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The Six Isomers of the Cyclohexanol Dimer: A Delicate Test for Dispersion Models

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Abstract: *The cyclohexanol homodimer is a delicate test model of the role of dispersion forces in intermolecular association. While phenol produces a single dimer, suppression of π interactions and larger conformational flexibility in cyclohexanol results in multiple isomerism, as six competing dimers of the free molecule are observed in a supersonic jet expansion. Rotational spectroscopy reveals accurate structural data, specifically the formation of homo- and heterochiral diastereoisomers and the presence of both equatorial and axial forms in the dimers. Four dispersion-corrected density-functional molecular orbital calculations were tested against the experiment, with B3LYP-D3(BJ) offering good structural reproducibility with an Alrich's triple- ζ basis set. However, the prediction of the dimer energetics is largely model-dependent, offering a testbed for validation of dispersion-corrected computational models.*

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The competition between a leading hydrogen bond (HB) and weak dispersion forces produces multiple isomerism in the cyclohexanol dimer, as six different species were observed in a jet expansion.

Chiral recognition is as a pervasive molecular player in biological and supramolecular Chemistry, directly influencing ligand binding and macromolecular assembly.^[1] Experiments in gas-phase contribute with structural, dynamical and energetic information on the non-covalent interactions observed in the association of free chiral molecules,^[2-4] with the ultimate goal of understanding the molecular basis of enantioselectivity. However, the lack of a general and applicable aggregation model, the multiple intermolecular forces, the variety of interaction energies, the cooperative and competitive effects and the need of accurate empirical data to validate quantum mechanical models call for additional experiments on chiral recognition between isolated molecules.

Chiral recognition is primarily affected by the stereomutation barriers. Low stereomutation barriers are denoted transient chirality and the molecular recognition process, which might involve a structural readaptation, has been categorized as chirality synchronization.^[2] Homodimers with transient chirality are interesting because the formation of the cluster quenches stereomutation, offering the possibility to detect separately the hetero- and homochiral diastereomeric clusters and insights into the recognition process.

Torsional chirality has been mostly studied in alcohols, because of the moderately strong O-H \cdots O H-bond and the use of the O-H stretching vibration as structural probe in IR,^[5] Raman,^[6] IR/UV^[7,8] or IR/IR/IR^[9] spectroscopy. Microwave spectroscopy offers higher (sub-Doppler) resolution, unambiguous structural identification and general applicability.^[4,10] However, the number of rotational studies on transiently chiral dimers is scarce.^[11-19] The analysis of the cyclohexanol dimer explores the balance of intermolecular forces and the differences with phenol aggregation.^[20] Our results reveal a rich isomerism, arising unexpected questions. In particular, how non-covalent forces

affect isomerism? Can density functional theory (DFT) account for the energetics and structure? and, finally, can you invert a cyclohexanol ring in a jet expansion?

Cyclohexanol offers a variety of structural families, based on axial (A) /equatorial (E) inverting chairs and large-amplitude vibration of the hydroxyl group in Figure 1. The most stable equatorial conformer is a fluxional structure tunneling between two symmetry-equivalent equatorial-gauche (EG+ and EG-) isomers, splitting the ground-vibrational state into two torsional-rotation sublevels ($\Delta E_{01}=52(2)$ GHz).^[21] The equatorial-trans (ET) conformer adopts a non-degenerate rigid structure. The axial conformers (ca. 2-6 kJ mol⁻¹), previously observed for 1-methylcyclohexanol,^[22] were not detected for cyclohexanol.^[21] On formation of the cyclohexanol dimer the gauche stereomutation is broken and the two enantiomers become distinguishable, producing distinct diastereoisomers. Assuming that the dimer is primarily stabilized by a conventional O-H...O H-bond, the two oxygen lone-pairs in the proton acceptor offer six (2 E/A and 3 G+/G-/T) possibilities for each of the six proton donor cases, forming 72 isomer families in 36 enantiomeric pairs. However, previous vibrational investigations could only identify a single EG-EG isomer.^[9] Recent FTIR and Raman jet spectra have suggested at least four isomers,^[23] demanding conclusive investigations.

