

Chiral self-recognition in the gas phase: the case of glycidol dimers

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Supersonic jet FTIR spectra of the OH-stretching bands of glycidol monomers and clusters are presented. Chiral discrimination leads to marked differences in the absorption patterns of *RR* (*SS*) vs. *RS* glycidol dimers. The dominant absorption peaks are located at 3492 (*RR*, *SS*) and 3488 cm⁻¹ (*RS*) within a rich line spectrum with sizeable variations between enantiomerically pure and racemic dimers. A spectral difference technique is used to emphasize the intermolecular diastereomeric effects. Glycidol is possibly the first and likely the smallest molecule for which chiral self-recognition has been experimentally demonstrated in the gas phase. It thus lends itself very well to accurate quantum chemical calculations of the chiral discrimination effect. Qualitative results of exploratory calculations are reported.

Chiral recognition has fascinated researchers ever since Emil Fischer developed his lock-and-key principle.¹ It provides an essential basis for most biochemical processes and a major challenge in bio-organic synthesis. Enantioselective reactions are typically preceded by a diastereomeric complex, whose properties can be studied by vibrational spectroscopy. Intermolecular interactions lead to characteristic frequency shifts in the normal modes of the interacting molecules. The OH stretching vibration is particularly sensitive to details of the interaction and would appear to be well suited for such a study. However, it is inhomogeneously broadened in a liquid environment due to thermal, structural and cooperative effects. Dilution of the diastereomeric complexes in inert solvents helps to resolve the broad OH band to the extent that intensity effects can be studied.² In contrast to small thermochemical differences between enantiomerically pure and racemic alcohols,³ spectral intensity differences between homochiral (*RR* or *SS*) and heterochiral (*RS*) butan-2-ol dimers were found to be substantial.² If these differences are entirely due to dimer concentration differences (rather than band strength differences or other effects), they are consistent with an energy difference of about 3 kJ mol⁻¹ between the more stable homochiral dimer and the less stable heterodimer.² It should be noted that this chiral discrimination effect could not be confirmed in a recent re-investigation.⁴ Hence, the question of IR chiral discrimination in butan-2-ol solutions remains open.

For a more accurate and solvent-free determination of binding energy differences and for the detection of spectral shifts between homochiral and heterochiral dimers, supersonic jet spectroscopy is better suited.^{5–10} It provides the low temperatures necessary to freeze out inhomogeneous broadening effects. One can obtain resolved spectra for one or several conformations of the diastereomeric pair. However, the spectroscopic techniques employed so far in this field rely on the availability of an aromatic chromophore which is suitable for laser induced fluorescence or resonant two-photon ionization detection.^{5–10} While these techniques have substantial advantages in terms of the determination of relative binding energies,^{11,12} they involve relatively large molecules, which are not easily amenable to rigorous *ab initio* calculations.^{13,14} Furthermore, the aromatic chromophore introduces important

dispersive interaction sites, which compete with the classical hydrogen bond and repulsive contacts. An investigation of smaller, non-aromatic systems allows for a more rigorous quantum-chemical modeling and it should help in assessing the relative importance of hydrogen bonding vs. dispersive interactions in chiral recognition. A very recent microwave study of butan-2-ol,¹⁵ which focuses on the monomer conformations, mentions the observation of unassigned lines which are likely to arise from butan-2-ol dimers. Microwave jet spectroscopy clearly has the potential to unravel the structure of diastereomeric complexes in much detail.

A complementary and possibly simpler approach towards the detection of chiral discrimination effects is offered by broad-band direct absorption IR spectroscopy.¹⁶ The recently developed ragout-jet FTIR technique¹⁷ provides sufficient sensitivity and stability to compare racemic and enantiomerically pure dimer spectra of chiral substances. It is based on a pulsed slit jet featuring giant seeded gas pulses (up to 1 mol in up to 1 s at up to 0.1 Hz repetition rate), which are synchronized to full interferometer scans and buffered in a 15 m³ vacuum chamber before being pumped out by a series of roots pumps. The substance concentration in the carrier gas is adjusted by the temperature of the saturator, through which the gas is conducted. The jet is probed 16 mm downstream of the nozzle by an IR beam of about 20 × 10 mm cross section, in which the cluster concentration is found to be more or less constant.

