

Vibrational Circular Dichroism Study of Optically Pure Cryptophane-A

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Abstract: Vibrational circular dichroism (VCD) measurements and density functional theory (DFT) calculations were used to obtain the absolute configuration of optically pure cryptophane-A molecule. This large molecule (120 atoms) that possess a globular shape, but no chiral centers, exceeds the molecular size of published structures for which VCD has been used to determine the absolute configuration. VCD spectra recorded in CDCl₃ solution for the two resolved enantiomers are near mirror images, and very good agreement between the observed IR and VCD spectra and intensity calculations performed at the DFT (B3PW91/6-31G*) level establish, besides the absolute configuration, the preferential anti conformation of the aliphatic linkers of the chloroform–cryptophane-A complex. Experiments performed in CD₂Cl₂ and C₂D₂Cl₄ solutions show no significant modifications in the IR and VCD spectra, indicating that the conformation of the aliphatic linkers is similar for empty (C₂D₂Cl₄ solution) and encaged (CDCl₃ and CD₂-Cl₂ solutions) cryptophane-A molecules.

Introduction

Vibrational Circular Dichroism (VCD) is the differential absorption of a chiral molecule to left- and right-handed circularly polarized radiation in the infrared (IR) region.¹ During the past decade, VCD appeared as a very promising tool for the study of the conformational analysis of chiral organic compounds.² This vibrational spectroscopic technique now becomes as popular as Electronic Circular Dichroism (ECD) in the UV–vis range or even Nuclear Magnetic Resonance (NMR) to extract important conformational information of organic compounds. The interest of this emerging spectroscopic technique is also a consequence of the recent progress made in computational quantum mechanical calculation used for the prediction of IR and VCD spectra. Both methods are complementary and cannot be dissociated for a complete analysis of vibrational spectra, but a combination of them usually provides important information, such as the absolute configuration and the conformation of the studied organic molecules.³ Unfortunately, since VCD ab initio quantum calculations are time demanding, only molecules with a moderate number of atoms have been reported so far in the literature. Additionally, most of the molecules studied by VCD in the literature usually refer

to molecules bearing asymmetric carbons, and only few examples of molecules exhibiting a structural chirality have been investigated by VCD spectroscopy. Nafie et al. reported both a theoretical and a VCD study of (–)-heptathiophene (C₂₂H₁₈-Br₂S₇Si₂), a helical molecule with C₂-symmetry,⁴ of a D₂-symmetric dimer of 1,1'-binaphthyl (C₄₀H₂₄),⁴ and of a molecule with a C₂-chiral axis (gossypol, C₃₀H₃₀O₈).⁵ They showed that, even for such large molecules, ab initio quantum calculations allow one to predict with a high degree of precision both the IR and VCD spectra of these molecules as well as their absolute configurations. Similarly, Bürgi et al. determined the absolute configuration of heptahelicene (C₃₀H₁₈) from theoretical and VCD studies.⁶ Finally, in a recent study, Urbanova et al. determined the predominant conformation in the cyclic tetramer of (S)-2,2'-dimethylbiphenyl-6,6'-dicarboxylic acid and showed that VCD spectroscopy can be used to determine the structure of a supramolecular species.⁷ In all these studies, IR and VCD spectra were calculated at the density functional theory (DFT) level, using B3LYP or B3PW91 functionals and 6-31G* or larger basis sets.

Encouraged by these recent studies, we performed VCD measurements and ab initio calculations for large molecules with C₃- and D₃-symmetry, such as cryptophane molecules. Cryp-

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tophanes are nearly spherical cage molecules composed of two cyclotrimeratrylene (CTV) bowls connected by three aliphatic linkers. The rigid bowl-shape structure of the cavity of cryptophane makes these molecules very attractive for the investigation of host–guest interactions.⁸ The study of cryptophane molecules by VCD spectroscopy represents an interesting and a challenging problem. Indeed, cryptophane-A, whose chemical formula is C₅₄H₅₄O₁₂ (120 atoms), is the smallest of the series of cryptophanes whose optical resolution have been successfully achieved. Both (+)-cryptophane-A, (+)-**1**, and (–)-cryptophane-A, (–)-**1**, have been obtained from a recent procedure used for the optical resolution of cryptophanol-A.⁹ This procedure gives sizable amount of both compounds with a very high optical purity (close to 100%). By far, this chiral molecule represents one of the largest molecules ever investigated by ab initio calculation and VCD spectroscopy for the determination of its absolute configuration.

A second point of interest for studying these molecules by VCD spectroscopy is the globular shape of cryptophanes, which possess a lipophilic cavity able to encapsulate small neutral molecules, such as halogenomethanes or even xenon atom in organic solution. In particular, it should be interesting to show if the encapsulation of an organic molecule by cryptophane-A can perturb the conformation of the host molecules (in particular, the aliphatic linkers) and consequently is able to change the VCD spectra with respect to the empty cryptophane. Indeed, strong interaction between guest molecules and cryptophane derivatives has been evidenced by NMR studies.^{8d–j} Moreover, vibrational modifications on the guest molecules have been observed by Raman microspectrometry, in particular, for the chloroform–cryptophane-A complexes.¹⁰

In this study, IR and VCD measurements and theoretical ab initio quantum calculations were used to determine the absolute configuration of (+)-**1** or (–)-**1** in CDCl₃ solution. The calculations of the IR and VCD intensities of this very large molecule have been made at the DFT level (B3LYP and B3PW91 functionals) with 3-21G and 6-31G* basis sets. Others DFT calculations have been performed (B3PW91 functional and 6-31G* basis set) considering anti or gauche conformations of the ethyl linkers for empty cryptophane-A and the chloroform–cryptophane-A complex. Finally, an investigation of both IR and VCD spectra of cryptophane-A with empty cavities (in C₂D₂Cl₄ solution) or with guest entities (in the CDCl₃ and CD₂-Cl₂ solutions) is discussed.