Cyclohexanol was first probed in a neon jet expansion using broadband chirped-pulsed microwave spectroscopy^[24,25] (see Supporting Information, SI). The spectrum in Figures 2 and S1-S2 (SI) is dominated by the monomer, but contains other weak (5-10%) features from plausible clusters. The spectral assignment started from trial rotational constants and iteratively led to the identification of six isomers of the homodimer (I-VI). The rotational transitions (Tables S1-S6, SI) were fitted to a semirigid-rotor Hamiltonian,^[26] with spectroscopic parameters in Table 1. A second experiment in helium did not identify additional species. Experiments with argon showed only isomers II, III and IV,

confirming that the global minimum is one of these species and the presence of conformational relaxation.^[27]

The experiment was rationalized with molecular orbital calculations. The PES was expected quite shallow and corrugated, with multiple local minima of small energy, low isomerization barriers and multiple interconversion paths. Our computational strategy (SI) used molecular mechanics (MM) screening followed by DFT^[28] optimizations to probe the maximum conformational space, as in previous experiments.^[29] The 60 most stable isomers of the initial 203 MM structures ($<20 \text{ kJ mol}^{-1}$) were reoptimized with three hybrid or meta-GGA functionals, including B3LYP,^[30] MN15-L^[31] and M06-2X,^[32] using Ahlrichs' polarized triple-zeta basis def2-TZVP.^[33] Minnesota functionals were assumed parametrized for dispersion. B3LYP was supplemented with D3^[34] dispersion corrections and Becke-Johnson damping.^[35] Finally, the isomers located with each method were reoptimized with the other two functionals. Geometry convergence was very sensitive, with minor changes in the initial geometries resulting in different final structures. Tables S7-S9 (SI) collect the conformational search.

All observed isomers could be identified with one of the predicted structures. However, the three DFT methods describe the experiment differently. MN15-L and M06-2X behaved similarly and reproduced the rotational constants with larger relative deviations ($\sim 2.0\text{-}5.0\%$). B3LYP-D3(BJ) offered the best agreement, with maximum relative deviations below 3% (i.e., IV and V) and best agreements of 0.1-1.0% (i.e., III and VI). Table S10 (SI) compares experiment and theory for B3LYP-D3(BJ). The results support the argument that Minnesota functionals might need corrections for long-range dispersion.^[28] Despite the good agreement, both the multiple geometry convergence pathways and the fact that small structural changes (exchange of donor/acceptor or hydroxyl internal rotation) may produce similar rotational constants and conformational

energies, turn the structural conclusions model-dependent. Model-dependence was confirmed a posteriori by an independent conformational search using PW6B95-D3^[36,37] and a ω B97X-D^[38] reoptimization of the six observed dimers in Table S10 (SI).

Isomer identification is given in Table 1 and Figure 3, with labels indicating the equatorial/axial and gauche/trans orientations for the proton donor and acceptor, respectively, the (+/-) gauche chirality (relative to a ¹C₄ chair) and the bridging oxygen lone pair position (1/2) at the proton acceptor. The equatorial-gauche appears in all isomers, as expected from its larger stability in the monomer. However, one of the two monomers occasionally adopts other geometries (see 3-D Figures S3-S8 and Tables S11-S16, SI). Specifically, three isomers contain an axial-gauche moiety (III=EG-(1)AG-, IV=EG-(1)AG+, V=AG-(1)EG+) and one isomer contains the axial-trans orientation (I=AT(2)EG-). The two remaining isomers are composed exclusively of equatorial-gauche forms (II=EG-(2)EG-, VI=EG-(1)EG+). The present computational model and the spectral intensities give population ratios of I:II:III:IV:V:VI = 1.0(4):0.7(4):0.6(3):0.5(2):0.3(1):0.3(1). This calculation is only approximate, as it additionally assumes a linear fast-passage polarization regime proportional to the squared dipole moments and uniform instrumental response.^[25] No attempt was made to derive experimental conformational energies since jet populations are affected by conformational relaxation^[27] and initial monomer concentrations.^[39]

The presence of axial forms is noticeable. Unlike 1-methylcyclohexanol, where the bulkier methyl group stabilizes the axial hydroxyl,^[22] cyclohexanol has preference for the equatorial conformations (Figure S9, SI).^[21] In order to explain the axial forms we compared the equatorial-to-axial potential barriers both in the monomer and the dimer. The inversion barrier for the cyclohexanol chair was estimated as 47-54 kJ mol⁻¹ in the coordinate scan of Figure S10 (SI, no transient-state calculation). A similar calculation in

the dimer starting from each of the observed geometries and averaging over six inversion paths rendered comparatively similar barriers of 44-51 kJ mol⁻¹ in Figure S11 (SI). We conclude that there are no plausible ring inversion paths of reduced energy, so the presence of axial forms is due to energetic collisions at the initial stages of the expansion. Collisional stabilization of specific isomers undetected in the monomers has been observed in jets for other clusters.^[40-42]

