An Experimental Comparison of Vibrational Circular Dichroism and Raman Optical Activity with 1-Amino-2-propanol and 2-Amino-1-propanol as Model Compounds

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Abstract: Mid-IR vibrational circular dichroism (VCD) and the corresponding Raman optical activity (ROA) spectra of 1-amino-2-propanol and 2-amino-1-propanol in neat solution are compared to yield insight into the dominant structural sensitivity of each technique. The ROA spectra for these isomeric compounds are quite similar while their VCD spectra are substantially different. The contrast between the results with these two techniques can be empirically interpreted to imply that VCD is more sensitive to the overall chirality of a molecule, conformation plus configuration, while ROA is more dependent on the nature of the local environment, or the configuration, of the functional groups. This observation would correlate with VCD having a significant dipolar coupling contribution that is highly dependent on conformation. This distinction between VCD and ROA sensitivities would be expected to be most appropriate for high dipole strength transitions in conformationally unconstrained, open-chain molecules. These observations directly reflect the contrast between current applications of VCD and ROA to biomolecular conformational analyses.

Introduction

Infrared (IR) and Raman spectroscopy are well-known to be complementary techniques for detecting and characterizing vibrational transitions in the ground state. With regard to vibrational optical activity (VOA), the IR form, vibrational circular dichroism (VCD), and the Raman form, Raman optical activity (ROA), are also assumed to be complementary.[1] Both techniques sense the overall chirality of a molecule, as exhibited by the complete sign reversal for spectra measured with opposite enantiomers. However, the two techniques differ due to the distinctive nature of the physical interactions responsible for each phenomenon.[1−3] VCD depends on the interaction (scalar product) of the vibrationally induced change in the electric dipole moment (whose square is proportional to the IR intensity) with the magnetic component. The ROA, on the other hand, depends on the vibrational change in the electric polarizability (again, which squared gives the variation in the normal Raman intensity) interacting with the respective magnetic or quadrupolar contributions. It is now well established that the ROA and VCD spectral intensity patterns have vanishingly little correlation for a given molecule.[1,4,5] These observations tend to verify the independent nature of the two techniques and to point out that they measure different physical properties of the molecules.

The remaining question is how best to utilize this differential sensitivity to answer stereochemical questions of interest. For example, the VCD band shapes for the characteristic amide vibrational transitions in peptides and proteins differ in frequency, intensity, and sign pattern for various secondary structures.[6] By contrast, ROA of the typical amide bands tend to maintain the same general shapes and sign patterns with the variations in structure primarily resulting in frequency shifts and modest intensity changes.[7] For such biopolymeric molecules, the configurations are uniform; the variation in structure is a conformational one. The modes studied in such molecules (at least for VCD) are those giving rise to characteristic group frequencies, in other words, those associated with functional group vibrations.

To explore this phenomenon, one can avoid the complications of the polymeric forms by targeting related small molecules whose chirality is dependent on functional group substitution. Small size means that the functional group modes can be better localized and assigned. Comparison of ROA and VCD for isomers having different geometries should lead to insight into the application of these different VOA intensity mechanisms. Previous studies along this line have utilized conformationally constrained ring molecules such as terpenes.[4,5] These give rise to large VCD and ROA signals, making possible detailed comparison of high-quality spectra. But these systems pose a problem with regard to sorting out correlations to conformation

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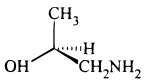
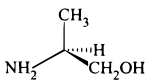
Chart 1



1

(*S*)-1-amino-2-propanol



2

(*S*)-2-amino-1-propanol

and configuration. Their mid-IR modes tend to be extended over the molecular framework resulting from the coupling of the ring deformations. Consequently, all modes will be affected by the conformation due to the nature of the vibration so that this structural manifestation would be independent of the mechanism of the technique used. Small linear, open-chain molecules can avoid that situation, but at the price of stereochemical averaging due to the near equivalence of several rotameric conformers. Since such linear molecules most directly relate to the biopolymeric questions of prime interest for VOA applications, we have chosen to study two small linear isomeric molecules differing by the interchange of functional groups.