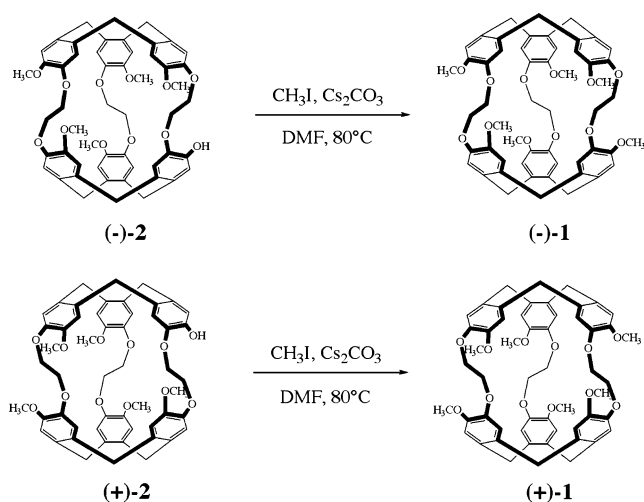


Figure 1. Preparation of enantiopure (+)-cryptophane-A [(+)-**1**] and (–)-cryptophane-A [(–)-**1**], from resolved cryptophanol (+)-**2** and (–)-**2**.

Table 1. Optical Rotations [α]_D²⁵ (10^{−1} deg cm² g^{−1}) of (+)-**1** and (–)-**1** at 25 °C^a

	concn ^b	[α] ₅₈₉	[α] ₅₇₇	[α] ₅₄₆	[α] ₄₃₆	[α] ₃₆₅
(+)- 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

^a Experimental errors on [α] values are estimated to $\pm 5\%$. ^b Concentration is given in grams per 100 mL. ^c Performed in chloroform.

Experimental Section

Synthesis of Resolved Cryptophane-A: Optically pure cryptophane-A (+)-**1** and (–)-**1** have been prepared from resolved cryptophanol (+)-**2** and (–)-**2** (see Figure 1), according to a known general procedure.⁹ (+)-**1** and (–)-**1** have been prepared in almost quantitative yield by reacting (+)-**2** and (–)-**2**, respectively, with methyl iodide in the presence of cesium carbonate in *N,N*-dimethylformamide (DMF) as previously reported. ¹H NMR spectra of (+)-**1** and (–)-**1** are identical to that previously reported for the racemic compound. Optical rotations of (+)-**1** and (–)-**1** were measured at several wavelengths on a Jasco P-1010 polarimeter with a 100 mm cell thermostated at 25 °C and are reported in Table 1. These optical rotations recorded in CHCl₃ have the same magnitudes with opposite signs (within the range of the experimental error) as expected for a pair of enantiomers.

VCD Measurements: The infrared and VCD spectra were recorded with a Thermo Nicolet Nexus 670 FTIR spectrometer equipped with a VCD optical bench.¹¹ In this optical bench, the light beam was focused by a BaF₂ lens (191 mm focal length) to the sample, passing an optical filter (depending on the studied spectral range), a BaF₂ 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 mm² HgCdTe (Thermo Nicolet, MCTA* E6032) detector. Absorption and VCD spectra were recorded at a resolution of 4 cm^{−1}, by coadding 50 and 24 000 scans (8 h acquisition time), respectively. Sample was held in a variable path length cell with BaF₂ windows. Spectra of (+)-**1** and (–)-**1** were measured in CDCl₃ solvent at a concentration of 0.015 M and at a path length of 250 μ m (500 μ m in the CH stretching region). Additional spectra were run in CD₂Cl₂ and C₂D₂Cl₄ solvents at a concentration of 0.0075 M and at a path length of 500 μ m. Baseline corrections of the VCD spectra were performed by subtracting the raw VCD spectra of the solvents. In all 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

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Thermo Nicolet 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 BaF₂ wire grid polarizer, following the experimental procedure previously published.¹² Finally, in the presented absorption spectra, the solvent absorption was subtracted out.

Theoretical Calculations

The minimum energy structure of the cryptophane-A cage was previously calculated for the xenon–cryptophane-A complex at the density functional theory level (B3LYP functional) using a 6-311G** basis set.¹³ In this work, the gauche conformation of the O–CH₂–CH₂–O bridges was retained to be consistent with the SPINOE experiments.^{8c} The geometry optimization was carried out only for a fragment representing 2/3 of the cage. The whole cage was then generated from this fragment. More recently, to calculate the Raman vibrational frequencies of the chloroform–cryptophane-A complexes, the minimum energy structure of the whole empty cryptophane-A cage was calculated at the HF level with a 6-31G* basis set, the vibrational frequencies supposed to be only slightly perturbed by the chloroform guest.¹⁰ Owing to the large molecular size of the cryptophane-A molecule, 1/3 of the CTV unit was first optimized. Then, the C₃-symmetry operations generated the CTV bowl. The O–CH₂–CH₂–O bridges were introduced between the two optimized CTV units by constraining the D₃-symmetry of cryptophane-A. This symmetry constraint generated an anti conformation of the ethyl linkers. This conformation was shown to be prevalent from the X-ray structures of chloroform–cryptophane-A complexes.¹⁰

