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Molecular Chirality

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Detection of Molecular Chirality by Induced Resonance Raman Optical Activity in Europium Complexes**

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Determination of the absolute configuration (AC) and enantiomeric excess (EE) of chiral molecules is crucial in the chemical synthesis of drugs,[1] the use of asymmetric catalysts,[2] and the structure determination of natural compounds.[3] However, conventional structure analysis provides rather limited means for the detection of molecular chirality. For example, although X-ray crystallography is often used as a standard technique, for many molecules it is difficult to obtain crystals of sufficient quality. The presence of a "heavy" atom in the crystal is also required for the reliable analysis of the diffraction pattern.

Alternative spectroscopic methods are in some aspects more versatile than X-ray diffraction. Most importantly, they are applicable to solutions. A very frequently used procedure, ultraviolet circular dichroism (UVCD), is only suitable if the compound absorbs light in the UV (typically over 190 nm) or visible regions.[4] It is thus impossible to apply this technique to many important molecules, including alcohols and sugars. Furthermore, the UVCD signal is often quite weak, depending on the arrangement of the chromophores and stereogenic centers. Finally, the spectra are difficult to interpret, and very different spectral shapes may be observed for the same compound in different solvents. The same is true for the optical rotatory dispersion (ORD), in spite of the considerable progress that has been made in the interpretation of the spectra.[5]

Although nuclear magnetic resonance (NMR) is in principle blind to chirality,[6] AC determination on the basis of NMR spectroscopy is also possible through the use of chiral shift reagents to discriminate between chiral molecules.[7] Still, a high concentration of the sample and long measurement times (about an hour) are typically required in such cases.

As a result of the limitations of other methods, two vibrational optical activity (VOA) methods, vibrational circular dichroism (VCD)[8] and Raman optical activity (ROA),[3,9,10] have started to prevail for chirality detection. Vibrational optical rotatory dispersion has also been suggested.[11] This technique may be available with newly designed spectrometers in the future.[12] Unlike for UVCD, the VOA spectra can be reliably reproduced by contemporary quantum-mechanical calculations. Furthermore, VOA spectra are more characteristic for molecular AC,[9] and in addition to the AC and EE parameters, they can also yield information about molecular conformations and interactions in solutions.[13,14] Unfortunately, for many applications, VOA is severely limited by the relatively long detection times (hours to days) and high sample concentrations required for the measurement.

In the current study, we explored resonance phenomena in Raman scattering for a more universal use of VOA. In the resonance, the signal is stronger; consequently, shorter detection times are possible. Resonance occurs when the energy of an electronic transition corresponds to the laser excitation wavelength.[15] Although this condition is rarely fulfilled in organic molecules, the high-spin Eu^{III} ion provides an electronic transition ($^7F_0 \rightarrow {}^5D_0$) that corresponds closely to the wavelength of 532 nm typically used in an ROA experiment (Figure 1).[16] Chiral compounds such as alcohols and ketones can also induce optical activity, as they readily form complexes with the Eu^{III} ion. This method thus combines the sensitivity of ROA for the structure with the enhanced sensitivity of resonance Raman spectroscopy. Not only is the Raman intensity enhanced, but the circular intensity difference (CID, ratio of the ROA and Raman intensities) increases as well as a result of the involvement of lower-energy Eu^{III} spin states. Typically, CID values of approx-

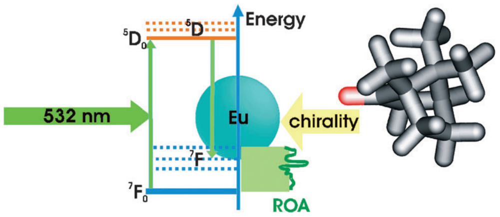

Figure 1. Schematic explanation for the induced resonance Raman optical activity. The sample is irradiated with green (532 nm) laser light, which is in approximate resonance with the $^7F_0 \rightarrow {}^5D_0$ electronic transition of the Eu^{III} ion. Raman frequencies correspond to the transitions within the ^7F states. The chirality is exclusively induced by the organic molecule.

