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ARTICLE

The axial/equatorial conformational landscape and intramolecular dispersion: new insights from the rotational spectra of monoterpenoids

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Intramolecular non-covalent interactions determine the conformational preferences of many molecules, and their understanding is relevant for a proper description of molecular structure. Here, by using rotational spectroscopy in combination with quantum chemistry calculations, we show that intramolecular dispersion forces involving a three-carbon substituent influence the relative energies and conformational landscape of the three monoterpenoids carvone, limonene and perillaldehyde. New equatorial and axial conformers have been identified for all three molecules. Comparison of experimental data with ab initio and density functional calculations shows that axial conformers are stabilised by dispersion interactions between the cyclohexene ring and the isopropenyl group of the monoterpenoids, and that an accurate account of these interactions is challenging for theoretical methods. This work demonstrates the potential of rotational spectroscopy for investigating non-covalent interactions and provides critical benchmarks for theory. Our results will inform future investigations of axial/equatorial isomerism and impact understanding of intramolecular dispersion in larger species.

Introduction

Molecular structure is a consequence of the forces established between atoms, an amalgamation of covalent bonds and non-covalent intramolecular interactions. Covalent interactions define the main molecular framework, which is further refined and tuned by non-covalent interactions. The latter include hydrogen bonds, dipole-dipole interactions and dispersion, and although they are weaker than covalent bonds by one or two orders of magnitude, they are crucial in determining three-dimensional molecular structure. The interplay of intramolecular non-covalent interactions is responsible for the secondary and tertiary structure of proteins[1], and the conformations of alkanes[2], among others.

Dispersion forces, which involve induced dipole-induced dipole interactions, are generally the weakest non-covalent interactions. Therefore they have been regarded as only making a small contribution to the overall energy, and considered relevant for large molecules where there are significant cumulative effects[3]. Examples include long linear alkanes[4,5] and alkylbenzenes[6], where folded conformations are preferred over linear ones once the alkyl chain is long enough; and diamondoid dimers with extremely long C–C bonds that are stabilised by the dispersion interactions among its many –CH$_2$ groups[7–9]. However, it is becoming increasingly clear that the influence that dispersion forces exert over molecular structure is significant even in small molecular systems. For example in strawberry aldehyde, dispersion interactions between the benzene ring and a five-carbon substituent chain were found to stabilise *cis* conformers[10]. An accurate description of dispersion is therefore key to advancing our understanding of molecular behaviour and chemical bonding.

Essential in our understanding of dispersion is the close interplay between experiment and theory. The availability of accurate gas-phase experimental molecular structures and conformations, unadulterated by the environment, is crucial to benchmark various quantum chemical methodologies. For example, data from IR laser spectroscopy and microwave spectroscopy have been used to evaluate theoretical methods[11,12]. This has led to vigorous development, especially of density functional theory (DFT), where several new functionals and corrections improving the description of dispersion interactions have been implemented[3,13–17].

In this paper we demonstrate the crucial role of intramolecular dispersion forces in the stabilisation of the axial conformers of three monoterpenoids, carvone (C$_{10}$H$_{14}$O), limonene (C$_{10}$H$_{16}$) and perillaldehyde (C$_{10}$H$_{14}$O), through interactions involving a short substituent chain of only three carbon atoms. Monoterpenoids are terpene derivatives produced from the combination of two isoprene molecules. They are volatile molecules emitted by plants to the

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atmosphere, where they get oxidised forming the precursors of secondary organic aerosols[18]. They are also the main constituents of essential oils and are widely used as fragrance ingredients in household products, perfumes and cosmetics[19]. Investigation of monoterpenoid conformations is of relevance to understand their reactions in the atmosphere and interactions with other molecules.
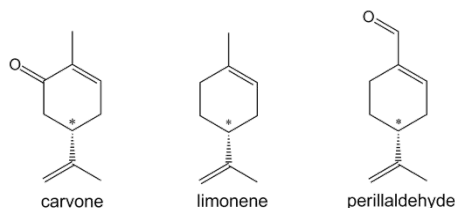

Figure 1. Molecular structures of the three terpenoids studied.