The cryptophane-A molecule studied here possesses no asymmetric group, and its optical activity has only a structural origin. Thus, the analysis of its VCD spectrum requires at least the geometry optimization of the whole empty molecule. Calculations were performed on (+)-**1** at DFT level (B3LYP and B3PW91 functionals, 3-21G and 6-31G* basis sets) with the Gaussian 03 program¹⁴ on up to four processors on a SGI Altix3300. The same computational method as that previously described¹⁰ was used. Nevertheless, the –OCH₂CH₂O– bridges were introduced between the two optimized CTV bowls by constraining either 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 differ in the position of the CH₂ groups with respect to the O–O direction) or either a gauche conformation (60° dihedral angle) of which there are two possibilities (gauche – for a –60° dihedral angle and gauche + for a 60° dihedral angle). The two anti conformations (labeled T₁ and T₂) as well as the two gauche conformations (labeled G_– and G₊) are presented in Figure 2. It is noteworthy that the anti conformations for the three aliphatic linkers (labeled T₁T₁T₁ and T₂T₂T₂) give rise to D₃-symmetry of the molecule, whereas the gauche conformations (labeled G_–G_–G_– and G₊G₊G₊) give rise to C₃-symmetry. Calculations with the introduction of a chloroform molecule inside the cryptophane cavity were also performed, considering either T₁ or G_– conformation for the three aliphatic linkers (T₁T₁T₁ and G_–G_–G_– conformers) or a mixture of these two conformations (G_–T₁T₁ and G_–G_–T₁ conformers).

Calculation of the optimized geometry of the empty cryptophane-A (120 atoms) requires 702 basis functions, 1152 primitive Gaussians for the 3-21G basis set, and 1098 basis functions, 2064 primitive Gaussians for the 6-31G* basis set. Calculation of the optimized geometry of the chloroform–cryptophane-A complex (125 atoms), only performed with the 6-31G* basis set, requires 1172 basis functions and 2252 primitive Gaussians. Vibrational frequencies and IR and VCD

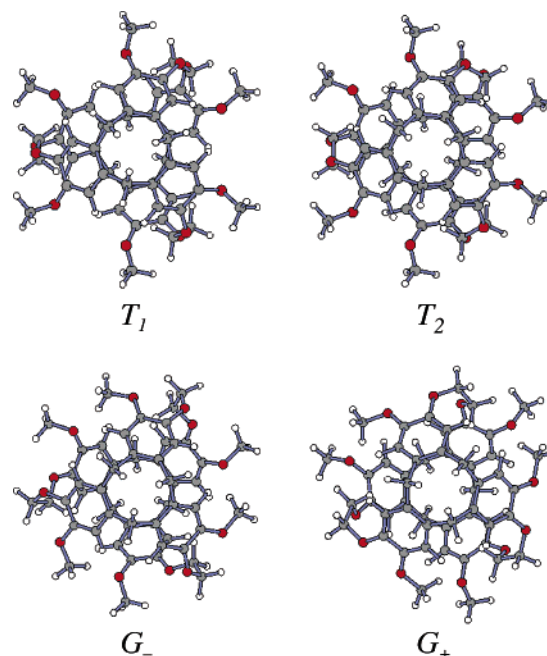


Figure 2. Optimized geometries of T₁, T₂, G₊, and G_– conformations of the (+)-cryptophane-A molecule (view along the C₃-symmetric axis).

intensities were calculated at the same level with Gaussian 03, utilizing the magnetic field perturbation method with gauge-invariant atomic orbitals.¹⁵

For comparison to experiment, the calculated frequencies were scaled by 0.984 (B3LYP/3-21G), 0.98 (B3PW91/3-21G), and 0.968 (B3PW91/6-31G*), and the calculated intensities were converted to Lorentzian bands with half-width of 7 cm^{–1}.

Results and Discussion

Experimental IR and VCD Spectra of (+)-**1** and (–)-**1**.

The experimental IR and VCD spectra of (+)- and (–)-cryptophane-A in CDCl₃ solvent are reported in Figure 3 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, and the VCD spectra are nearly perfect mirror images in the two spectral ranges, indicating identical optical purity. The VCD spectra were obtained with a very good signal-to-noise ratio since the band intensities observed in the CH stretching region are lower than 10^{–5} in differential absorbance. The low noise of our optical setup for long time acquisition ($\Delta A \approx 10^{-6}$) allows us to reveal the complexity of the VCD spectrum in this spectral range (Figure 3a). Indeed, it is possible to identify for each enantiomer the VCD sign of the 12 components (3065.4, 3032.8, 3005.5, 2985.5, 2958.4, 2936.8, 2921.7, 2902.4, 2889.1, 2866.6, 2853.3, and 2831.4 cm^{–1}) which can be resolved by Fourier self-deconvolution of the absorption spectrum. Nevertheless, this region is very difficult to analyze due to the anharmonicity of the CH stretching modes and to the Fermi resonances occurring in this spectral range. The IR and VCD spectra measured in the 1700–950 cm^{–1} region (Figure 3b) are simpler and more easily analyzed. The frequencies observed on these spectra for the most important bands as well as their assignments are reported in Table 1 of Supporting Information.

