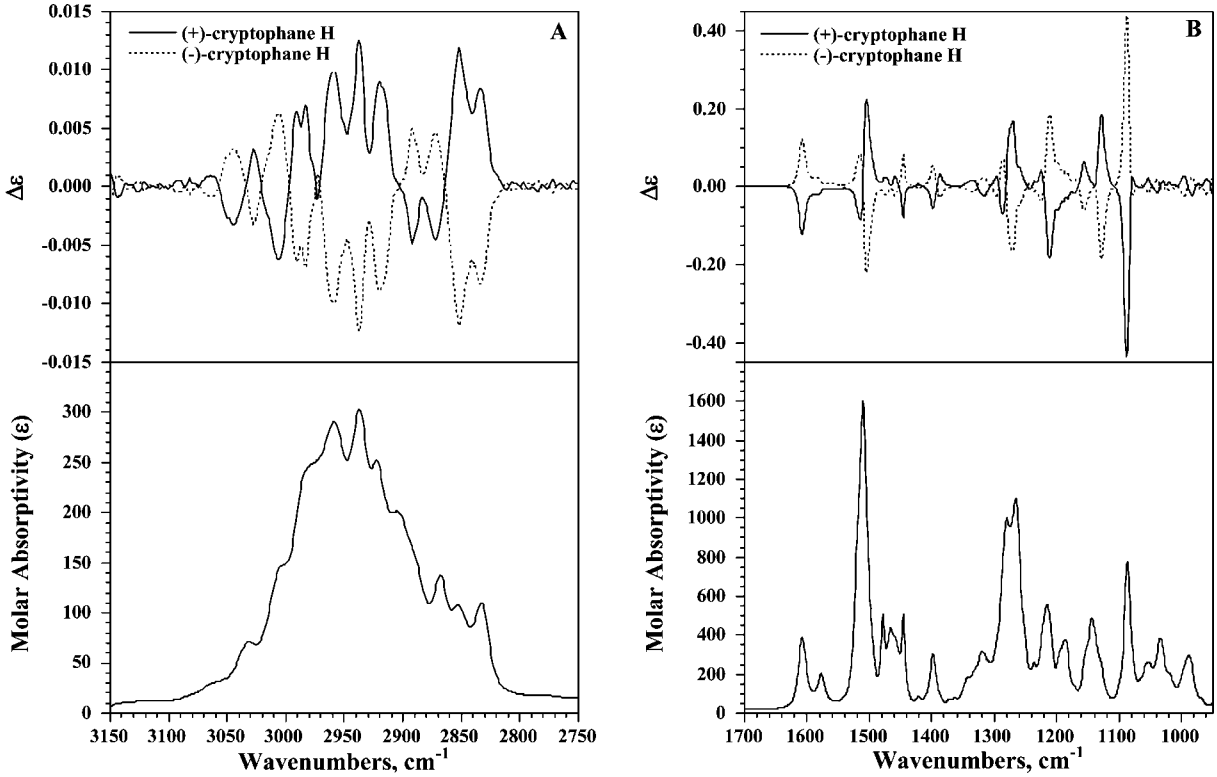

Figure 2. Experimental IR (lower frame) and VCD (upper frame) spectra of (+)-**2** (−) and (−)-**2** (- - -) in $CDCl_3$ solvent in (A) the 3150−2750 cm^{-1} and (B) the 1700−950 cm^{-1} regions. Solvent spectra are subtracted from the IR and VCD spectra of each sample.

the light beam was focused on the sample by a BaF_2 lens (191 mm focal length), passing an optical filter (depending on the studied spectral range), a BaF_2 wire grid polarizer (Specac), and a ZnSe photoelastic modulator (Hinds Instruments, type II/ZS50). The light was then focused by a ZnSe lens (38.1 mm focal length) onto a 1 × 1 mm^2 HgCdTe (ThermoNicolet, MCTA* E6032) detector. Absorption and VCD spectra were recorded at a resolution of 4 cm^{-1}, by coadding 50 scans and 24 000 scans (8 h acquisition time), respectively. Samples were held in a variable path length cell with BaF_2 windows. Spectra of (+)-**2** and (−)-**2** were measured in $CDCl_3$ solvent at a concentration of 0.015 M and at a path length of 250 μm (1 mm in the CH stretching region). Additional spectra were run in the mid-IR spectral range in CD_2Cl_2 and $C_2D_2Cl_4$ solvents at a concentration of 0.015 M and at a path length of 250 μm. Baseline corrections of the VCD spectra were performed by subtracting the raw VCD spectra of the solvents. In all of the experiments, the photoelastic modulator was adjusted for a maximum efficiency at 1400 cm^{-1} (3000 cm^{-1} for experiments in the CH stretching region). Calculations were done with the standard ThermoNicolet software, using Happ and Genzel apodization, de-Haseth phase-correction, and a zero-filling factor of 1. Calibration spectra were recorded using a birefringent plate (CdSe) and a second BaF_2 wire grid polarizer, following the experimental procedure previously published.[34] Finally, in the presented absorption spectra, the solvent absorption was subtracted out.