Carvone, limonene and perillaldehyde have closely related structures consisting of a cyclohexene ring with an isopropenyl group, and additional substituents (see Fig. 1). They are flexible molecules, with different conformations that arise from the axial or equatorial configuration of the isopropenyl group; its rotation; and in the case of perillaldehyde, the rotation of the aldehyde group. There are 6 possible conformations for carvone and limonene, and 12 for perillaldehyde (see Fig. 2 for carvone and Figs. S1-S3).
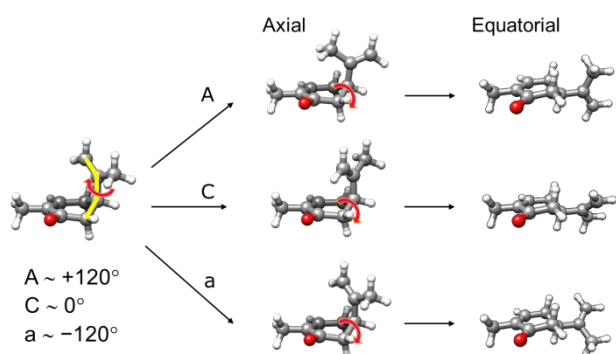

Figure 2. Possible conformations of carvone.

The conformations of carvone, limonene and perillaldehyde have been investigated in the liquid phase by vibrational circular dichroism, infrared and Raman spectroscopies[20–22], and in the gas phase by cavity Fourier transform microwave spectroscopy[23,24], infrared spectroscopy[25], resonance enhanced multiphoton ionisation[26], photoelectron circular dichroism[27–29], and electron diffraction[30]. Definite identification of the conformations present in the gas phase was provided by rotational spectroscopic studies[23,24], which can distinguish minute differences in structure due to the close relationship between rotational frequencies and molecular mass distribution.

Rotational investigations confirmed the presence of two equatorial conformers, Eq-A and Eq-C (see Fig. 2), for each of limonene, carvone and perillaldehyde. As part of our interest in the interactions of these molecules with water and other binding partners, we reinvestigated their rotational spectra. Transitions from the previously observed conformers were easily identified and removed from the spectra. However, many unidentified lines still remained, which led us to speculate whether other conformations were present and prompted the investigation presented here. Additional conformers were identified for all monoterpenoids. We found that axial and equatorial conformers were described to different standards by several theoretical methods. Dispersion interactions were found to significantly contribute to the stabilisation and actual structure of axial conformers, and thus have a crucial effect on the conformational landscape.

Methods

Experimental

The rotational spectra of carvone, limonene and perillaldehyde were recorded using a bespoke 2-8 GHz broadband rotational spectrometer at King's[31,32]. This instrument operates in a cyclic manner. Each cycle starts with a molecular pulse that creates a supersonic jet of the target molecules, heavily diluted in a carrier gas (Ne, He or Ar) at backing pressures of 5 bar, by expanding the mixture into a vacuum chamber through a pulsed nozzle. The molecules are then polarised by four microwave pulses (each 4 μs long) spaced 30 μs and spanning the 2-8 GHz frequency range. Free induction decays are collected for 20 μs after each polarisation pulse, and transformed to the frequency domain using a fast Fourier transform algorithm. Final spectra were obtained by coherently adding 1.1 million FIDs for carvone, 1.0 million FIDs and perillaldehyde, and 1.5 M FIDs for limonene.

The three terpenes have relatively low vapour pressures and so they were placed in a bespoke heated nozzle and were slightly heated to temperatures of 380 K (carvone), 340 K (limonene) and 406 K (perillaldehyde) to increase their concentration in the gas phase.

Computational

We extended previously reported theoretical calculations[20,23–25,33] to optimise the structures of all conformers and calculate their relative energies. DFT (including B3LYP and M062X with and without corrections to dispersion) and ab initio theory (MP2) calculations, all with the 6-311++G(d,p) basis set, were performed using Gaussian[34]. Harmonic frequency calculations to predict relative energies including zero-point corrections and relative free Gibbs energies (at the experimental temperature) were also carried out. Interestingly, the predicted energy difference between axial and equatorial conformers is very dependent on the model theory used, with B3LYP predicting a much larger energy gap than M062X and MP2 (see Tables S1-S3). Inclusion of corrections to dispersion in B3LYP, especially adding the Becke-Johnson damping to Grimme's D3[13], decreases significantly the axial-equatorial energy gap. No significant changes were found when including the D3 correction for the M062X functional (see Sup. Inf.), which is expected considering

that this functional provides a better account of medium-range non-covalent interactions. Another striking result is that the rotational constants predicted for equatorial conformers are very similar at all levels of calculation, while those predicted for axial conformers vary dramatically, in some cases differing by more than 100 MHz. This is illustrated for carvone in Table 1.