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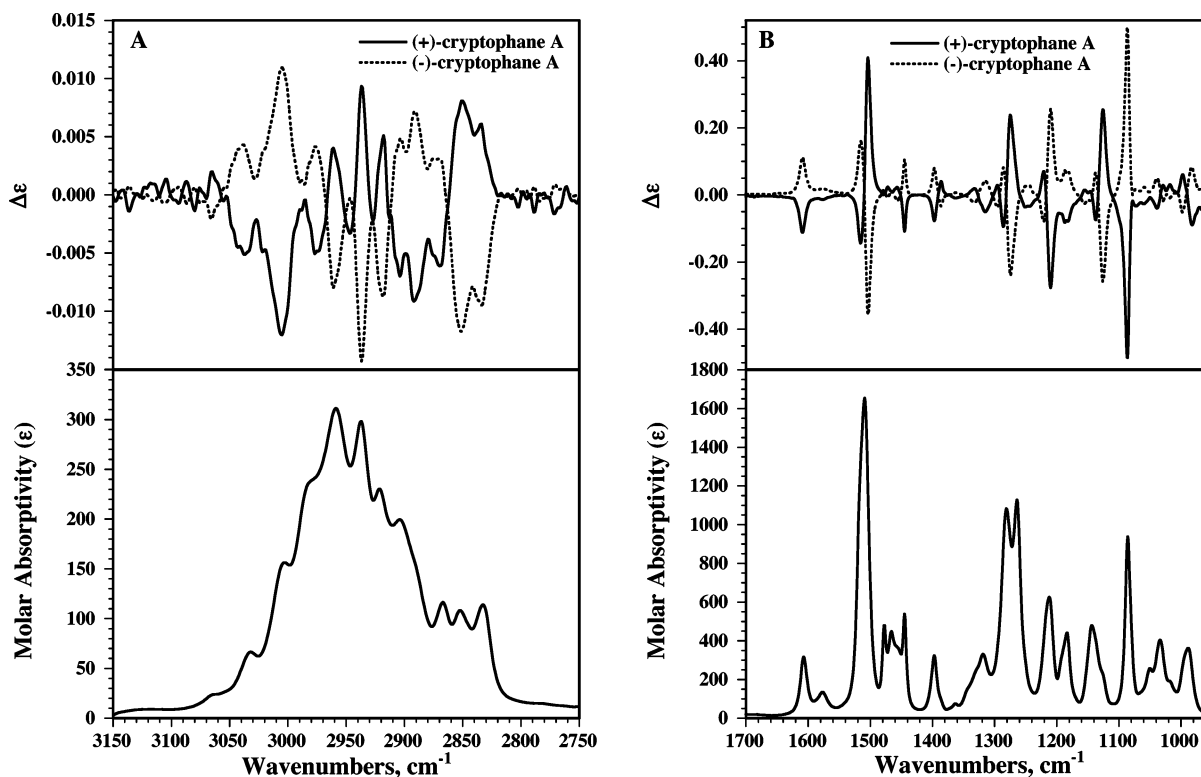


Figure 3. Experimental IR (lower frame) and VCD (upper frame) spectra of (+)-cryptophane-A (full line) and (-)-cryptophane-A (dashed line) in CDCl₃ solvent in (A) the 3150–2750 cm⁻¹ and (B) the 1700–950 cm⁻¹ regions. Solvent spectra are subtracted from the IR and VCD spectra of each sample.

The assignment has been performed from the literature¹⁶ and on the basis of the visual observation with GaussView software of the fundamentals calculated at the B3PW91/6-31G* level (vide infra). The bands due to the $\nu_{8a}C=C$, $\nu_{8b}C=C$, and $\nu_{19a}C=C$ stretching vibrations of the rings occur at 1607, 1577, and 1509 cm⁻¹, respectively. The deformation vibrations of CH₂ and CH₃ groups give rise to the bands observed in the 1480–1420 cm⁻¹ spectral range. The region between 1400 and 1250 cm⁻¹ is more complex because the observed bands correspond to coupled modes involving wagging and twisting vibrations of the CH₂ groups (chains and bowls). The bands associated to the anti-symmetric (as) and symmetric (s) stretching vibrations of C_{ring}–O–C in C_{ring}–O–Me and C_{ring}–O–Et groups occur at 1212 and 1034 cm⁻¹, respectively.¹⁷ Finally, the bands at 1183, 1144, and 1086 cm⁻¹ are assigned to the aromatic C_{ring}–H in-plane deformation vibration, to the rocking modes of CH₂ and CH₃ groups, and to the stretching vibration of C_{ring}–C, respectively. Even though the cryptophane-A molecule does not possess asymmetric carbons, the VCD spectrum exhibits strong bands (differential absorbance up to 2×10^{-4}) across this spectral range. These large VCD intensities on most of the bands are certainly due to large magnetic dipole contributions from charge circulation in the two CTV bowls.

Conformational Analysis of (+)-1. The analysis of the IR and VCD spectra of (+)-1 begins with the prediction of its optimized geometries. As mentioned above, various conformations are possible for the three ethyl linkers. Indeed, each O–CH₂–CH₂–O bridge gives rise to four conformations (*T*₁, *T*₂, *G*₋, and *G*₊), leading to 20 nonequivalent conformations of

the cryptophane-A molecule. In these 20 nonequivalent conformations, only the four conformers with an identical conformation of the three linkers have *D*₃- or *C*₃-symmetry. All the other conformers present a *C*₁-symmetry. We have built and optimized the structures of the four conformers of highest symmetry (see Figure 2). 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 have been calculated at the same level in order 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 (angle around the *C*₃ axis of a benzene ring of the upper bowl and the corresponding benzene ring of the lower bowl), 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 are ranged between 36 and 53°. On the other hand, the optimized energies are very dependent on the ethyl linker conformations; the *G*₋*G*₋*G*₋ conformer has a much lower energy than the other studied conformations. On the basis of the ab initio predicted Gibbs free energies, it can be concluded that the *G*₋ conformation of the ethyl linkers is favorable for the empty cryptophane-A. Nevertheless, it is important to note that these calculations have been achieved for isolated molecules. To have a more realistic system, similar calculations were performed for the chloroform–cryptophane-A complex. The lower symmetry of the complex (with respect to the empty molecule) increases significantly the computational times, and only the most stable forms of anti and gauche conformations (*T*₁*T*₁*T*₁ and *G*₋*G*₋*G*₋ conformers) have been considered. Under this condition, the *T*₁ conformation

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(17) The band observed at 997 cm⁻¹ can also be assigned to the symmetric stretching vibration of C_{ring}–O–C.