To realize this approach of obtaining both VCD and ROA data from two very simple organic molecules, which are isomeric and thus closely related in terms of structures and physical properties (similar boiling points and optical rotations), we measured the IR, VCD, Raman, and ROA for identical neat liquid samples of 1-amino-2-propanol (**1**) and 2-amino-1-propanol (**2**) (Chart 1). A previous, preliminary report from another laboratory of a measurement of the VCD of these compounds in solution has appeared.[8] As will be shown, the isomeric differences in these two compounds, involving only exchange of the positions of the two functional groups, lead to their having quite different relative response as sensed with VCD and ROA spectra. It is this differential spectral response to otherwise identically handled samples which in turn exemplifies the basic physical differences in the two methods.

Experimental Section

Optically pure (>95%) samples of the (*S*) and (*R*) enantiomers of **1** and **2** were purchased from Aldrich and used as neat liquids without further purification.

For IR and VCD experiments, a very small amount (1−2 drops) of neat liquid was squeezed between two KBr windows without using a spacer. This allowed the path length to be minimized so that the IR absorbances of the samples could remain below ∼0.8 for improved VCD accuracy. The IR and VCD spectra were measured with an FTIR-based (BIO-RAD FTS-60A) VCD spectrometer, whose design has been previously discussed in detail.[9]

The Raman and unpolarized, incident circularly polarized (ICP) ROA spectra were obtained with use of a 180° backscattering geometry ROA spectrometer, based on an Ar^+ laser and an electrooptic modulator for excitation and a holographic notch filter, 0.64-m monochromator, and intensified diode array for detection. The instrumental design, testing, and operation of this spectrometer have been discussed in detail elsewhere.[10] For the Raman and ROA measurements, neat liquids were placed in a 1-cm quartz fluorescence cuvette (Hellma) with a polished bottom window that passed both the excitation and scattered light.

For both compounds, the VCD and ROA spectra of both optical enantiomers were measured and subtracted from each other to improve the signal-to-noise (S/N) ratio and to correct the baselines (for VCD).

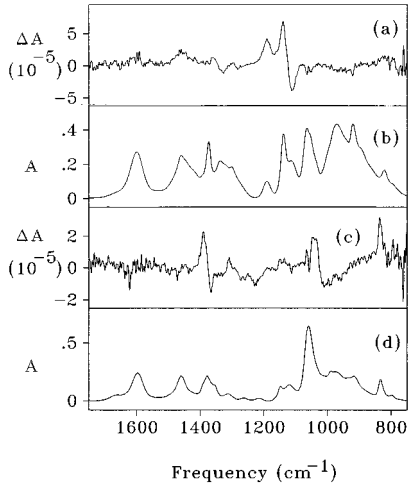


Figure 1. The (a) VCD and (b) IR absorption spectra of (*S*)-1-amino-2-propanol as compared to the (c) VCD and (d) IR absorption spectra of (*S*)-2-amino-1-propanol. Each VCD spectrum was the average of 16 blocks (8 each optical isomer) of 4096 scans at a resolution of 4 cm^{-1}. The total data acquisition time for each VCD spectrum (difference of two enantiomers) was 12 h.

Results

The VCD and IR absorption spectra for 1-amino-2-propanol (Figure 1, spectra a and b) and 2-amino-1-propanol (Figure 1, spectra c and d) are shown in Figure 1. There is a surprising level of qualitative variation in the IR absorption spectra for these two isomeric compounds. It is noteworthy that the VCD spectra of **1** and **2** in neat liquid are in close agreement with that obtained for these molecules in solution,[8,10] indicating that there is relatively little effect of intermolecular interaction on the measured VCD. The IR intensities of **1** are similar for most of the vibrational bands in this mid-IR region, whereas for **2**, the intense band at ∼1050 cm^{-1} (C−O stretching mode[11]) dominates the IR spectrum. However, the IR spectra of the two compounds do show comparable "group frequencies", for example, the NH_2 scissoring mode at ∼1600 cm^{-1}, the asymmetric CH_3 deformation (mixed with the O−H bending mode) at ∼1450 cm^{-1}, and the NH_2 wagging mode mixed with CH_2 rocking at ∼840 cm^{-1}.