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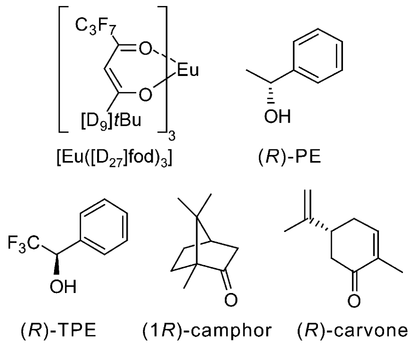
imately 10^{-2} are possible under the conditions of induced resonance ROA (IRROA), whereas in nonresonant vibrational ROA experiments CID values of only approximately 10^{-4} are observed.

Such an IRROA signal has been reported for a chiral europium complex.[17] However, the preparation of chiral europium complexes may restrict many IRROA applications. We instead explored mixtures of a nonchiral europium complex ([Eu([D$_9$]fod)$_3$], Scheme 1) with chiral alcohols and ketones. We found that the resulting adducts also exhibit IRROA. The complex is coordination-unsaturated; chiral analytes can compete with or replace the [D$_9$]fod ligands, and the [Eu([D$_9$]fod)$_3$] molecule can thus function as a universal probe of the chirality of other organic molecules. Our study based on a selection of alcohols and ketones suggests that the method is generally applicable to chiral organic compounds that form adducts with the Eu ion to expand its coordination number to about eight.



Scheme 1. Chiral compounds used in this study: the deuterated Eu^{III}–tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate-d$_{27}$) complex [Eu([D$_9$]fod)$_3$], (*R*)-1-phenylethanol ((*R*)-PE), (*R*)-2,2,2-trifluoro-1-phenylethanol ((*R*)-TPE), (1*R*)-camphor, and (*R*)-carvone.

A mixture of the [Eu([D$_9$]fod)$_3$] probe and the analyte 1-phenylethanol (PE) exhibited very strong ROA ($\Delta I = I_R - I_L$) and Raman ($I = I_R + I_L$) signals, in particular at wavenumbers greater than 1600 cm^{-1} (Figure 2). The electronic transitions of the Eu^{3+} ion in this region (e.g. $^7F_0 \rightarrow {}^7F_4$ at 2439 cm^{-1}, $^7F_0 \rightarrow {}^7F_3$ within the range 2200–1600 cm^{-1}, and $^7F_0 \rightarrow {}^7F_2$ within the range 1100–600 cm^{-1}) were previously identified in other europium complexes.[16,18] The ROA peak at 1525 cm^{-1} may have a vibrational contribution from the ligands.[17] The CID values are quite large, with a maximum of 0.02 at 2063 cm^{-1}.

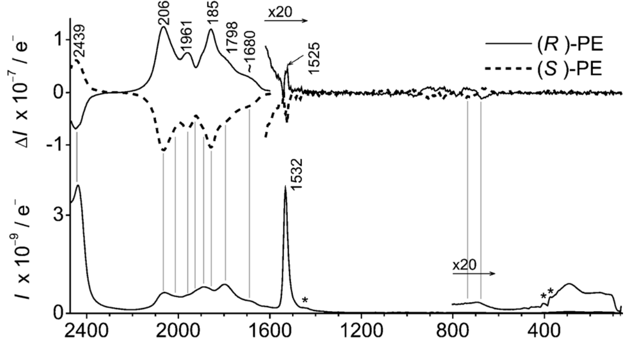


Figure 2. Top: IRROA spectra of the mixtures of [Eu([D$_9$]fod)$_3$] with (*R*)- and (*S*)-PE; bottom: corresponding Raman spectrum. *n*-Hexane was used as the solvent; possible solvent interference is marked by asterisks (*). [[Eu([D$_9$]fod)$_3$]] = 1 mM, [PE] = 10 mM, laser power at the sample: 30 mW, exposure time: 16 min.

As expected, the ROA signals of the PE enantiomers are opposite in sign (Figure 2). As the individual components exhibit no (for the plain [Eu([D$_9$]fod)$_3$] complex) or very weak ROA (CID ≈ 10^{-4} for PE), the observed signals can be attributed exclusively to the PE–[Eu([D$_9$]fod)$_3$] adduct. Indeed, the nonresonant vibrational ROA of plain PE is much weaker (Figure 3). In terms of the maximal ROA intensities, a 6×10^4-fold enhancement was observed for the adduct.