The intermolecular interactions have been mapped using non-covalent-interactions plots in Figures 4 and S12-S17 (SI), based on a reduced gradient $s \left(= \frac{1}{1(3\pi^2)^{1/3}} \frac{|\nabla\rho|}{\rho^{4/3}} \right)$ of the electron density.^[43] All the observed structures exhibit an O-H \cdots O H-bond with predicted distances $r_e=1.891$ - 1.904 Å (B3LYP-D3(BJ)), longer for the AT proton donor (1.948 Å). In some isomers additional weak C-H \cdots O H-bonds are apparent (2.65-2.82 Å). In all cases, the two cyclohexyl moieties avoid near-stacking structures. The H-bond distance is intermediate between the phenol dimer^[20] (O \cdots H: $r_0=1.837(23)$ - $1.879(38)$ Å, $r_e=1.87$ - 89 Å; O \cdots O: $r_0=2.830(36)$ - $2.833(21)$ Å) and the water dimer (O \cdots O: $r_0=2.976$ Å, $r_e=2.952$ Å). Additional insight into the nature of the non-covalent interactions was obtained by energy decomposition. SAPT2+(3)/aug-cc-pVDZ^[44] results in Table S17 (SI) for cyclohexanol and six related dimers show that while the primary interaction is electrostatic (159% of a binding energy of -29.2 kJ mol⁻¹), the dispersion component is very significant (91%) and similar to the phenol dimer (104%).

In conclusion, we characterized the association between two neutral free molecules of cyclohexanol in a jet expansion. Compared to the phenol dimer,^[20] the suppression of π - π or C-H \cdots π stabilization forces and larger flexibility results in multiple isomerism. The alcohol stereomutation is quenched in the dimers, so the gauche chiral species collapse into different diastereoisomers. However, there is no indication of a dominant

stereoselectivity as both homochiral and heterochiral species are observed in the dimer. In other small-alcohol dimers both homochiral^[11,12] and heterochiral^[13,14,17] preferences have been observed, anticipating sensitive isomerization equilibria in shallow multiconformational PES.

Because of the competition between multiple low-energy species the computational survey was difficult. All three DFT methods showed indications of: a) a quite flat potential energy surface, with final structures very dependent of the initial geometry and computational method, b) considerable model changes in the determined isomer energies, and c) deficiencies to assess the relative energy ordering and global minimum. As a result, the dimer DFT energetics turns out model-dependent and proves an interesting testbed for the predictability of more advanced computational models describing non-covalent interactions. This issue can be related to the most general search of benchmark clusters and appropriate dispersion models within the “DFT zoo”, as advocated by Grimme.^[28] This result evidences how the combination of rotational data with computational methods offers a synergic benefit to characterize weakly-bound chirality recognition models in gas phase.

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Keywords: Homodimers, Molecular recognition, Hydrogen bonding, Cyclohexanol, Rotational spectroscopy, Jet spectroscopy.

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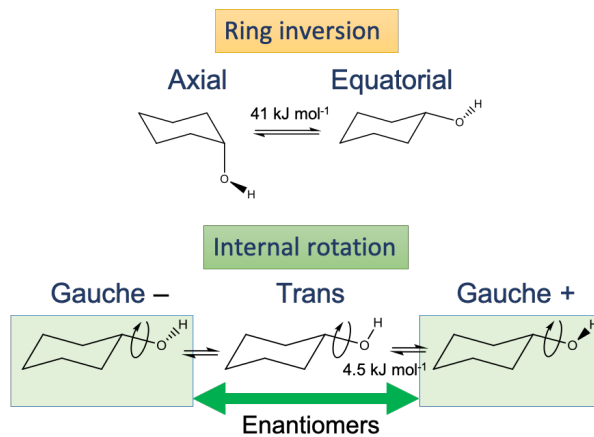
Figure 1. Large-amplitude motions in the cyclohexanol monomer.

Figure 2. The microwave spectrum of the cyclohexanol dimer and a 240 MHz expansion, showing transitions from six different isomers.