Table 1. Experimental and theoretical equilibrium rotational constants of the observed conformers of carvone.

Eq-A					
	Exp.	MP2	M062X	B3LYP	B3LYP-D3	B3LYP-D3BJ
A[a] (MHz)	2237.2055(11)[b]	2226.1	2252.8	2214.5	2239.1	2241.7
B (MHz)	656.27834(29)	658.4	660.3	646.9	653.1	655.1
C (MHz)	579.64159(29)	581.3	582.0	571.0	576.8	578.4

Eq-C					
	Exp.	MP2	M062X	B3LYP	B3LYP-D3	B3LYP-D3BJ
A (MHz)	2256.91513(93)	2246.7	2276.4	2234.9	2258.8	2262.3
B (MHz)	672.90566(26)	673.9	679.1	663.4	668.6	671.4
C (MHz)	554.50351(25)	556.7	553.4	547.0	551.8	553.0

Eq-a					
	Exp.	MP2	M062X	B3LYP	B3LYP-D3	B3LYP-D3BJ
A (MHz)	2212.7903(13)	2195.6	2223.0	2191.5	2215.0	2218.1
B (MHz)	684.52333(27)	680.8	680.8	673.4	679.6	682.5
C (MHz)	554.73193(25)	562.3	562.3	548.2	552.4	553.7

Ax-a					
	Exp.	MP2	M062X	B3LYP	B3LYP-D3	B3LYP-D3BJ
A (MHz)	1621.8211(18)	1581.7	1612.6	1651.7	1649.5	1638.2
B (MHz)	904.92320(51)	941.1	923.6	858.3	879.8	893.2
C (MHz)	780.45872(54)	806.0	792.9	742.4	761.9	771.1

Ax-C					
	Exp.	MP2	M062X	B3LYP	B3LYP-D3	B3LYP-D3BJ
A (MHz)	1687.7984(26)	1618.4	1674.1	1722.3	1719.3	1706.3
B (MHz)	878.27624(98)	921.2	896.2	840.2	855.4	867.9
C (MHz)	771.3069(12)	810.0	783.9	733.3	749.6	761.3

[a] A, B and C are the rotational constants. [b] Standard error in parentheses in units of the last digit.

Results and discussion

Considering predictions, we searched for patterns in the rotational spectra that could correspond to additional conformers, which led to the identification of the Eq-a and Ax-a conformers for all terpenoids, and the Ax-C conformer for carvone. Overall, we observed five conformers for carvone,

four for limonene and four for perillaldehyde. The rotational and centrifugal distortion constants of Tables 1 and S4-S6, were determined from the fit of the measured rotational transitions (Tables S7-S19) to the Watson Hamiltonian in the A reduction and the I[r] representation using Pickett's programs[35].
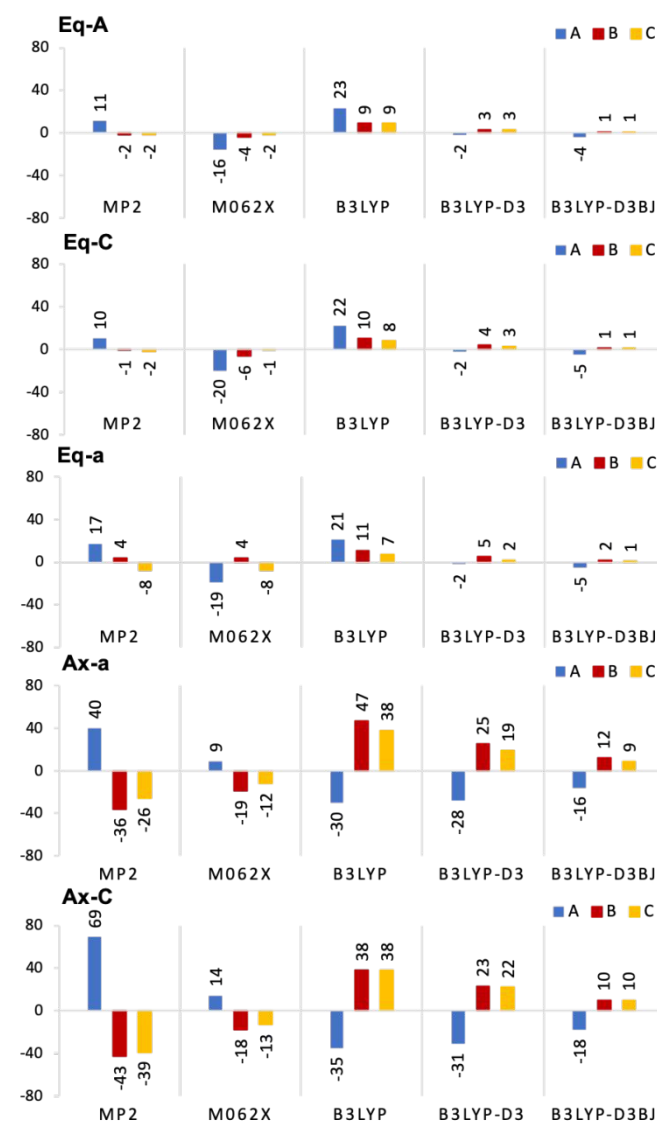
Figure 3. Differences between experimental and theoretical equilibrium rotational constants (in MHz) at different levels of theory for carvone.