Table 2. Conformations and Energies of (+)-Cryptophane-A

conformer	Converged Geometries		Energy ^a		ΔG^b (kcal/mol)
	twist angle between the 2 CTV units	dihedral angle O–C–C–O	electronic	Gibbs	
Cryptophane-A					
$T_1T_1T_1$	36.5°	168.7°	–2991.662823	–2990.763092	4.25
$T_2T_2T_2$	46.7°	–173.1°	–2991.663895	–2990.759669	6.40
$G-G-G-$	43.6°	–63.6°	–2991.676488	–2990.769868	0.0
$G+G+G+$	53.1°	68.3°	–2991.671084	–2990.763570	3.95
CHCl ₃ –Cryptophane-A					
$T_1T_1T_1$	34.6°	167.1°	–4410.763333	–4409.852895	2.06
$G-G-G-$	39.8°	–68.3°	–4410.766447	–4409.849924	3.93
$G-T_1T_1$	38.1°	–66.2°	–4410.769881	–4409.856186	0.0
	37.0°	168.0°			
	36.6°	169.4°			
$G-G-T_1$	39.4°	–68.4°	–4410.768627	–4409.853239	1.85
	38.4°	–66.3°			
	37.7°	170.2°			

^a In Hartrees. ^b Relative Gibbs energy difference.

of the aliphatic linkers yields a final optimized structure of the complex 1.87 kcal/mol lower in energy than that of the $G-$ conformation. The addition of a chloroform molecule in the cryptophane-A 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 Å³) and the cryptophane cavity in its anti conformation (ca 82 Å³).¹⁸ Moreover, this result is in agreement with the X-ray structure of the crystalline CHCl₃–cryptophane-A complex, showing a preferential anti conformation of the aliphatic linkers.¹⁰ However, a more precise examination of the X-ray structures observed on rhomb and rod crystals for the CHCl₃–cryptophane-A complexes indicates that the three O–CH₂–CH₂–O bridges are nonequivalent: two aliphatic linkers show an anti conformation and the third linker can be in a gauche conformation. Thus, the $G-T_1T_1$ conformer has been considered in our calculations leading to the lowest Gibbs free energy. Indeed, the $T_1T_1T_1$ and $G-G-G-$ conformers are 2.06 and 3.93 kcal/mol higher in free energy, respectively. Moreover, the Gibbs free energy of the $G-G-T_1$ conformer also investigated is 1.85 kcal/mol higher than that of the $G-T_1T_1$ one. Then, the results obtained for the optimized geometry calculated for the CHCl₃–cryptophane-A complexes are in perfect agreement with the geometry of the cage in the solid state. Finally, for the CHCl₃–cryptophane-A complexes, the converged twist angles between the two CTV units seem to be independent of the linker conformations and are close to 38°.

Calculated IR and VCD Spectra of (+)-1. The IR and VCD spectra of the $T_1T_1T_1$ conformer of (+)-cryptophane-A calculated at the B3LYP/3-21G, B3PW91/3-21G, and B3PW91/6-31G* levels are compared to the experimental spectra of (+)-1 in Figure 4. It is noteworthy that, whatever the functional or the basis set used, the calculated VCD spectra reproduce fairly well the intensity and the sign of the bands observed on the experimental spectrum, allowing the definitive determination of the configuration ((+)-1) of the molecule. The VCD spectra calculated using B3LYP or B3PW91 functional and 3-21G basis set are very similar. Even though these VCD spectra are in satisfactory qualitative agreement with the experimental spectrum, the 3-21G basis set is certainly not appropriate to reveal

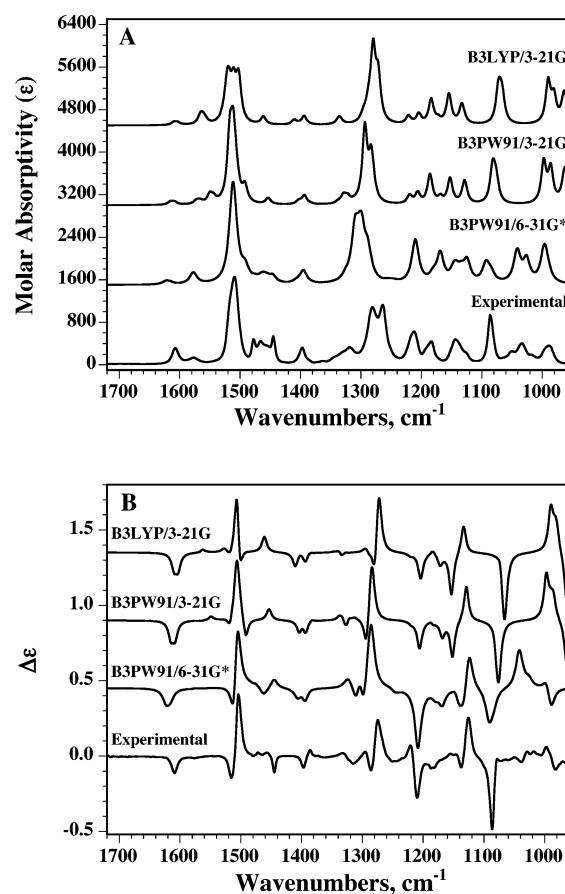


Figure 4. Comparison of experimental IR (A) and VCD (B) spectra of (+)-cryptophane-A with calculated spectra for the $T_1T_1T_1$ conformer of (+)-1 at the B3LYP/3-21G, B3PW91/3-21G, and B3PW91/6-31G* levels.