The VCD spectra of the two aminopropanols are also very distinctive in terms of both sign patterns and VCD intensities. The overall VCD intensity for **1** is about twice that for **2**, and the overall VCD intensity for **2** is about an order of magnitude weaker, in terms of $\Delta A/A$, than that for α-pinene, an accepted instrumental standard.[1,9,12] As is apparent from the data in Figure 1, the more intense VCD signals for the two aminopropanols come from quite different vibrational motions. To aid in determining a qualitative assignment of these spectra to internal motions of the molecules, we carried out force field (FF) computations for each isomer at one of its energy minimized geometries. These results, from both HF/6-31G** and DFT/LDA level calculations, though yielding only approximate absolute frequencies, provide a useful guide to the relative ordering and nature of transitions in the two isomers. Due to the rotameric averaging in these molecules, the intensities are not well-represented by these single conformation calculations, much as seen in the previous study.[8] Hence detailed spectral simulations are not presented nor are they useful for the main goal of this study. The most intense VCD bands for **1** at ∼1130 cm^{-1} can be assigned to a C−C stretching mode

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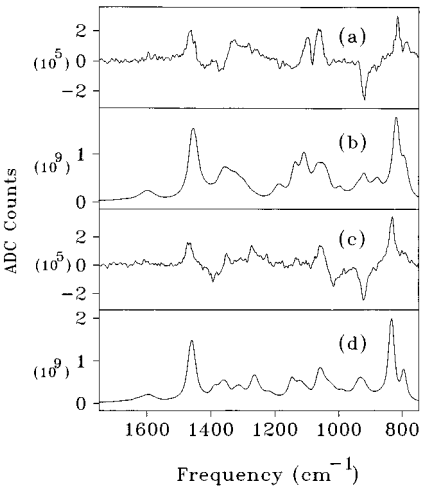

Figure 2. The (a) ROA and (b) Raman spectra of (*S*)-1-amino-2-propanol as compared to the (c) ROA and (d) Raman spectra of (*S*)-2-amino-1-propanol. The total data acquisition time for each ROA spectrum was 40 h on our instrumentation, when collected as ICP with 180° backscattering as the difference of two enantiomers. The Raman and ROA spectra were recorded at a resolution of 8−10 cm^{-1}.

mixed with CH_2 twisting and C−N stretching. As for **2**, the most intense VCD band is found at ∼1380 cm^{-1}, assigned to the symmetric CH_3 deformation mode mixed with the O−H bending mode. Other intense VCD bands for **2** can also be found at ∼1030 cm^{-1} (a C−C stretching mode) and at ∼840 cm^{-1} (the NH_2 wagging mode mixed with the CH_2 rocking mode), both of which are fairly weak in **1**. The other weaker distinctive VCD bands observed in each sample also have little in common; for example, there is a hint of a very small positive VCD signal for the NH_2 scissoring mode at ∼1600 cm^{-1} in **1** while the same VCD band is negative for **2**. This implies that the dominant VCD in these two molecules arises from extended coupling of the motions (transition dipoles) and not from the local nature of the oscillators.

The Raman and ROA spectra of 1-amino-2-propanol and 2-amino-1-propanol are arranged in Figure 2 as the IR and VCD were in Figure 1 for direct comparison. In contrast to the IR, the two Raman spectra (Figure 2, spectra b and d), while still distinguishable, are remarkably similar as far as relative intensities are concerned. In both Raman spectra, the most intense Raman bands are those corresponding to the NH_2 wagging mode (mixed with the CH_2 rocking) at ∼840 cm^{-1} and the asymmetric methyl deformation (mixed with the O−H bending) at 1450 cm^{-1}. In the 1100−1400-cm^{-1} region, where the vibrational frequencies of the two compounds do differ, the overall pattern of Raman intensities still remains comparable.