For equatorial conformers, all theoretical rotational constants are very close to the experimental ones (differences are typically below 1%) at all the levels of theory used. This is shown for carvone in Fig. 3 and for limonene and perillaldehyde in Figs. S4, S5. The behaviour is different for axial conformers, where theoretical and experimental rotational constants show discrepancies of up to 5%. Percentage discrepancies for axial conformers of 2-3% have been incidentally reported for limonene oxide[36], and very recently for perillyl alcohol[37]. These reports, together with the data presented in this paper, show that it is generally

challenging for theoretical methods to describe axial conformations.

For all conformers the B3LYP-D3BJ method provides a much better description than B3LYP, highlighting the need of including dispersion corrections. These corrections have the effect of making axial conformers become less prolate, by 3.6% for Ax-a and 1.2% for Ax-C.

It should be noted that we are comparing equilibrium rotational constants from theory (A_{eq}, B_{eq}, C_{eq}) with those obtained experimentally for the molecules in their ground vibrational state (A_0, B_0, C_0). This is standard practice in the field for molecules of this size due to the computational cost of running anharmonic calculations to include vibrational corrections to the rotational constants. To check the relevance of vibrational contributions, we performed exemplary calculations on the observed carvone conformers at MP2, B3LYP and B3LYP-D3BJ levels of theory using vibrational secondary perturbation theory (VPT2). The theoretical vibrationally-corrected A_0, B_0, and C_0 constants display the same trends as A_{eq}, B_{eq}, C_{eq}, that is, that the discrepancies with experimental rotational constants are larger for axial conformers than for equatorial ones (see Table S20 and Fig. S6), with values generally above 2% even for MP2 and B3LYP-D3BJ. This shows that the different performance of the theoretical methods for axial and equatorial conformers is not due to vibrational corrections, and points to a poor description of intramolecular interactions in axial conformers. For comparison, recent benchmarking of several molecular data sets quotes expected differences between theoretical and experimental constants of about 1%.[11,38]

Differences in the theoretical description of axial and equatorial conformers are also manifest when comparing theoretical and experimental carbon backbone substitution (r_s) structures. We observed all the ^{13}C isotopologues of the two most stable equatorial conformers of carvone and limonene (Eq-A and Eq-C), and of all the observed conformers of perillaldehyde (see Sup. Inf.). Their rotational constants were used to determine their substitution (r_s) structures by applying Kraitchmann equations[39,40] and their effective (r_0) structures by fitting the experimental moments of inertia[41]. For perillaldehyde, the overlay of the experimentally determined positions of the C atoms with the theoretical ones shows that they are in excellent agreement for the equatorial conformers but there are disagreements at all levels of theory for the axial conformer (see Fig. S7).

Observation of axial and equatorial conformers indicates that the energy differences between them are relatively small. We estimated the conformational abundances of the three monoterpenoids in He, Ne and Ar as carrier gases, because heavier carrier gases can induce conformational relaxation by collisions with the seeded molecules[42]. We measured common a-type transitions and considered that in our experiment line intensity is proportional to the square of the dipole moment component. Considering relative abundances in He, since being the lightest carrier gas it is the least efficient in producing conformational relaxation, our results (see Table 2) show that Eq-A and Eq-C conformers[23,24] are considerably