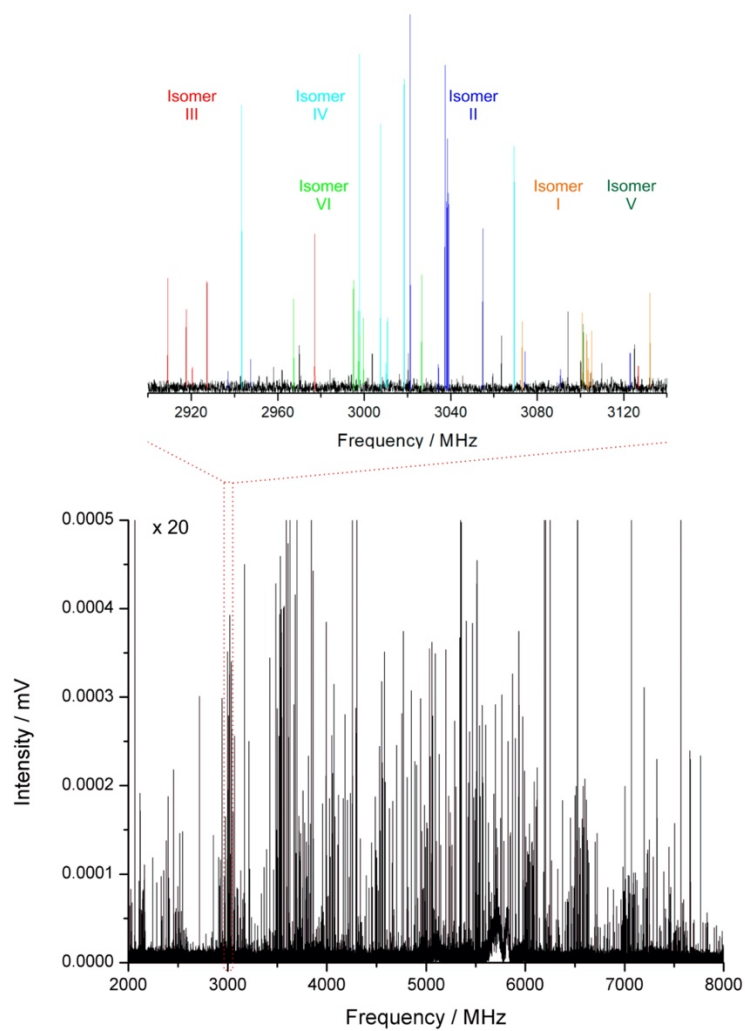


Figure 3. Conformational assignment of the six isomers of the cyclohexanol dimer and hydrogen bond distances according to B3LYP-D3(BJ)/def2-TZVP.

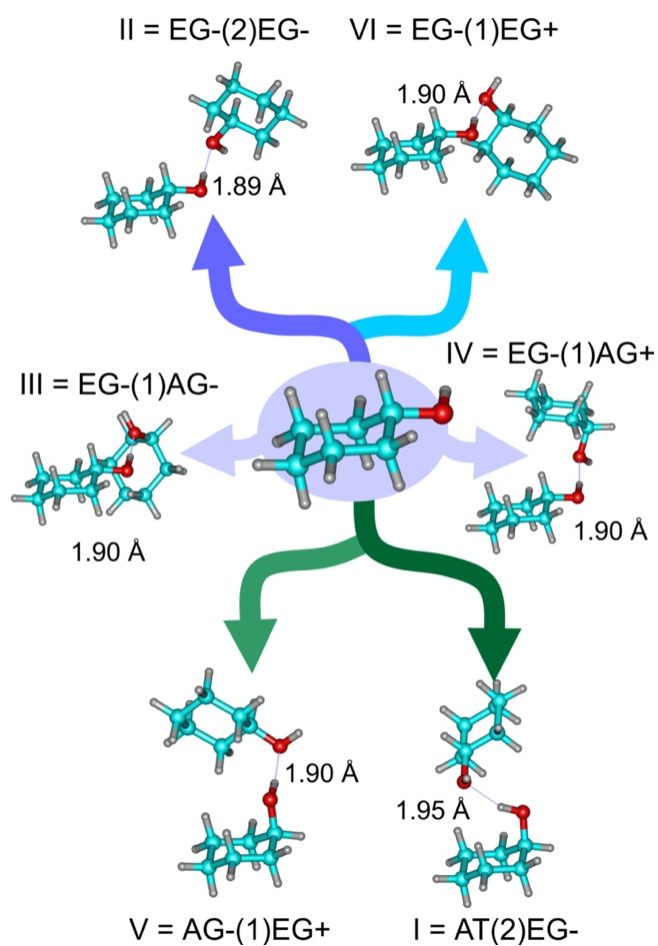


Figure 4. The spatial distribution of the non-covalent interactions in isomer IV of the cyclohexanol dimer, according to a NCIPLOT analysis. The O-H \cdots O H-bond (blue) is accompanied by broad weak dispersive interactions (green shades) and repulsive zones (red). The lower graphic shows the reduced electronic density gradient representation for the water (blue), phenol (green) and cyclohexanol dimers (red), see SI.

