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Backscattering Dual Circular Polarization Raman Optical Activity in Ephedrine Molecules

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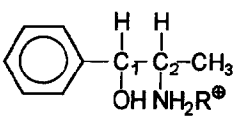
Abstract: We report the first measurements of Raman optical activity (ROA) in ephedrine molecules. In-phase dual circular polarization (DCP_I) ROA spectra have been recorded for (1S,2R)-ephedrine, (1S,2R)-norephedrine, (1S,2S)-pseudoephedrine and (1S,2S)-norpseudoephedrine as hydrochloride salts in H_2O solution. The spectra are interpreted in relation to the small changes in molecular structure among these four molecular species.

Introduction

Within the past several years, the speed and quality of Raman optical activity (ROA) measurements[1-5] has increased by more than two orders of magnitude. Use of charge coupled detectors (CCDs)[6,7] and backscattering optical configurations[8,9] has yielded most of the increased sensitivity. Alternative polarization modulation schemes, beyond the traditional circular polarization modulation of the incident beam (ICP), to include CP modulation of the scattered beam (SCP),[7,10] and both the incident and scattered beams, either in-phase (DCP_I) or out-of-phase (DCP_{II}), have been introduced theoretically[11] and experimentally.[9,12] Two ROA instrumental set-ups have been described in detail.[7,13] As a result of these advances, ROA measurements of biologically significant molecules in aqueous solutions have been carried out using unpolarized ICP backscattering and DCP_I backscattering for amino acids, peptides, carbohydrates and nucleosides.[3,4,12,14-19] In this article, we extend such measurements to the class of ephedrine molecules.

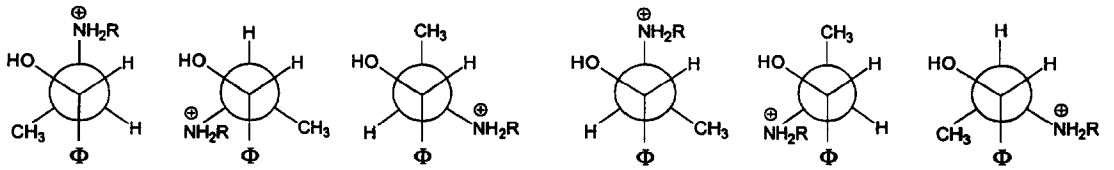
We compare here the Raman and ROA spectra of aqueous solutions of the hydrochloride salts of (1S,2R)-ephedrine, **1**, (1S,2R)-norephedrine, **2**, (1S,2S)-pseudoephedrine, **3**, and (1S,2S)-norpseudoephedrine, **4**. The ephedra class of molecules are orally active sympathomimetic drugs. Pseudoephedrine



R=H : norephedrine, norpseudoephedrine
R=CH_3 : ephedrine, pseudoephedrine

hydrochloride is widely used as a nasal decongestant. Ephedrine hydrochloride is a bronchodilator used in the treatment of bronchial asthma. Both norephedrine and norpseudoephedrine hydrochlorides have been used as appetite suppressants.

The ROA spectra are sensitive both to the absolute configuration and the solution conformations of these drug molecules. A number of investigations have addressed the conformational preferences of the ephedrines in terms of the conformer populations of rotamers I, II and III for ephedrine and norephedrine and I', II' and III' for pseudoephedrine and norpseudoephedrine.[20-28] I and I' are referred to as extended



R=CH_3 : (1S,2R)-Ephedrine (1)
R=H : (1S,2R)-Norephedrine (2)

R=CH_3 : (1S,2S)-Pseudoephedrine (3)
R=H : (1S,2S)-Norpseudoephedrine (4)

conformers, whereas the others have been described as folded conformers. For the conjugate acid forms, the crystal structures of ephedrine[20] and pseudoephedrine[21] correspond to I and I', respectively, where the phenyl and amino groups are trans. Recent proton NMR studies[22] indicate that the relative abundance in aqueous solution of the conformers with trans hydrogens is 19% for the conjugate acid of ephedrine (conformer III) and 86 % for the conjugate acid of pseudoephedrine (conformer I'). A 21% relative abundance for conformer III for norephedrine hydrochloride has also been determined previously from proton NMR measurements.[24] The relative conformer populations of the gauche forms cannot be determined from the vicinal proton-proton coupling constants.[22-25] However, quantum mechanical calculations employing the PCILO method indicate that conformers I and II are closer in energy for ephedrine (calculated relative populations 0.72 (I) and 0.28 (II)) than for norephedrine (calculated relative populations 0.96 (I) and 0.04 (II)).[26] A preference in solution for the conformer adopted in the solid is suggested by comparison of the observed electronic absorption spectra of ephedrine and pseudoephedrine conjugate acids with spectra calculated with INDO procedures.[27]