DFT Calculations. The geometry optimizations, vibrational frequencies, absorption, and VCD intensities were calculated via the Gaussian 03 program[35] on the CIS-IBM (with 16 processors) at the M3PEC computing center of the University Bordeaux I. Calculations of the optimized geometry of (+)-**2** were performed at the density functional theory level using B3PW91 functional and 6-31G* basis set. The theoretical framework for geometry optimization of cryptophane molecule has been previously published.[16] In a first step, we have performed DFT calculations for the empty cryptophane-H molecule. The three $-OCH_2CH_2O-$ bridges were considered either with an anti conformation (referring to the bonds to the O atoms having a 180° dihedral angle), of which there are two possibilities (the two anti conformations labeled T_1 and T_2 differ in the position of the CH_2 groups with respect to the O−O direction), or with a gauche conformation (60° dihedral angle), of which there are two possibilities (G_- for a −60° dihedral angle and G_+ for a +60° dihedral angle). In a second step, geometry optimizations with the introduction of a chloroform molecule inside the cryptophane cavity were performed, considering either T_1 or G_- conformation for the three ethoxy linkers ($T_1T_1T_1$ and $G_-G_-G_-$ conformers) or a mixture of these two conformations ($G_-T_1T_1$ conformers). Finally, calculations with the C−H bond of the chloroform pointing toward symmetrical and nonsymmetrical bowls were also performed for the $T_1T_1T_1$ conformers. Vibrational frequencies, IR, and VCD intensities were calculated at the same level of theory, utilizing the magnetic field perturbation method with gauge-invariant atomic orbitals.[36] For comparison to experiment, the calculated frequencies were scaled by 0.968, and the calculated intensities were converted to Lorentzian bands with a half-width of 7 cm^{-1}.

3. Results and Discussion

Polarimetric Measurements of (+)-2 and (−)-2. Optically pure derivatives **1** and **2** were first characterized by polarimetry in various solvents ($CHCl_3$, CH_2Cl_2, and $C_2H_2Cl_4$), and their optical rotation recorded at several wavelengths is reported in Table 1. The optical rotation values measured for **2** in chloroform are slightly lower than those previously reported for **1** in the same experimental condition (see Table 1).[16] The optical rotation values of **2** and **1** decrease in $C_2H_2Cl_4$ solution and to a smaller extent in CH_2Cl_2 solution. Although the behavior is the same for the two compounds, the magnitude is

more important for **2**. Indeed, the decrease of the optical rotation values in $C_2H_2Cl_4$ solution with respect to those measured in chloroform is almost double that for **2** (42% for cryptophane-H and 24% for cryptophane-A). This discrepancy is certainly associated with conformational changes of the aliphatic linkers of **2** in $C_2H_2Cl_4$, a solvent that cannot enter into the cavity of cryptophane.

Experimental IR and VCD Spectra of (+)-2 and (−)-2. The experimental IR and VCD spectra of (+)-**2** and (−)-**2** in $CDCl_3$ solvent are reported in Figure 2 in the 3150−2750 and 1700−950 cm^{-1} regions. The IR spectra of the two samples overlay nearly exactly, indicative of similar high purity of the two samples. Furthermore, the VCD spectra are nearly perfect mirror images in the two spectral ranges, indicating identical optical purity. The IR and VCD spectra of cryptophane-H seem to be similar to those previously published for cryptophane-A.[16] Nevertheless, a closer examination of the VCD spectrum reveals an overall decrease of the band intensities. This feature has not been observed for monofunctionalized cryptophanes with electron-donating substituents.[17] Therefore, the spectral modifications observed in the VCD spectra of (+)-**2** and (−)-**2** cannot be attributed to the lack of symmetry of cryptophane-H. On the other hand, the absence of an electron-donating methoxy group in one of the bowls strongly affects the global electronic circulation in the CTV units, and consequently may decrease the VCD band intensities.