small spectral changes due to conformational modifications of the ethyl linkers. On the other hand, the larger 6-31G* basis set produced some improvement in agreement with experiment, particularly for the IR spectrum, as shown in Figure 4a. Using this basis set, despite the high computation time needed to successfully perform the calculations, IR and VCD spectra are predicted in the best agreement with experiment. Nevertheless, few discrepancies are observed between experimental and predicted spectra, which may originate from (i) the modest basis

(18) The volume of the cryptophane cavity with its three spacer bridges in gauche conformation can be estimated at ~65 Å³.

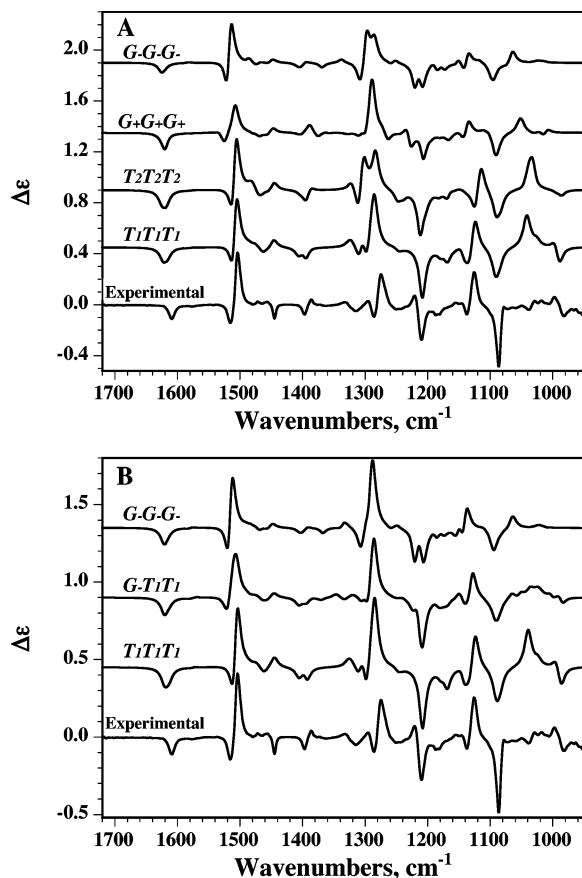


Figure 5. (A) Comparison of experimental VCD spectra of (+)-cryptophane-A with calculated spectra at the B3PW91/6-31G* levels for $T_1T_1T_1$, $T_2T_2T_2$, $G_+G_+G_+$, and $G_-G_-G_-$ conformers of (+)-**1**. (B) Comparison of experimental VCD spectra of the CHCl_3 -(+)-cryptophane-A complex with calculated spectra at the B3PW91/6-31G* levels for $T_1T_1T_1$, $G-T_1T_1$, and $G_-G_-G_-$ conformers of the CHCl_3 -(+)-**1** complex.

set used in this study (it has been shown in the literature¹⁹ that VCD spectra predicted using larger basis sets are more accurate); (ii) the calculations done for the empty cryptophane-A molecule in the gas phase, whereas experiments were performed in CDCl_3 solution (encaged cryptophane-A); (iii) the calculations done for the $T_1T_1T_1$ conformer of (+)-**1**, but others conformations are possible for the three ethyl linkers.

To investigate the relevance of this last point, 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 (+)-**1** are compared to the experimental spectra of (+)-cryptophane-A in Figure 5a. Harmonic vibrational frequencies, dipole strengths, and rotational strengths for these four conformers are given in Table 2 of Supporting Information for fundamentals 172–300 (i.e., for modes observed in the 1650–1080 cm^{-1} spectral range on the experimental spectra). Since cryptophane-A molecules contain six rings, six capping and chain CH_2 groups, and six OCH_3 groups, six modes are calculated for each group vibration. For example, the $\nu_{19a}\text{C}=\text{C}$, $\nu_{8b}\text{C}=\text{C}$, and $\nu_{8a}\text{C}=\text{C}$ stretching modes of the rings observed at 1509, 1577, and 1608 cm^{-1} give rise to fundamentals 283–288, 289–294, and 295–300, respectively. For $T_1T_1T_1$ and $T_2T_2T_2$ conformers with D_3 -symmetry, the six calculated modes consist of two degenerated modes of