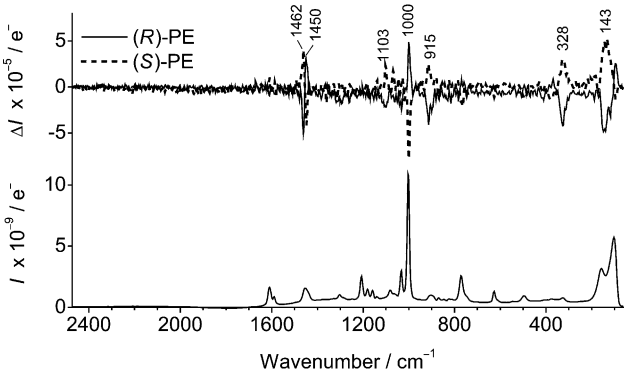


Figure 3. ROA (top) and Raman (bottom) spectra of plain (*R*)- and (*S*)-PE in *n*-hexane. [PE] = 1.0 M, laser power at the sample: 190 mW, exposure time: 70 min.

The high CID enables fast IRROA detection (within minutes) with low sample amounts. For example, for the experiment carried out at a 0.2 mM concentration, 2.4 μg of PE was needed in a sample volume of 100 μL. Only fine spectral features appear to be concentration-dependent (compare the spectra obtained at 1.0 and 0.20 mM concentrations of PE in Figure 4). As much as several milligrams of

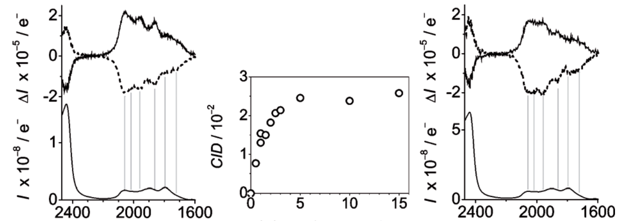


Figure 4. IRROA and Raman spectra of the adducts of [Eu([D$_9$]fod)$_3$] with (*R*)- and (*S*)-PE at high (left, 1.0 mM) and low concentrations (right, 0.20 mM) of PE in *n*-hexane. The CID ratio of the ROA and Raman intensities at 2063 cm^{-1} is plotted in the middle as a function of the concentration. Left: [[Eu([D$_9$]fod)$_3$]] = 0.10 mM, laser power at the sample: 190 mW, exposure time: 47 s; middle: [[Eu([D$_9$]fod)$_3$]] = 1 or 2 mM, laser power at the sample: 15 or 30 mW, exposure time: 2 min; right: [[Eu([D$_9$]fod)$_3$]] = 0.10 mM, laser power at the sample: 220 mW, exposure time: 200 s.

the compound would be required for comparable nonresonant vibrational ROA measurements.

The dependence of the ROA spectral pattern on the concentration (Figure 4) can be attributed to changes in the coordination number of the PE–[Eu([D$_9$]fod)$_3$] adduct. This hypothesis is supported by the dependence of the CID at 2063 cm^{-1} on the concentration ratio of (*R*)-PE to [Eu([D$_9$]fod)$_3$], as plotted in the middle of Figure 4. We speculate that a 1:1 complex may be formed at low (*R*)-PE/[Eu([D$_9$]fod)$_3$] concentration ratios, whereas at higher ratios, 2:1 and higher adducts are formed as well, with the possible replacement of the [D$_9$]fod ligands with PE. We therefore plan a more detailed characterization of the complex structure in a later study.

UVCD spectroscopy in particular would appear a promising method to provide complementary information about the stoichiometry and electronic states of these lanthanide complexes.[19,20] However, its use with [Eu([D$_9$]fod)$_3$] is problematic. The signal of the f–f transition is weak, and the concentration of the chiral analyte needs to be above 0.04 M.[21] Sometimes a stronger ligand (e.g. an amino alcohol) causes the appearance of UVCD at around 300 nm, but this peak is very weak for other chiral analytes (e.g. alcohols).[19,20]