Solvent Effect on the IR and VCD Spectra of (+)-2. The effect of the nature of the solvent has been investigated. Experiments have been performed in $CDCl_3$ and CD_2Cl_2 (two solvents that enter into the cavity of cryptophane-H) and in $C_2D_2Cl_4$ (a solvent that does not enter into the cavity of cryptophane derivatives). The experimental IR and VCD spectra of (+)-**2** recorded in these three solvents are reported in Figure 3 in the 1700−1100 cm^{-1} region. The VCD spectra recorded in CD_2Cl_2 and $C_2D_2Cl_4$ solutions reveal an overall decrease of the band intensities with respect to that recorded in $CDCl_3$ solution. A correlation between the dielectric constants of the three solvents (i.e., $\varepsilon = 4.9$ for $CHCl_3$, $\varepsilon = 8.93$ for CH_2Cl_2, and $\varepsilon = 8.42$ for $C_2H_2Cl_4$) and the tendency observed in the VCD spectra of (+)-**2** can be noted. Consequently, the changes in the VCD spectra could be due to the physical properties of the bulk solvent and induced conformational change of the cryptophane-H. On the other hand, a conformational change of the ethoxy linkers induced by the presence or absence of a guest molecule could also explain these spectral modifications. Indeed, the van der Waals volume of chloroform (72.2 $Å^3$)[20,37] is close to the size of the cryptophane cavity in its anti conformation (ca. 95 $Å^3$).[38,39] In contrast, for the two others solvents, the van der Waals volumes are significantly smaller (57.6 $Å^3$ for CD_2Cl_2)[20,37] and larger (104 $Å^3$ for $C_2D_2Cl_4$)[37] than the volume of the cryptophane cavity. Consequently, the aliphatic linkers could adopt gauche conformations to stabilize either the CD_2Cl_2@cryptophane-H complex[40] or the empty dissymmetrical derivative. This assumption is supported by the fact that the bands observed in the 1250−1300 cm^{-1} spectral range, involving wagging and twisting vibrations of the CH_2 chains, are strongly perturbed by the nature of the solvent. Indeed, the relative intensities of the two components at 1264 and 1280 cm^{-1} in the IR spectrum as well as the positive component at 1270 cm^{-1} in the VCD spectrum are very dependent on the solvent.

Conformational Analysis of (+)-2. Various conformations of the aliphatic linkers are possible for the cryptophane-H molecule, because each O−CH_2−CH_2−O bridge gives rise to four conformations (T_1, T_2, G_-, and G_+). It is not possible to calculate all conformers for this large molecule having C_1-symmetry because optimized geometries required about 20 days on a monoprocessor CIS-IBM computer, while their VCD spectra were obtained in 40 days. We then built and optimized the structures of the four conformers in which the three linkers have the same conformation. Using the starting O−C−C−O dihedral angles close to 180° for T_1 and T_2 conformations and ±60° for G_+ and G_- conformations, the geometries of the empty cavity were optimized at the B3PW91/6-31G* level. Harmonic vibrational frequencies were calculated at the same level to confirm that all structures are stable conformations and to enable free energies to be calculated. The converged twist angles between the two CTV bowls, O−C−C−O dihedral angles, and optimized energies are listed in Table 2. The converged twist angles between the two CTV units are slightly dependent on the bridge conformations and range between 41° and 54°. On the other hand, the optimized energies are very dependent on the ethoxy linker conformations; the $G_-G_-G_-$ conformer has a much lower energy than the others studied conformations. On the basis of the ab initio predicted Gibbs free energies, it can be concluded that the G_- conformation of the ethoxy linkers is favorable for the empty cryptophane-H. The optimized geometries of the three others conformers are more than 2 kcal/mol higher in free energies.