From comparison of spectra a and c in Figure 2, the relative ROA intensities and sign patterns for the two compounds are also seen to be strikingly similar. The overall ROA intensities, in terms of $(I_R - I_L)/(I_R + I_L)$,[2] are only about a factor of 2 weaker than that observed for α-pinene.[13] There is only one major difference in the ROA of these two molecules, which arises from the more extended C−C−C framework stretching modes. In the 1000−1150-cm^{-1} region, there are two positive ROA bands for 1-amino-2-propanol (Figure 2, spectrum a) as compared to a couplet-like ROA feature for 2-amino-1-propanol (Figure 2, spectrum c). For the functional group modes such as the asymmetric methyl deformation mode mixed with the O−H bending (∼1450 cm^{-1}), the symmetric CH_3 deformation mode mixed with O−H bending (∼1380 cm^{-1}), the CH_3 rocking mode (∼920 cm^{-1}), and the NH_2 wagging mode mixed with the CH_2 rocking (∼840 cm^{-1}), the intense ROA signals from both aminopropanols are practically the same.

Discussion

It has previously been demonstrated that VCD and ROA intensities are uncorrelated.[1,4,5] As shown by a comparison of ROA and VCD spectra of terpenes, ROA and VCD can be analyzed individually to yield complementary information with regard to molecular chirality.[4] Our experimental data agree with this argument, since the ROA and VCD spectra of either of the two aminopropanols are apparently unrelated. However, the relative change between the two isomers, exemplified by the ROA for **1** and **2** being very similar while their VCD spectra are very different, leads to further insight into the source of this difference between the two forms of VOA.

The similarities in the Raman intensities of **1** and **2** show that the overall changes in polarizabilities for these two aminopropanols due to their molecular vibrations are roughly the same and imply that these changes are highly local in nature, or that they do not depend strongly on the position of the functional groups. These similarities also suggest an underlying parallelism in terms of the electronic structures of these two molecules, which provides a rationale for using them as model compounds in this experimental study. Another indication of their close relationship in molecular and electronic structures is the transferability of "group frequencies" between these two compounds. Our FF calculations imply that the functional groups give rise to characteristic modes in each isomer.

The differences in VCD spectra and the similarities in ROA spectra for the two aminopropanols clearly show that VCD and ROA provide independent information with respect to different aspects of the molecular chirality. In this case, when the arrangement of substituents about the central carbon is altered, the VCD signals from C−O−H bending, CH_3 deformation, NH_2 scissoring motions, and other motions change as well. By contrast, only the carbon skeleton modes (∼1100 cm^{-1}) give rise to a significant difference in ROA for **1** and **2**, while those for other vibrational motions of the ROA spectra remain roughly the same. Therefore, the ROA signals seen for the C−O−H bending, CH_3 deformation, and NH_2 wagging imply an independence from the detailed positioning of the −OH and $-NH_2$ groups on the carbon backbone. The ROA spectra can then be attributed to the local characteristics of each functional group and its electronic environment.

On the other hand, VCD is sensitive to the change in overall molecular chirality and the attendant conformational changes. Dipolar coupling of different groups, through space, leads to an important VCD intensity mechanism, even if the local modes are not significantly mixed by the force field. Consequently, VCD can, in some sense, be said to reflect, primarily, the conformation and ROA the configuration of these molecules. Due to the different information contents offered by VCD and ROA, they can be considered to be true complementary techniques in terms of their preferential sensitivities toward different aspects of molecular chirality.