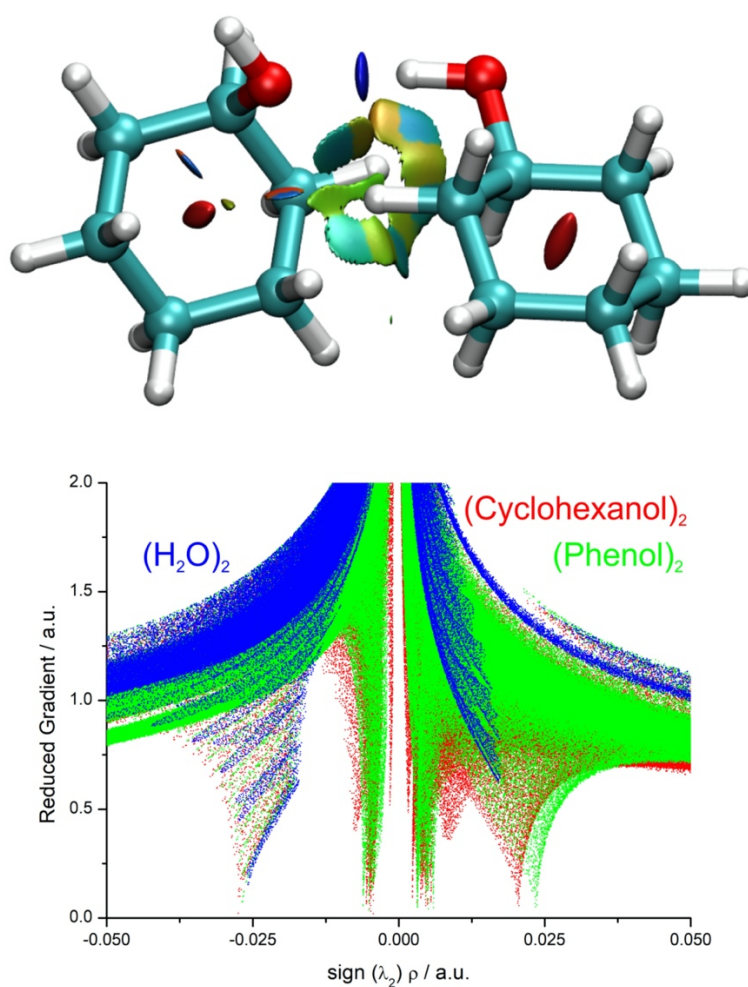


Table 1. Rotational parameters for isomers I-VI of the cyclohexanol dimer.

| | Isomer I | Isomer II | Isomer III | Isomer IV | Isomer V | Isomer VI |
|------------------------|----------------------------|---------------|---------------|---------------|---------------|---------------|
| | AT(2)EG- | EG-(2)EG- | EG-(1)AG- | EG-(1)AG+ | AG-(1)EG+ | EG-(1)EG+ |
| $A / \text{MHz}^{[a]}$ | 1218.11(23) ^[c] | 1273.9599(22) | 1203.5721(82) | 1167.877(41) | 1039.694(67) | 1311.72(22) |
| B / MHz | 316.22133(97) | 255.99343(18) | 303.99025(48) | 313.51209(51) | 328.52277(90) | 254.73673(31) |
| C / MHz | 304.41165(91) | 250.38848(19) | 279.76964(43) | 288.25106(51) | 304.34728(85) | 244.86010(34) |
| D_J / kHz | 0.0583(13) | 0.05908(57) | 0.06469(69) | 0.06942(56) | 0.2037(13) | 0.06438(54) |
| D_{JK} / kHz | -0.1976(88) | -0.4638(99) | -0.2661(34) | -0.2290(26) | -0.475(11) | -0.5107(72) |
| D_K / kHz | [0.0] | 1.45(34) | [0.0] | [0.0] | [0.0] | [0.0] |
| d_I / kHz | -0.0043(19) | [0.0] | -0.01083(87) | -0.01058(97) | -0.0286(20) | [0.0] |
| $N^{[b]}$ | 71 | 129 | 101 | 106 | 69 | 100 |
| σ / kHz | 13.0 | 13.3 | 10.3 | 8.3 | 12.2 | 13.5 |

^[a]Rotational constants (A , B , C) and Watson's S-reduction centrifugal distortion constants (D_J , D_{JK} , D_K , d_I , d_2 =[0.0]).

^[b]Number of transitions (N) and rms deviation (σ) of the fit. ^[c]Standard errors in units of the last digit.