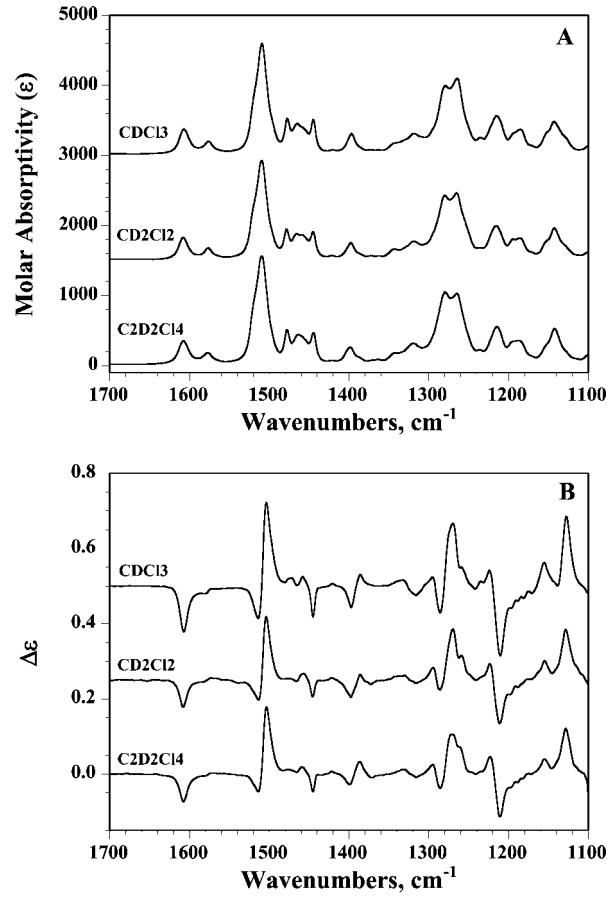

Figure 3. Comparison of experimental IR (A) and VCD (B) spectra of (+)-**2** in $CDCl_3$, CD_2Cl_2, and $C_2D_2Cl_4$ solvents.

Similar calculations were performed for the chloroform@cryptophane-H complex. Because of the longer computational time, only $T_1T_1T_1$ and $G_-G_-G_-$ conformers have been first considered. Under these conditions, the T_1 conformation of the aliphatic linkers yields a final optimized structure of the complex 1.62 kcal/mol lower in energy than the G_- conformation. The

TABLE 2: Conformations and Energies of (+)-2

conformer	converged geometries: twist angle between the 2 CTV units	converged geometries: dihedral angle O−C−C−O	energy[a]: electronic	energy[a]: Gibbs	ΔE^b (kcal/mol)
		Empty Cryptophane-H			
$T_1\ T_1\ T_1$	49.0°	175.0°	−2877.195293	−2876.323496	2.63
$T_2\ T_2\ T_2$	41.1°	−174.9°	−2877.193821	−2876.324148	2.22
$G_-\ G_-\ G_-$	42.1°	−63.1°	−2877.202099	−2876.327683	0.0
$G_+\ G_+\ G_+$	53.9°	69.1°	−2877.198073	−2876.321728	3.74
		$CHCl_3$@Cryptophane-H			
$T_1\ T_1\ T_1$[c]	38.3°	169.2°	−4296.290400	−4295.410757	1.85
$T_1\ T_1\ T_1$[d]	39.5°	170.5°	−4296.290236	−4295.408141	3.49
$G_-\ G_-\ G_-$[c]	38.9°	−67.8°	−4296.293455	−4295.408167	3.47
	35.0°	−63.6°			
$G_-T_1\ T_1$[c]	36.2°	167.3°	−4296.297278	−4295.413703	0.0
	35.5°	168.4°			

[a] In hartrees. [b] Relative Gibbs energy difference. [c] C−H bond of $CHCl_3$ points toward symmetrical bowl. [d] C−H bond of $CHCl_3$ points toward nonsymmetrical bowl.

addition of a chloroform molecule in the cryptophane-H cage stabilizes the $T_1T_1T_1$ conformer. This result is not surprising due to the better size matching between the chloroform (ca. 72.2 Å^3) and the cryptophane cavity in its anti conformation (ca. 95 Å^3). However, the presence of two different CTV bowls having different electronic densities may induce a preferred orientation of the chloroform molecule in the cavity. Therefore, we have calculated the optimized geometry of the $T_1T_1T_1$ conformer considering the C−H bond of the chloroform pointing toward either symmetrical or nonsymmetrical bowls. The complex with the C−H bond oriented toward the bowls having the higher electronic density is stabilized. We have also calculated the optimized geometry for the $G_-T_1T_1$ conformer because this conformation of the aliphatic bridges has been determined from the X-ray structure of crystalline $CHCl_3$@cryptophane-A complex.[41] The $G_-T_1T_1$ conformer leads to the lowest Gibbs free energy. Indeed, the $T_1T_1T_1$ and $G_-G_-G_-$ conformers are 1.85 and 3.47 kcal/mol higher in free energy, respectively. Finally, for the $CHCl_3$@cryptophane-H complexes, the converged twist angles between the two CTV units seem to be independent of the linker conformations and are closed to 38°. These values are lower than those calculated for the empty cryptophane and are associated with the small increase (∼2%) of the distance between the two CTV units in the presence of a chloroform molecule. However, these structural modifications of the cryptophane cavity are scarcely perceptible on the optimized geometries reported in the Supporting Information.