Our choice of an appropriate chiral molecule is influenced by several constraints. The vapor pressure is currently required to exceed 0.1 mbar. The racemic mixture and at least one enantiomer should be available in sufficiently pure form. The conformational flexibility of the monomer should be restricted to minimize spectral congestion due to the existence of several isomers. In this respect, the two torsional degrees of freedom in butan-2-ol^{11,15} are somewhat unfavorable. Oxiranes have been recognized previously as being well suited in this context.^{13,14,18} The availability of two complementary functional groups in each monomer helps to reduce the dimer flexibility and can be expected to enhance the chiral recognition effect.¹⁰ Glycidol (C₃H₆O₂, 2,3-epoxypropan-1-ol, oxiranemethanol), a cyclic ether with an additional alcohol functionality, fulfills these requirements. While it also has two torsional degrees of freedom, two of the monomer conformations are strongly favored over the others due to the formation of a weak internal hydrogen bond.¹⁹ We have therefore recorded the OH stretching spectrum of its *R/S* homo- and heterodimers. Racemic glycidol (Fluka, 90%) and *R* as well as *S* glycidol (Fluka, 97%) were used as supplied. The magnitude of the optical rotation for the *R* and *S* probes was found to be equal. The presence of a ≤10% impurity in the racemic probe was confirmed by NMR spectroscopy. Because of this moderate chemical purity, we compared spectra of the commercial racemate with a 1 : 1 mixture of *R* and *S* forms and found no difference in the jet spectra. The absence of a spectral pattern evolution with substance consumption in the saturator confirms that any impurities are either non-volatile or do not absorb in the OH stretching range.

To the best of our knowledge, glycidol has not yet been studied in supersonic jet expansions, inert solutions, matrix isolation or with other techniques suitable for the detection of clusters. Fig. 1 provides 3 μm spectra of the racemic mixture (*RS* glycidol) recorded in different states of aggregation. The spectra are scaled such that they represent comparable numbers of molecules, as judged by the C–H absorptions. The gas phase spectrum hints at conformational isomerism of the monomer,¹⁹ and the band positions indicate a weak form of internal hydrogen bond, if compared to ethanol or propanol.^{20,21} The liquid phase spectrum shows a typical broad hydrogen-bonded OH-stretching absorption with no sizeable contribution from free OH groups. The intensity enhancement from the monomer to the liquid is slightly less than in aliphatic alcohols.²² In the spectrum of the He expansion (about 0.2% glycidol, tungsten lamp, CaF₂ optics, InSb detector, 2.5–3.5 μm optical filter), the two conformations of the monomer¹⁹ are well separated (3608 (M1) and 3641 cm^{-1} (M2)), in contrast to the gas phase.¹⁹ The lower frequency absorption (M1) corresponds to the most stable conformation, as it gains intensity relative to the higher frequency band upon cooling. From *ab initio* band strengths, we estimate that the monomer concentration in the expansion is of the order of $3 \times 10^{13} \text{ cm}^{-3}$. In the dimer region around 3500 cm^{-1} , there are more than 20 reproducible peaks superimposed on the slope of a broad band which extends down to 3200 cm^{-1} . Pressure dependence studies confirm that at least the strongest of these peaks are due to dimers, whereas the broad band