E -symmetry species and of two modes of A_1 - (IR-forbidden) and A_2 -symmetry species. For $G_-G_-G_-$ and $G_+G_+G_+$ conformers with C_3 -symmetry, the six calculated modes stem from two groups, each including a degenerated mode of E -symmetry species and a mode of A -symmetry species. The sign of the experimental VCD spectrum for the $\nu\text{C}=\text{C}$ stretching modes of the rings is well reproduced for the four conformers, in particular, the bisignate shape of the 1509 cm^{-1} band. This feature is due to the coupling of vibrations with E -symmetry species in the two CTV units of the cryptophane-A molecule. The calculated VCD intensities are also in good agreement with the experimental ones, except for the $G_+G_+G_+$ conformer, which presents lower intensities. On the other hand, the VCD spectra calculated in the 1350–950 cm^{-1} region vary greatly with the conformation of the aliphatic linkers. Indeed, the rotational strengths calculated for wagging and twisting vibrations of CH_2 groups (bands occurring in the 1350–1250 cm^{-1} spectral range) and for anti-symmetric stretching vibration of $\text{C}_{\text{ring}}-\text{O}-\text{C}$ (band at 1212 cm^{-1}) are very dependent on the conformation of the bridges. This is not surprising since these modes are directly associated with the $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$ groups. Accordingly, calculated and experimental VCD spectra are in qualitative agreement with regard to the principal spectral features only for the $T_1T_1T_1$ conformer. Indeed, the VCD spectrum calculated for this conformer reproduces fairly well the signs and the intensities of the major bands observed on the experimental spectrum, except the bands located at 1445 and 1050 cm^{-1} . This result is also supported by the comparison of experimental and calculated IR spectra of the four conformers of (+)-cryptophane-A (see Figure 1 of Supporting Information).

The VCD spectra were calculated for the empty cryptophane-A molecule in the gas phase, whereas experiments were performed in CDCl_3 solution. The lack of chloroform interactions with the host molecule produces certainly some discrepancies between experimental and predicted VCD spectra. In addition to the solvent effect, the formation of stable complexes between cryptophane-A molecules and chloroform molecules may perturb the conformation of the host molecules and consequently may change the VCD spectra with respect to the empty cryptophane. To investigate this point, the 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 the CHCl_3 -(+)-**1** complex and are compared to the experimental spectra of (+)-cryptophane-A in Figure 5b. The VCD spectrum calculated for the $T_1T_1T_1$ conformer of the CHCl_3 -(+)-**1** complex is quasi identical to that calculated for the empty molecule. The presence of chloroform in the cryptophane cavity does not affect the conformation of the host molecule, suggesting weak interaction between guest and host molecules. This result is corroborated by the similar values of the converged geometries calculated for the two systems (Table 2). On the other hand, the VCD spectrum calculated for the $G_-G_-G_-$ conformer of the CHCl_3 -(+)-**1** 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}) and with rocking modes of CH_2 and CH_3 groups (1125 cm^{-1}). Since the cavity volume of the $G_-G_-G_-$ conformer of (+)-**1** is lower than that of $T_1T_1T_1$, the encapsulation of chloroform molecule should modify the conformation of the host molecule (the twist angle between the two CTV bowls

(19) Stephens, P. J.; Delvin, F. J.; Aamouche, A. In *Chirality: Physical Chemistry*; ACS Symposium Series; Hicks, J. M. Ed.; American Chemical Society: Washington, DC, 2002; Vol. 810, Chapter 2, pp 18–33.

decreases and becomes closer than that of the $T_1T_1T_1$ conformer). Consequently, the spectral modifications between the calculated VCD spectra for the $T_1T_1T_1$ and $G-G-G-$ conformers of $\text{CHCl}_3-(+)\text{-1}$ are less marked than those observed for empty cryptophane. Finally, the VCD spectrum calculated for the $G-T_1T_1$ conformer of the $\text{CHCl}_3-(+)\text{-1}$ complex is also in good agreement with the experimental VCD spectrum. In particular, the $1400\text{--}1300\text{ cm}^{-1}$ spectral range and the 1050 cm^{-1} band are best reproduced, but the VCD intensities are weaker than those calculated for the $T_1T_1T_1$ conformer. Since the experimental VCD spectrum is best reproduced by the calculated VCD spectra of $T_1T_1T_1$ and $G-T_1T_1$ conformers, this study reveals the preferential anti conformation of the aliphatic linkers of the cryptophane-A molecule. This result is however in contradiction with the NMR experiments performed by Luhmer et al. on the xenon-cryptophane-A complex in tetrachloroethane.^{8e} Indeed, their results suggest a preferred gauche conformation of the alkyl chains when xenon is encapsulated into the cavity of cryptophane-A. Since xenon (42 \AA^3) is smaller than chloroform (72.2 \AA^3), the xenon-cryptophane-A complex is certainly stabilized when the cryptophane cavity has its minimum size, that is, for a gauche conformation of the three $\text{O-CH}_2\text{-CH}_2\text{-O}$ groups.

Since the predicted VCD spectra for the $T_1T_1T_1$ conformer are not modified by the presence (or not) of a guest molecule, we have tried to confirm experimentally this result in recording experimental IR and VCD spectra of $(-)$ -cryptophane-A in $\text{CD}_2\text{-Cl}_2$ solution (molecule having a van der Waals volume of 57.6 \AA^3) and in $\text{C}_2\text{D}_2\text{Cl}_4$ solution (molecule having a van der Waals volume of 104 \AA^3 , significantly larger than the volume of the cryptophane cavity). As shown in Figure 6b, the experimental VCD spectra of empty ($\text{C}_2\text{D}_2\text{Cl}_4$ solution)²⁰ or encaged (CDCl_3 and CD_2Cl_2 solutions) cryptophane are quasi identical, indicating that the size of the guest molecule as well as its nonpresence in the cavity does not modify significantly the conformation of the host molecule. Nevertheless, a more detailed analysis of the VCD spectra in the C-H stretching region (data not shown) reveals that the introduction of chloroform inside the cavity leads to a more structured spectrum. This result, as already observed in many cases by NMR spectroscopy, suggests that the encapsulated guest rigidifies the host molecule mainly by preventing the alkoxy bridges from adopting several conformations. Finally, the agreement between the calculations (for an isolated gas-phase molecule) and the experimental spectra recorded in various solutions reflects the weak interaction of the cryptophane-A molecule with the three solvents used in this study.