Experimental

The hydrochloride salts of (1R,2S)- and (1S,2R)-norephedrine, (1R,2S)- and (1S,2R)-ephedrine, (1S,2S)- and (1R,2R)-pseudoephedrine, and (1R,2R)-norpseudoephedrine were purchased from Aldrich; (1S,2S)-norpseudoephedrine was obtained from Indofine Chemical Co., Somerville, MA. All the salts were recrystallized twice from ethanol, and prepared as 1M solutions in distilled H_2O. The ROA instrument, which was constructed at Syracuse University, has been described in detail elsewhere.[7] For the spectra of the ephedra molecules, an exciting wavelength at 488 nm with 1 W power was used. The resolution for all spectra was 20 cm^{-1} and the total exposure time was 33.6 h for ephedrine·HCl, 36.7 h for pseudoephedrine·HCl, 34.8 h for norephedrine·HCl, and 27.1 h for norpseudoephedrine·HCl. For each pair of enantiomers, the summation of their backward scattering Raman spectra and the difference of their DCP_I ROA spectra were obtained, in order to minimize interference from artifacts in the ROA spectra.

Results and Assignments

The Raman and ROA spectra of the hydrochloride salts of (1S,2R)-ephedrine, (1S,2R)-norephedrine, (1S,2S)-pseudoephedrine and (1S,2S)-norpseudoephedrine are compared in Figure 1. The exposure times differed somewhat in recording the spectra of the four compounds; the number of counts has been scaled to the largest Raman band for ease of comparison of the Raman or ROA spectra.

The Raman spectra of **1** to **4** are strikingly similar in pattern, which reflects the similarity in structure of the four compounds. In contrast, ROA features arising from corresponding Raman bands in **1** to **4** exhibit both similarities and distinct differences in sign and magnitude, which provide information on local absolute configuration and conformation. An ROA feature that serves as a configurational marker for carbon-1 will change sign in going from the (1S,2R) species to the (1S,2S) species, whereas a configurational marker for carbon-2 will be the same sign in all four compounds. There is an overall similarity between the ROA spectra of (1S,2R)-ephedrine and (1S,2R)-norephedrine, or of (1S,2S)-pseudoephedrine and (1S,2S)-norpseudoephedrine, which is indicative of similar conformations for the pairs of compounds with the same absolute configuration at both chiral centers. However, substitution of $NH_2CH_3^+$ for NH_3^+ also results in distinct differences in ROA intensity for some features, which may also reflect differences in conformation.

The two most prominent Raman features for all four compounds derive from vibrations of the monosubstituted phenyl group.[29] The sharp, intense band at 1603 cm^{-1} and weaker feature at 1586 cm^{-1} derive from a degenerate e_{2g} ring-stretching mode of benzene. In both ephedrines, **1** and **2**, these two modes give rise to a (-,+) ROA couplet (A in Fig. 1), whereas no corresponding ROA features are observed for these modes in the pseudoephedrines, **3** and **4**. Such ROA couplets are sometimes observed for degenerate modes that are split due to chiral substitution. We note that in the most abundant conformer (I) for **1** and **2**, the orientation of the phenyl group is restricted by the close proximity of the gauche 1-OH and 2-CH_3 groups, whereas in **3** and **4**, these two groups are trans, and the phenyl orientation is less restricted. The lack of an observed ROA couplet for the two phenyl modes in the pseudoephedrines may arise from cancellation of oppositely signed ROA couplets from various phenyl orientations, or from a weaker chiral perturbation of the phenyl modes by trans compared to gauche 1-OH and 2-CH_3 groups.

The second intense Raman feature is observed at 990 cm^{-1} is an in-plane ring deformation of the monosubstituted benzene.[29] The weak ROA features arising from this mode in **1** to **4** do not serve as configurational or conformational markers.