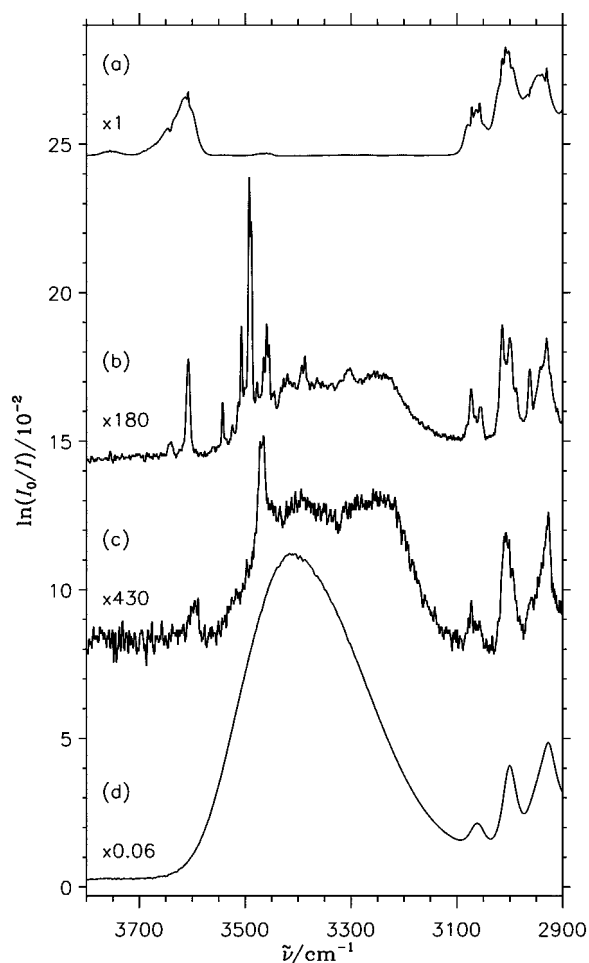


Fig. 1 FTIR spectra of *RS* glycidol at 2 cm^{-1} spectral resolution in various states of aggregation. From top to bottom: (a) gas phase (≈ 1 mbar in 640 mbar He at 334 mm path length); (b) jet expansion, $\approx 0.2\%$ in He, stagnation pressure $p = 1.2$ bar, 100 s acquisition time at a duty cycle of about 0.2%; (c) jet expansion, $\approx 0.2\%$ in Ar, $p = 0.3$ – 1.2 bar, 40 s acquisition time at a duty cycle of about 0.5%; (d) liquid in transmission.

is mostly caused by larger clusters. This assignment is further supported by a comparison to spectra of alcohol–ether dimers and oligomers.²³ The most prominent dimer absorption consists of a closely spaced doublet (3492 (D3) and 3488 cm^{-1} (D4)). The doublet is somewhat better resolved further downstream of the nozzle, whereas an enhancement of the spectral resolution (1 cm^{-1}) had only minor effects. The total dimer concentration is roughly an order of magnitude lower than the monomer concentration, based on *ab initio* predictions of the band strength. The absorption below 3400 cm^{-1} , where larger clusters with cooperative hydrogen bond sequences are expected to absorb, is less structured.

A dilute expansion in argon provides a different picture. The dominant monomer band is broadened and shifted to lower frequency ($\approx 3595 \text{ cm}^{-1}$). Most of the detailed structure in the dimer region collapses to a broad and intense peak at $\approx 3470 \text{ cm}^{-1}$, which is also red-shifted relative to the center of gravity of the free dimer absorptions. In analogy to our findings for HCl,¹⁷ MeOH,²⁰ water²⁴ and carboxylic acids,²⁵ we assume that the spectra are due to glycidol clusters coated with Ar, *i.e.* surrounded by a kind of nanomatrix environment.