For the other chiral molecules studied, TPE, camphor, and carvone (Scheme 1), the IRROA spectra were similar in magnitude to that for PE. However, whereas the Raman signals were almost identical, their IRROA patterns were highly specific for each alcohol or ketone (normalized spectra in Figure 5; see Figures S1–S3 in the Supporting Information for the original spectra). This high specificity opens the additional possibility of identifying the chiral analyte from the IRROA spectral pattern. Clearly, the energy levels and dipolar electronic transitions that determine the Raman shift are rather indifferent to adduct formation, whereas the specific ligand determines how the symmetry of the complex is lowered and how mixing occurs with the magnetically allowed transitions needed for IRROA.[22]

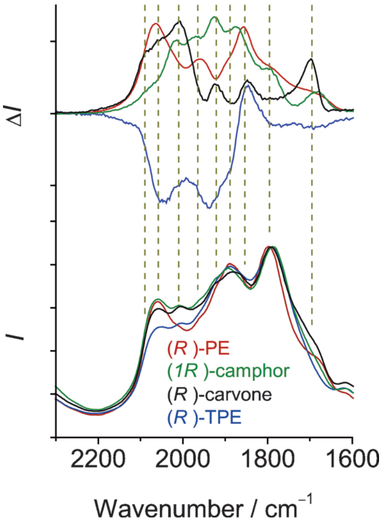


Figure 5. Normalized ROA (top) and Raman (bottom) spectra of the adducts of [Eu([D$_9$]fod)$_3$] with the *R* enantiomers of PE (red), camphor (green), carvone (black), and TPE (blue) in *n*-hexane. [[Eu([D$_9$]fod)$_3$]] = 1.0 mM, [chiral molecule] = 10 mM, laser power at the sample: 13–32 mW, exposure time: 13–16 min.

The possibility of enhancing the ROA signal by mixing with electronic states has been discussed previously.[23] Nonresonance ROA spectra of transition-metal complexes can themselves be modeled by density functional methods.[14,24] However, we are not aware of any ab initio software that would provide a more detailed theoretical background for the interpretation of these spectra to reflect the relatively complex electronic (relativistic, open-shell) and vibrational structure. So far, IRROA spectra have to be interpreted in an empirical way, similarly to the NMR[25] or UVCD[19] spectra recorded for chiral compounds in the presence of lanthanide probes.

We can conclude that the [Eu([D$_9$]fod)$_3$] complex exhibits a strong affinity to form adducts with four model compounds and thus enhances the chiral signal. The results suggest that the complex can act as quite a universal reagent to bind small organic molecules and thus aid the determination of their chirality. The strong signal and high CID ratio ensure that the induced resonance Raman optical activity (IRROA) technique can be used for sensitive chirality detection in alcohols and ketones. An exceptionally large (6×10^4-fold) enhancement of the chiral signal relative to that observed by nonresonant vibrational ROA enabled the IRROA measurements to be performed with very low sample concentrations. For example, in the case of the 0.2 mM solution, the measurement took about 3 min, and only about 2 µg of the sample was needed. The IRROA method thus significantly expands the field of ROA applications, including the determination of the absolute configuration and enantiomeric excess of chiral compounds.

Experimental Section

[Eu([D$_9$]fod)$_3$] (Stohler Isotope Chemicals) was dissolved in *n*-hexane (Aldrich) to a final concentration of 0.10–2.0 mM and mixed in *n*-hexane with a chiral reagent ((*R*)-PE, ≥ 98.5 %, Fluka; (*S*)-PE, ≥ 98.5 %, Fluka; (*R*)-TPE, 99 %, Aldrich; (*S*)-TPE, 99 %, Aldrich; (1*R*)-camphor, 98 %, Aldrich; (1*S*)-camphor, ≥ 99.0 %, Fluka; (*R*)-carvone, 98 %, Aldrich; (*S*)-carvone, 96 %, Aldrich) to a final concentration of 0.20–15 mM.

Backscattering Raman and ROA SCP (scattered circular polarization) spectra were recorded on a BioTools ROA spectrometer with laser excitation at 532 nm, an edge filter (Semrock) with a frequency cutoff at 90 cm^{-1}, and a resolution of 7 cm^{-1}. The sample solution (ca. 100 µL) was placed in a glass cell; the laser power at the sample was 15–220 mW. Third-order five-point Savitzky–Golay smoothing was applied to the ROA spectra, and the solvent background signal was subtracted from the Raman spectra, as exemplified in Figure S4 in the Supporting Information. Intensities are expressed as the number of electrons (e$^-$) recorded by the CCD detector.

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