The prominent Raman feature at 1450 cm^{-1} in **1** to **4** arises primarily from the antisymmetric methyl deformations at carbon 2. The antisymmetric N-CH_3 deformation is observed as a high frequency shoulder to this band in (1S,2R)-ephedrine and (1S,2S)-pseudoephedrine. Although a stretching mode of the monosubstituted phenyl group is also observed near this frequency, the Raman intensity of the latter is weak, and the phenyl mode is usually obscured by the Raman scattering from the methyl deformation.[29] In the ROA spectra of **1** to **4**, the 1450 cm^{-1} mode gives rise to an ROA feature (B in Fig. 1) that is positive for the two (1S,2R) ephedrines and negative for the two (1S,2S) pseudoephedrines. The methyl deformation band thus serves as a configurational marker for the $-C^*HCH_3(NH_2R^+)$ chiral center at carbon 2. This observation is in contrast to the VCD and ROA spectra of substituted phenylethanes.[30,31] In the VCD spectra of $C_6H_5C^*HCH_3X$, where X = OH, NH_2, or NCO, a monosignate negative band is observed at 1450 cm^{-1} for the R-configuration.[30] However, it was demonstrated that a contribution from the phenyl mode is a dominant source of the VCD intensity, since the negative VCD feature shifts to 1405 cm^{-1} when the phenyl contribution