Fig. 2 shows the racemic spectrum obtained in the He expansion together with a spectrum of the pure *R* or *S* enantiomer recorded under identical conditions. Indistinguishable spectra were obtained for the separate *R* and *S* compounds. Hence, the spectra of all racemic and all enantiomerically pure

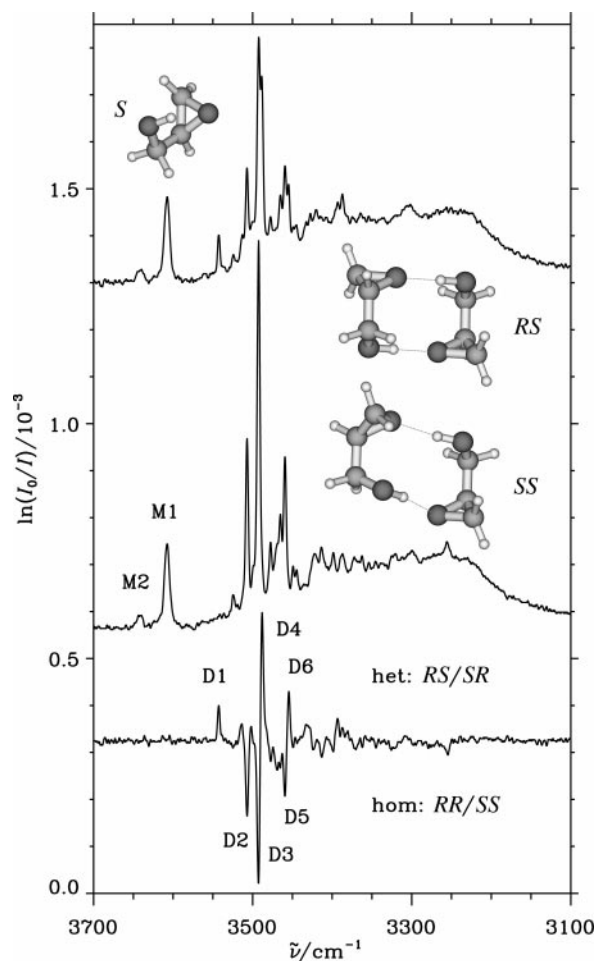


Fig. 2 Ragout-jet FTIR spectra of racemic *RS* glycidol (top trace, from Fig. 1, together with the most stable, internally hydrogen-bonded monomer structure of *S* glycidol according to MP2/6-31+G* calculations and a favorable conformation of the *RS* dimer at B3LYP/6-31+G* level) and enantiomerically pure *R/S* glycidol (middle trace, 100 s acquisition time, together with a favorable conformation of the *SS* dimer at B3LYP/6-31+G* level). The bottom trace shows the difference ($R + S$) – (S or R) (racemate – enantiomer) on the same scale. Monomer peaks are marked M1, M2. Dimer peaks are labeled D1–D6. See text for the interpretation of the difference spectrum.

compounds were separately coadded to improve the signal-to-noise ratio. It can be seen that the enantiomerically pure compound has less spectral structure in the dimer OH stretching region. On the other hand, the monomer absorption is indistinguishable in both spectra. Disregarding subtle parity violation effects,^{13,16} this is of course expected. A similar behavior is observed for the CH absorptions, which are not very sensitive to intermolecular interactions. As a consequence, the monomer and CH absorptions cancel in the difference spectrum ($R + S$) – (S or R) (racemate – enantiomer), whose OH-stretching part is also shown in Fig. 2. In the cluster OH region, the difference spectrum exhibits positive and negative peaks. Positive absorptions arise from the heteroclusters, which are only possible if both R and S forms are present. Negative absorptions are due to enantiomerically pure clusters, which should be more abundant in the pure compound than in the racemic mixture. If the energy difference between homochiral and heterochiral dimers is small or if dimer formation in the jet is kinetically controlled, one expects twice as much homodimers in the pure compound than in the racemic mixture. In this case, the area under the negative peaks should be close to that under the positive peaks. This is approximately the case for the difference spectrum shown in Fig. 2. Spectra recorded at higher concentration indicate a slight preference for the formation of homodimers rather than heterodimers,⁶ which may be related to a larger binding energy. However, more detailed investigations are necessary to verify and quantify this effect. Where the spectral difference between the diastereomers is within the width of the absorptions (such as for the largest dimer peak), a dispersion-like difference signal arises. None of the major peaks in the dimer region vanishes completely upon difference formation. Furthermore, the integral of all dimer peak areas in the difference spectrum (irrespective of their sign) amounts to about one half of the integral of all sharp contributions to the racemic spectrum. Therefore, a significant amount of the dimer OH absorptions show a resolved diastereomeric splitting. However, the size of the splitting varies between relatively small ($\approx 4 \text{ cm}^{-1}$ in the large band), and very large ($> 35 \text{ cm}^{-1}$ for an isolated band at 3543 cm^{-1} which is only present in an RS mixture). The small negative peak near 3255 cm^{-1} may even indicate the preferred formation of a cooperatively stabilized homo-oligomer, *e.g.* a tetramer. In contrast, a preliminary difference analysis of the spectra obtained in Ar expansions does not reveal significant diastereomeric effects. Under these conditions, any chiral discrimination is obviously masked by the inhomogeneous broadening of the absorption band.