Calculated VCD Spectra of (+)-2. The VCD spectra calculated at the B3PW91/6-31G* level for $T_1T_1T_1$, $T_2T_2T_2$, $G_+G_+G_+$, and $G_-G_-G_-$ conformers of empty (+)-**2** are compared in Figure 4a to the experimental spectrum of (+)-cryptophane-H in $C_2D_2Cl_4$ solution. The experimental spectrum of (+)-**2** in $C_2D_2Cl_4$ solution has been chosen because $C_2D_2Cl_4$ cannot enter into the cavity of cryptophane-H molecule. The VCD spectra predicted for the four conformers reproduce the sign of the major bands observed on the experimental spectrum, allowing the definitive determination of the configuration ((+)-**2**) of the molecule. Nevertheless, the intensities of the VCD bands are very dependent on the conformation of the aliphatic linkers. It is noteworthy that the calculated VCD spectra for the $G_-G_-G_-$ conformer reproduce fairly well the intensity and the sign of the bands observed on the experimental spectrum, establishing the preferential $G_-G_-G_-$ conformation of the aliphatic linkers. This result is in perfect agreement with the conformational analysis presented above.

We have shown that the experimental VCD spectrum of (+)-**2** changes significantly when chloroform solvent is used. To understand this effect, VCD spectra have been calculated at the B3PW91/6-31G* level for $T_1T_1T_1$, $G_-T_1T_1$, and $G_-G_-G_-$ conformers of $CHCl_3$@(+)-**2** complex and are compared in Figure 4b to the experimental spectrum of (+)-cryptophane-H in $CDCl_3$ solution. The DFT calculations have been performed considering that the C−H bond of the chloroform points toward symmetrical CTV bowls. The VCD spectrum calculated for the $T_1T_1T_1$ conformer of $CHCl_3$@(+)-**2** complex is similar to that calculated for the empty molecule and is in satisfactory agreement with the experimental spectrum. Moreover, the VCD

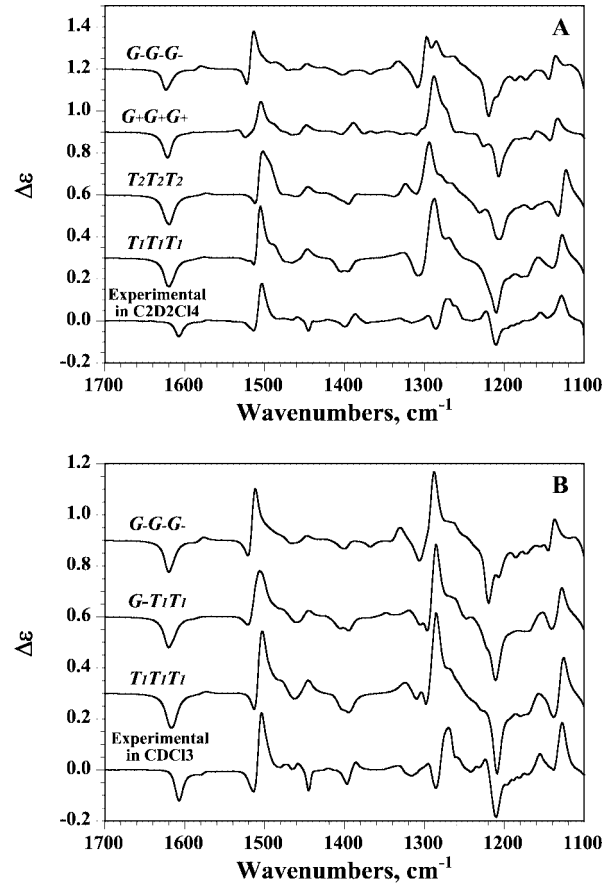

Figure 4. (A) Comparison of experimental VCD spectrum of (+)-**2** in $C_2D_2Cl_4$ solvent with calculated spectra at the B3PW91/6-31G* levels for $G_-G_-G_-$, $G_+G_+G_+$, $T_1T_1T_1$, and $T_2T_2T_2$ conformers of (+)-**2**. (B) Comparison of experimental VCD spectrum of (+)-**2** in $CDCl_3$ solvent with calculated spectra at the B3PW91/6-31G* levels for $T_1T_1T_1$, $G_-T_1T_1$, and $G_-G_-G_-$ conformers of $CHCl_3$@(+)-**2** complex.