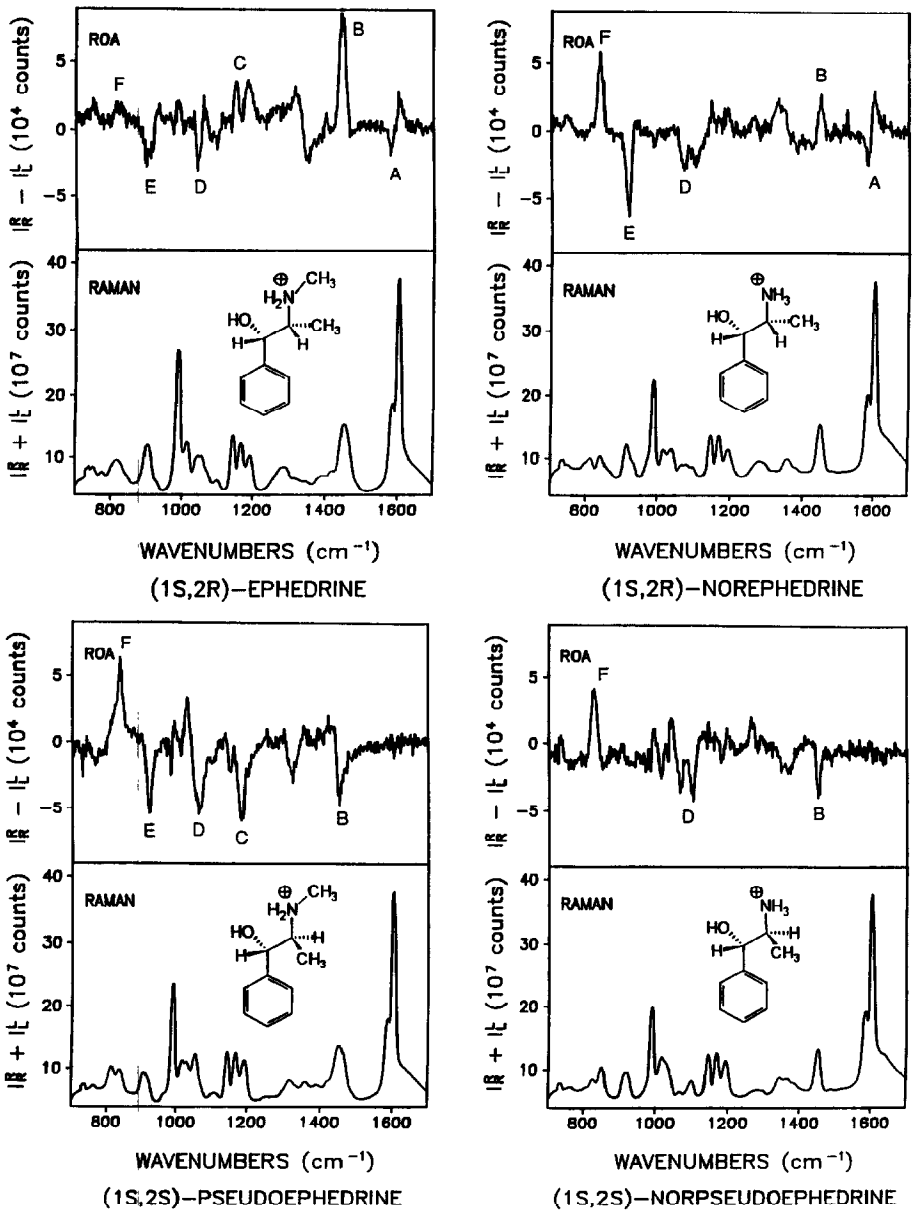


Figure 1. Depolarized backscattered DCP_I Raman and ROA spectra of hydrochloride salts of (1S,2R)-ephedrine, (1S,2R)-norephedrine, (1S,2S)-pseudoephedrine and (1S,2S)-norpseudoephedrine, 1M in H_2O solution.

is shifted to that frequency by bromo substitution in the para position. In the ROA spectra of the substituted phenylethanes,[31] a distinct ROA couplet is associated with the 1450 cm^{-1} feature, which was originally ascribed to the splitting of the degenerate methyl deformation. However, p-bromo substitution of the phenyl group was shown to result in the disappearance of the ROA couplet and the appearance of a monosignate ROA feature at 1402 cm^{-1}; thus, the phenyl and methyl motions must be coupled in $C_6H_5C^*HCH_3X$. In the ephedrines, the phenyl and methyl groups lie on different chiral centers, and the vibrational modes of the two groups are unlikely to mix as extensively. The monosignate character of the ROA feature at 1450 cm^{-1} for **1** to **4** does suggest some contribution to these normal modes from other groups, particularly those at carbon 2.

The difference in intensity for the 1450 cm^{-1} ROA feature in (1S,2R)-ephedrine and (1S,2R)-norephedrine suggests that the molecular conformation also influences the ROA intensity. In the two gauche conformers (I and II) of (1S,2R)-ephedrine and (1S,2R)-norephedrine, the proximity of the 2-methyl and 1-hydroxyl group is different and, for example, contributions from the COH deformation to the 1450 cm^{-1} feature may differ for I and II and affect the ROA intensity. The larger ROA intensity for the 1450 cm^{-1} feature for (1S,2R)-ephedrine may, therefore, reflect the proposed increased abundance of conformer II compared to conformer I, relative to the populations of those conformers in (1S,2R)-norephedrine.

The prominent ROA features near 840 cm^{-1} (F in Figs. 1 and 2) are positive for three of the four compounds, **2**, **3**, and **4**. In (1S,2R)-ephedrine, **1**, weak positive ROA intensity is observed in this region. Since the bands are of the same sign for the (1S,2R) and (1S,2S) configurations, the vibrational motion is probably localized at carbon 1. A reasonable assignment for the major contribution to this feature is the symmetric CCO stretch, which should occur in this region. In conformers I and I', the relative phenyl, OH and NH_2R^+ orientations are similar. In conformer II, the OH and NH_2R^+ groups are in a different gauche orientation. The decreased ROA intensity near 840 cm^{-1} in the spectrum of (1S,2R)-ephedrine compared to that of (1S,2R)-norephedrine may thus also arise from an increased abundance of conformer II for **1** compared to **2**.

A prominent negative ROA feature (band E) is observed near 910 cm^{-1} in (1S,2R)-norephedrine, **2**, and (1S,2S)-pseudoephedrine, **3**; a weaker negative band is observed in (1S,2R)-ephedrine, **1**, but no distinct feature is observed at this frequency for (1S,2S)-norpseudoephedrine, **4**. The antisymmetric CCO stretch may be contributing in this region, resulting in a configurational ROA marker band for carbon 1 for two of the compounds, but, clearly, differing contributions from other motions or overlap with other normal modes is also occurring that obscures the feature in the other two compounds.

Other notable features in the ROA spectra include the oppositely signed features in (1S,2R)-ephedrine and (1S,2S)-pseudoephedrine in the 1180 cm^{-1} region (band C) and bands of the same sign near 1060 cm^{-1} (band D).

Discussion

It is clear from this preliminary analysis that the ROA spectra are sensitive to both configurational and conformational aspects of the solution structure of the ephedrine molecules. Several ROA bands appear to be strong candidates for configurational markers. In general, ROA appears to be sensitive to the local stereo-environment of the structural elements principally responsible for the origin of the parent Raman band. The power of ROA to elucidate stereochemical features is clearly evident from the variation of ROA spectra for these molecules in the presence of very little or no variation in the parent Raman spectra.

Acknowledgments

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