The complex structure observed in the free dimer region may have various origins. Isomerism is a conceivable cause,⁸ even though glycidol monomer is relatively rigid and the line intensity ratios are insensitive to a change in expansion conditions. Anharmonic couplings to dark states can also give rise to complex band patterns,²⁵ as can combination transitions with low frequency modes.²⁶ In both cases, the patterns may differ between homo- and heterodimers. The collapse of the band structure in the Ar nanomatrix is consistent with both interpretations. We have observed a similar behaviour in the well-studied case of methanol trimer.²⁰ It will be interesting to follow the spectral fingerprint of the Ar coating as a function of stagnation pressure.

The origins of diastereomeric frequency splittings and energy differences have been discussed in detail for aromatic systems^{7,8} and also for smaller model systems which are not characterized experimentally, yet.¹⁴ Through-bond and through-space mechanisms have been discussed.¹⁴ In aromatic systems, it is believed that the effects are dominated by dispersive interactions. Our results for glycidol provide the first experimental non-aromatic reference system. Once spectrally assigned, they can be used to isolate the effect of more local interactions, in particular hydrogen bonding.

Electronic structure calculations can provide structural, energetical and dynamical information to assist this spectral

assignment. Here, we only provide a concise summary of the results obtained so far. We find a subtle stability balance between two glycidol dimer hydrogen bond topologies. In one of these topologies, both glycidol OH groups act as hydrogen bond donors towards the oxirane oxygens of the other molecule, thus forming two equivalent hydrogen bonds within an eight-membered ring of heavy atoms (see Fig. 2). Alternatively, the two functional groups of one glycidol molecule can chelate the OH group of the second, leading to a cooperative, but strained hydrogen bond pattern in a five-membered ring of heavy atoms and a dangling oxirane ring. This structure is similar to the one proposed for amino-propanol complexes.¹⁰ At the HF/3-21G level, five- and eight-membered rings are within a few kJ mol^{-1} . The RS pair appears to favor the five-membered ring and the SS (RR) dimer is more stable in the eight-membered ring structure. At the B3LYP/6-31+G* level, our preliminary results indicate that eight-membered ring structures are somewhat more stable than five-membered ring structures and again, the SS (RR) dimer appears to be more stable than the RS dimer. Higher level calculations are required to firmly establish such energetic relationships.

We have reported the first direct absorption IR detection of diastereomeric interaction between chiral molecules in a supersonic jet. Glycidol, an important chiral synthon, appears to be the lightest molecule (74.08 u) with the smallest number of electrons (40) and atoms (11) for which chiral (self-)recognition has been experimentally demonstrated *in vacuo*. It therefore lends itself very well to rigorous quantum-chemical benchmark calculations of the chiral discrimination phenomenon. Such calculations are currently under way. A ragout-jet FTIR study of chiral recognition in the more flexible butan-2-ol dimer, whose monomer exists in at least three monomer conformations in a supersonic jet expansion,¹⁵ is in progress. In this case, the spectral differentiation between homo- and heterochiral dimers appears to be less pronounced.

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