This comparison between VCD and ROA sensitivities can also be observed in studies of peptides and proteins. It has been demonstrated through extensive model peptide studies and confirmed with protein spectra that the VCD patterns are quite different, to the extent of complete sign reversals as well as wide ranging intensity and band shape variations, for different molecular conformations.[6] In all these biomolecules the configuration is determined by the L-α-amino acids making up the biopolymers. However, in the ROA data collected by Barron and co-workers for many of these same proteins, the spectra were amazingly invariant.[7] This latter work has evidenced its greatest sensitivity to secondary structure through frequency shifts in the protein ROA spectra and through what might be

termed "fingerprint modes", which have major contributions from delocalized coupled C−C and C−N vibrations.[7] By contrast, the ROA spectra of the characteristic amide modes vary only a little in intensity and frequency but rarely in sign or band shape for proteins of widely varying structures. Understanding this difference is the key to understanding how to use VCD and ROA to interpret (large) biomolecular structures. These smaller molecules, **1** and **2**, have simpler spectra, allowing more accurate assessment of the normal modes involved and providing direct experimental illustration of the distinctive characteristics of ROA and VCD intensities.

Added evidence for this point of view is available from the contrast of intensities obtained for these molecules with those for "standard" test-case molecules. Comparing the aminopropanol data from the two vibrational chiroptical techniques, the VCD for both is quite weak but the ROA is only moderately so. Here it is important to take note of the relative intensities of the VCD and ROA measured for the aminopropanols as compared to those seen for other molecules, such as the terpenes.[4,5] In fact the ROA intensities are only about half of the ROA intensities of the rigid terpenes while the VCD intensities are much weaker, bordering on an order of magnitude less.[4,5,12] These linear chain molecules will sample a range of conformations leading to cancellations and loss of intensity for transitions whose properties are primarily dependent on conformation. By contrast, those transitions primarily dependent on configuration will be only secondarily affected by the conformational equilibrium. If the ROA were conformationally averaging out, and if conformational sensitivity were an important ROA mechanism, then the ROA intensity would be significantly reduced from that of a rigid molecule. That is what happens to the VCD. On the other hand, if the local chirality (configuration) were more important, the intensity would not be reduced as much for these linear, fluctional molecules. That is, indeed, what is observed for ROA. The data are self-consistent at this point; the similarity of the ROA spectra and the distinctiveness of the VCD spectra of **1** and **2** support this analysis both qualitatively and quantitatively.

Previously, VCD and ROA of a number of small cyclic organic molecules have been studied with both the experimental and theoretical approaches.[1−5,10,14,15] However, there are relatively few such studies of open-chained, linear organic molecules.[1,8,16] The major difficulty in theoretical simulation of the vibrational optical activity spectra of linear molecules comes from the large number of stable rotamers resulting from the low energy barrier of C−C bond rotations. Presumably, the aminopropanols in the liquid form do not consist of only one conformer, but, instead, of several that are close in energy, and co-existing in equilibrium. The dimension of this system becomes huge if one requires theoretical simulation for interpretation. That is why our single conformer calculations are not useful for either VCD or ROA simulations. Evidence of this was seen in the earlier attempt to calculate VCD for the aminopropanols.[8]

A related previous study by Yu et al.[17] dealt with the ROA of ephedrine molecules, which share the aminopropanol framework studied here but have an additional chiral center due to phenyl substitution. That study varied the configuration of one center and methyl substituted the amino group leading to a more complex spectral pattern. None-the-less, those authors empirically interpreted the resulting spectra as having specific features which were configurationally sensitive. This is consistent with our findings on a much simpler system for which we have full stereochemical variation and both VCD and ROA data. If, as we are proposing here for such less constrained molecules, ROA primarily senses configurational aspects of the structure and VCD conformational ones (aside from an obvious overall configurational sign dependence), coupling ROA with VCD to separate these two aspects of the structure may offer a route for simplification of the computational difficulties in analyzing spectra of open-chain molecules. This remains a challenge left here for future theoretical work.

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