

Specific optical rotation for the identification of the locus of solubilization of chiral molecules in achiral micelles

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ABSTRACT

We present the first detailed experimental study of discrete wavelength resolved specific optical rotations (SORs) of chiral molecules embedded in achiral micelles. Eight different chiral compounds embedded in SDS and TX100 micelles have been used to analyze their SORs in comparison to those obtained for the same chiral molecules in achiral solvents. An important observation made is that the SORs of hydrophobic chiral molecules, α -pinene and 2-carene, in hydrophobic achiral solvents (dodecane, heptane and CCl_4) are greater than those of same chiral molecules embedded in hydrophobic core of SDS micelles. This difference is envisioned to be due to the differences in microenvironments provided by achiral SDS micelle and organic solvents. The ratio of SOR for a chiral molecule in CCl_4 solvent and achiral micelles is found to reflect the locus of solubilization of chiral molecule in achiral micelle. The locus of solubilization of chiral molecules in TX100 micelles has been independently verified using ^1H NMR studies. The emerging general observations are: (a) when chiral molecule is located deep inside the hydrophobic core of the micelle, SOR in micelle is smaller than that in CCl_4 . (b) When chiral molecule is located at the interface of hydrophobic and hydrophilic regions of the micelle, SOR in micelle is slightly greater than, or equal to, that in CCl_4 . While quantum chemical (QC) calculations to explain these observations in micelles need significantly larger computational time line, the prospect for such calculations has been verified by undertaking QC predictions of SOR for a representative chiral molecule, fenchone, in water (with 4 Å solvation sphere), and comparing the predicted results with the corresponding experimental observations in water. The predictions and observations are found to be in good agreement. The present results are expected to provide impetus for understanding the microenvironment that influences most of the spectroscopic observations.

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1. Introduction

The chiroptical spectroscopic methods, specific optical rotation (SOR) [1–7], $[\alpha]$, electronic circular dichroism (ECD) [1,2,8,9] vibrational circular dichroism (VCD) [1,2,10–12] and vibrational Raman optical activity (ROA) [1,2,10,11], are being widely used to characterize chiral compounds. SOR and ECD probe electronic transitions whereas VCD and ROA probe vibrational transitions. These experimental spectroscopic measurements in conjunction with quantum chemical (QC) calculations serve as valuable tools to ascertain the absolute configurations of chiral organic and inorganic molecules dissolved in achiral organic (such as CCl_4 , CHCl_3 , etc) and inorganic (such dimethyl sulfoxide, water, etc) solvents. A large amount of literature is now available on such studies.

Investigations on chiral surfactants using chiroptical spectroscopies has been mostly restricted to ECD [13–16]. The literature studies on chiral surfactants using VCD [17–22] and ROA [23] are sparse. Limited studies on characterization of chiral surfactants using OR [24–28] are known. Menger et al. used SOR to suggest a “porous-cluster description” [29] for micelles. Abbate et al. [30] studied enantiomers of dimethyltartrate confined within dioctyl sodium sulfosuccinate (known as AOT) in CCl_4 and pointed out that the polarity probed by dimethyl-D-tartrate in AOT is intermediate between that in CCl_4 and DMSO. Our lab has focused on the utility of SOR in the characterization of chiral surfactants. We have shown that SOR can be used to determine the critical micelle concentration (CMC) of chiral surfactants [31], CMC of achiral micelles using chiral probe [32], to follow the growth of micelles [31–34] and to characterize diastereomers of surface active ionic liquids [33,34]. We further demonstrated that the increase in SOR of chiral micelles is a manifestation of increase in the aggregation numbers with concentration [17,35].

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The SORs of chiral molecules are known to depend on the achiral solvent in which they are solvated. The discussion of this dependence normally centers around apolar and polar nature, and hydrogen bonding ability, of achiral solvents. The physical properties often used to explain this solvent dependence are refractive index, dielectric constant, polarizability, etc. of the solvent medium [36]. More recent development is the QC prediction of SOR in different solvents using either solvent imitating models (such as polarizable continuum model (PCM)) [37] or explicit solvation models (which incorporate explicit solvent molecules surrounding the solute molecule).

The behavior of SOR for chiral molecules in achiral solvents need not be same as that for chiral molecules in achiral micelles. This is because, micelles provide both hydrophobic and hydrophilic environments. Previous experiments have shown that SOR can serve as a probe for monitoring the aggregation process, and to determine the CMC of achiral micelles through the use of a chiral guest [17,19,32,38]. When a chiral guest is dissolved in an achiral micellar medium, one encounters the difficulty of identifying the residence of chiral solute molecule in hydrophobic or hydrophilic regions of the achiral micelles. In these instances, one wonders if SOR can also shed light on the locus of solubilization of chiral guest molecules in achiral micelles.

In this work we demonstrate that: (1) the locus of solubilization of chiral compounds in achiral micelles can be ascertained by using discrete wavelength resolved SOR (i.e. optical rotatory dispersion (ORD) at discrete wavelengths) based on the fact that the SOR of a chiral solute can be influenced by the nature of surrounding environment. (2) The underlining phenomenon of SOR for chiral molecules in achiral micelles appears to be different from that for chiral molecules in achiral solvents.