Conclusion

In this study, we have reported both an experimental and a theoretical study of the infrared and VCD spectra of the two enantiomers of cryptophane-A. By far, cryptophane-A represents the largest molecular system (120 atoms) investigated by VCD spectroscopy and ab initio calculations for the determination of its absolute configuration. The ab initio calculations performed at the DFT level (B3PW91 functional) show that both the simulated IR and VCD spectra strongly depend on the chosen basis set used. Interestingly, despite the high computation time needed to successfully perform these calculations, we show

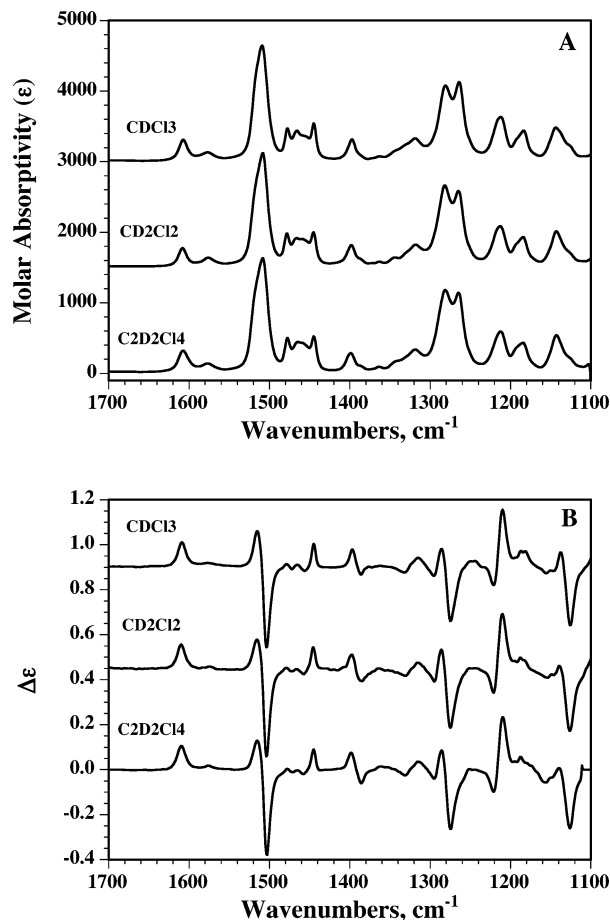


Figure 6. Comparison of experimental IR (A) and VCD (B) spectra of $(-)$ -cryptophane-A in CDCl_3 , CD_2Cl_2 , and $\text{C}_2\text{D}_2\text{Cl}_4$ solvents.

that even a small basis set (6-31G*) allows one to calculate, with a good degree of precision, the IR and VCD spectra of the cryptophane-A and thus to predict correctly its absolute configuration. In addition, the theoretical calculations performed for empty cryptophane and the CHCl_3 -cryptophane complex, considering an anti or a gauche conformation of the alkyl chains connecting the two cyclotrimeratrylene units, suggest that the alkyl chains mainly adopt an anti conformation even though the gauche conformation should contribute to a small part in the experimental VCD spectra. This result is in good agreement with the crystallographic structure obtained for the racemic compound of the chloroform-cryptophane-A complex, which shows a preferred anti conformation for the bridges. The original structural features of cryptophane-A, and in particular its extraordinary binding properties toward small neutral molecules, such as halogenomethane, also made this study very interesting to investigate the influence of a guest on the spectroscopic change observed in VCD spectra. The VCD spectra were found to be minimally dependent on both the solvent and the guest.

The interesting information extracted from both the ab initio calculations and the experimental VCD spectra of optically pure cryptophane-A shows that this technique can be used to extract valuable information about the configuration and the conformation of this complex molecule. It will be interesting to investigate the xenon-cryptophane-A complex since a different conformation of the aliphatic linkers has been suggested by NMR experiments. The VCD spectroscopy associated with theoretical calculations could be also used to study new original cryp-

(20) We cannot exclude the presence of dissolved gas (O_2 , N_2 , ...) inside the cryptophane cavities since no vacuum treatment has been performed.

tophane derivatives with C_1 -symmetry (presence of chiral or nonchiral substituents). Such works are in progress, and they will be published in due course. Finally, this study encourages us to develop cryptophane chemistry in order to find new efficient strategies for the optical resolution of cryptophane-E (propyl linkers) and related hosts molecules for future studies of their absolute conformations by VCD spectroscopy.

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Supporting Information Available: Experimental IR and VCD frequencies and assignment of the most important bands of (+)-**1** in the 1700–950 cm^{-1} spectral range. B3PW91/6-31G* frequencies, dipole strengths, and rotational strengths for $T_1T_1T_1$, $T_2T_2T_2$, $G-G-G-$, and $G_+G_+G_+$ conformers of (+)-**1** (modes between 300 and 172). Comparison of experimental IR spectra of (+)-cryptophane-A with calculated spectra at the B3PW91/6-31G* levels of $T_1T_1T_1$, $T_2T_2T_2$, $G_+G_+G_+$, and $G-G-G-$ conformers of (+)-**1**. Complete ref 14. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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