spectrum calculated with the C−H bond of the chloroform pointing toward the nonsymmetrical CTV bowl does not exhibit spectral modifications, suggesting weak interactions between guest and host molecules. On the other hand, the VCD spectrum calculated for the $G_-G_-G_-$ conformer of $CHCl_3$@(+)-**2** complex exhibits spectral modifications with respect to the empty molecule, in particular in the regions associated with wagging and twisting vibrations of CH_2 groups (1350−1250 cm^{-1}). Because the cavity volume of the $G_-G_-G_-$ conformer of (+)-**2** is lower than that of the $T_1T_1T_1$ one, the encapsulation of a chloroform molecule should modify the conformation of the host molecule (the twist angle between the two CTV bowls decreases and becomes closer to that of $T_1T_1T_1$ conformer). Consequently, the spectral modifications between the calculated VCD spectra for the $T_1T_1T_1$ and $G_-G_-G_-$ conformers are less marked than those observed for empty cryptophane. However, the VCD spectrum calculated for the $G_-G_-G_-$ conformer does not reproduce the experimental spectrum for wavenumbers lower than 1200 cm^{-1}. Finally, the VCD spectrum calculated for the $G_-T_1T_1$ conformer is also in good agreement with the experimental VCD spectrum, revealing the preferential anti conformation of the aliphatic linkers for $CHCl_3$@(+)-**2** complex.

The experimental VCD spectrum recorded in CD_2Cl_2 solution is quasi-identical to that recorded in $C_2D_2Cl_4$ solution. This result suggests a preferred gauche conformation of the aliphatic linkers when CD_2Cl_2 is encapsulated into the cavity of cryptophane-H. Because CD_2Cl_2 (57.6 $Å^3$) is smaller than chloroform (72.2 $Å^3$), the CD_2Cl_2@cryptophane-H complex is certainly stabilized when the cryptophane cavity has its minimum size, that is, for a gauche conformation of the three $O-CH_2-CH_2-O$ groups.

4. Conclusion

This Article demonstrates that DFT calculations associated with VCD experiments provide a detailed and accurate description of the conformation of optically pure cryptophane derivative having a C_1-symmetry. To show the potentiality of the methodology, we have investigated a cryptophane molecule with low symmetry (cryptophane-H) exhibiting different VCD spectra in various solvents. The solvents have been chosen because of their different physical and binding properties. We have found that the host molecule adopts a preferential anti conformation of the aliphatic linkers when the size of the guest molecule increases and becomes close to that of the cryptophane cavity, as evidenced by the $CDCl_3$@(+)-**2** complex. In contrast, a preferential gauche conformation of the aliphatic linkers has been revealed for empty cryptophane-H or when the size of the guest molecule is significantly smaller than that of the cryptophane cavity as shown with the CD_2Cl_2@(+)-**2** complex.

In addition, polarimetric measurements of (+)-**2** and (−)-**2** performed in several solvents also reflect the change of conformation of the bridges upon guest encapsulation. Whereas the cryptophane-A molecule gives to a moderate variation of the optical rotation ($[\alpha]_D$) values and no significant changes of its VCD spectrum as a function of the nature of the solvent, we have observed in contrast that cryptophane-H derivatives (+)-**2** and (−)-**2** exhibit large modifications of their $[\alpha]_D$ values with a change of the solvent properties. Moreover, a significant change of their experimental VCD spectra as a function of the solvent ($CDCl_3$, CD_2Cl_2, $C_2D_2Cl_4$) has been observed. These changes have been clearly correlated with a change of conformation of the linkers upon guest encapsulation. This assumption is supported by a recent VCD study of a new water-soluble cryptophane whose synthesis has been performed in our laboratory. Indeed, this derivative exhibits both large modifications of the $[\alpha]_D$ values and large modifications of their VCD spectra depending on the size of the species added into the aqueous solution (argon, xenon, CD_2Cl_2, $CDCl_3$, CCl_4). These results, which are still under investigation, will be published in due course.

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Supporting Information Available: Cartesian coordinates and view of the optimized geometries of the different conformers calculated for empty (+)-**2** and $CHCl_3$@(+)-**2** complex. This material is available free of charge via the Internet at http://pubs.acs.org.

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