Aqueous solutions of two achiral surfactants, sodium dodecylsulfate (SDS) and 4-(1,1,3,3-Tetramethylbutyl)phenyl-polyethylene glycol, known as Triton X-100 (TX100), are used for generating the achiral micellar media. The locus of solubilization of chiral molecules elucidated from ORD data at discrete wavelengths has been corroborated with independent ^1H NMR spectral measurements.

2. Methods

The chiral compounds studied here (Fig. 1) can be grouped as follows: (a) (+)-2-carene and (-)- α -pinene are hydrophobic. (b) (+)-fenchone, and (-)-bornyl acetate, represent polar molecules immiscible in water (note: fenchone has very slight solubility in water, *vide infra*). (c) (-)-ethyl mandelate, (+)-ethyl mandelate represent enantiomeric molecules that have the ability to hydrogen bond, but are hydrophobic (insoluble in water). (d) (-)-*N*-Benzyl- α -methylbenzylamine is hydrophobic with labile protons. (e) (+)-

2-chloropropanoic acid methyl ester represents a compound which appears to have contributions from shorter wavelength electronic transitions that depend on conformational freedom.

The above mentioned compounds, can be incorporated into aqueous micellar solutions, although at low concentrations. The solutions of chiral solute were prepared by adding 1 μL of chiral compound under study to 1.8 mL of 50 mM aqueous micellar solution (SDS/TX100) or CCl_4 solvent or H_2O solvent. The concentration chosen for the surfactants is based on the knowledge that SDS forms spherical micelles at 50 mM concentration. While other micellar shapes can provide challenges, spherical micellar shapes offer convenience, for future theoretical modeling and calculations. The solutions of chiral solutes in CCl_4 at the desired concentration were also prepared by successive dilution for cross verification.

Experimental optical rotations were measured using Autopol IV polarimeter and converted to SORs (in units of $\text{deg cc g}^{-1} \text{dm}^{-1}$). Because of the low concentrations used for chiral solutes in micelles, the magnitudes of observed rotations are small at longer wavelengths. As a consequence, in some cases SORs at longer wavelengths could not be reported. Errors in experimental SOR values were estimated through error propagation [39].

The molecular dynamics (MD) calculations were undertaken for (1*S*)-fenchone. MD parameters were assigned using Antechamber, which also assigns atomic charges using the AM1-BCC method [40–42]. A single fenchone molecule was placed in a rectangular box of 1446 TIP3P waters using tleap [43]. First a minimization with position restraints on fenchone was performed consisting of 250 steps steepest descent then 750 steps conjugate gradient. Then a 20 ps temperature and pressure equilibration MD simulation was performed with restraints on fenchone. Finally a 120 ns of MD simulation was performed using the GPU accelerated version of Amber12 [44]. From the MD trajectories 500 snapshots were taken at regular intervals using CPPTRAJ [45] and used for QC calculations. One set included fenchone and water molecules within 3 Å of the oxygen on fenchone, which is labeled “H-bond”. A second set included all water molecules within 4 Å of any atom belonging to fenchone, which is labeled “4 Å shell”. See supporting information for the representative snapshots showing water molecules around fenchone in these two data sets. These coordinates were taken directly from the trajectories and used in QC calculations of SOR at discrete wavelengths at the CAM-B3LYP/6-31+ G^* level with PCM [37] solvent with water parameters in Gaussian 09 [46]. The basis set is limited to 6-31+ G^* , because calculations become computationally intensive when explicit water molecules are included in the first solvation sphere. The average of SOR for all the snapshots was used to represent effects of solvation. The use of coordinates directly from the MD is justified in this case, because fenchone has only one conformation and can be considered a rigid molecule. The wavelength resolved SOR calculations

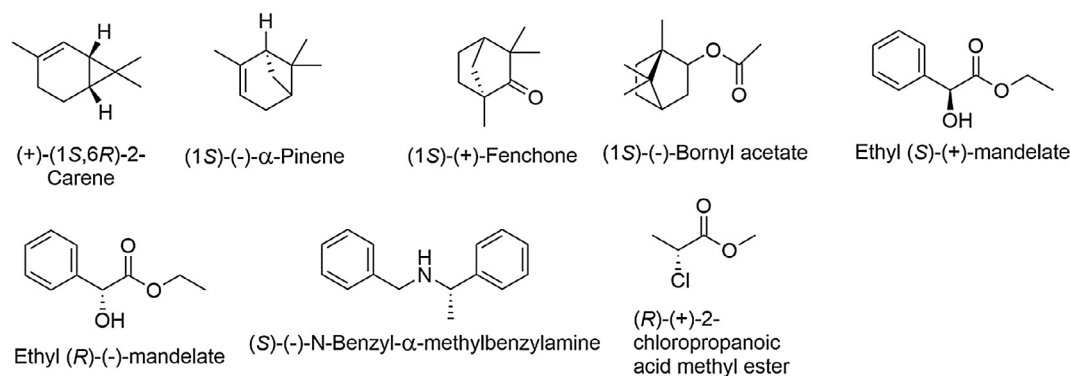


Fig. 1. Chemical structures of chiral molecules studied. Note that α -methylbenzylamine (α -MBA) is also known as 1-phenylethylamine.

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