more abundant than the others. Limonene and carvone axial conformers show smaller relative abundances than Eq-a conformers, while for perillaldehyde the axial conformer shows a slightly larger abundance to Eq-a. The theoretical Gibbs free energies at the corresponding pre-expansion temperatures, which can be related to conformational relative abundances[43–45], are not entirely consistent with experimental results. M062X values do not agree with experimental observations. For B3LYP, inclusion of dispersion corrections is necessary to obtain sizable abundances of the axial conformers. B3LYP-D3BJ/6-311++G(d,p) predicts Gibbs free energies in good agreement with the experimental ones for carvone and limonene but not for perillaldehyde, while MP2 Gibbs free energies are in good qualitative agreement with the experimental values for carvone, but not for limonene and perillaldehyde. Thus at the levels of theory sampled, there is not a method that consistently provides a good description of the target terpenoids. This is a bit surprising considering that their structures are closely related, and may be linked to differences in their functional groups. Similar discrepancies between different methods have been observed in the analysis of the limonene oxide[36] and perillyl alcohol[46].

Table 2. Estimated relative conformational abundances in He, Ne, and Ar for all the observed conformers of carvone, limonene and perillaldehyde.

	Carvone				
	Eq-A	Eq-C	Eq-a	Ax-a	Ax-C
He	1[a]	0.78	0.37	0.21	0.25
Ne	1	0.78	0.37	0.19	0.22
Ar	1	1.08	-	0.24	0.25
	Limonene				
	Eq-A	Eq-C	Eq-a	Ax-a	
He	1	0.54	0.17	0.11	
Ne	1	0.56	0.05	0.15	
Ar	1	0.53	-	0.11	
	Perillaldehyde				
	Eq-A	Eq-C	Eq-a	Ax-a	
He	1	0.73	0.22	0.33	
Ne	1	0.65	0.11	0.27	
Ar	1	0.70	-	0.28	

[a] Uncertainties are estimated to be 20% considering differences in line relative intensity from different measurements and dipole moment uncertainties. Results presented in the table correspond to estimations using MP2 dipole moments as they are expected to be slightly closer to experimental values, but we have also calculated conformational abundances using B3LYP-D3BJ dipole moments, and this informs our quoted uncertainties.

In addition, it has been observed that Eq-a conformers completely relax in Ar and partially relax in Ne, which is consistent with the predicted low interconversion barriers (100-200 cm^{-1}) of Eq-a to Eq-C conformers at MP2 (Figs. S8-S10) and B3LYP levels of theory[21,23,24]. The predicted small energy differences of 60-100 cm^{-1} between Eq-a and Eq-C conformers would explain the partial relaxation observed in Ne. It should be noted that axial → equatorial relaxation is expected to be hampered by very high interconversion barriers, predicted to be *ca.* 30 and 36 kJ/mol by B3LYP-D3BJ and MP2, respectively (see Fig. S11).
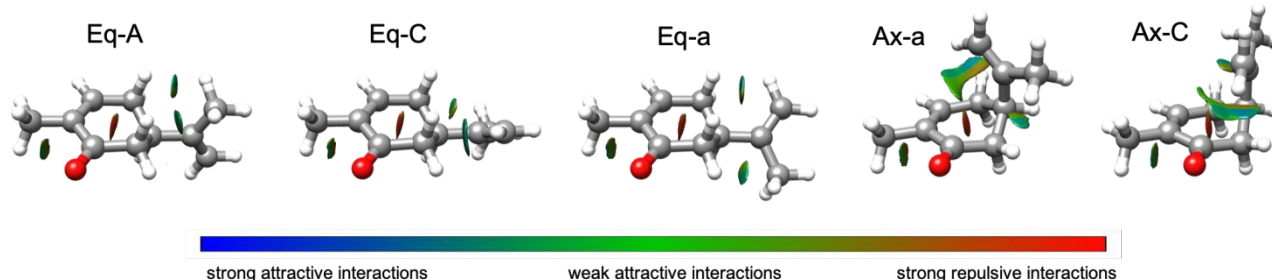
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Figure 4. NCI plots for the observed conformers of carvone showing the intramolecular interactions.

To get a better understanding of the intramolecular interactions stabilising the different conformations, and the effect of the substituents on the cyclohexene ring, we have used the Non-Covalent Interactions (NCI) approach[47,48]. This method, based on the analysis of the electron density and its derivatives, helps visualising non-covalent interactions by plotting the isosurfaces of the regions of space with low reduced density gradients. The NCI plots obtained using Multiwfn[49] are very similar for the same conformers of all terpenoids (see Figs. 4 and S12 for carvone and Figs. S13,S14 for limonene and perillaldehyde). In equatorial conformers, the $-CH_3$ and $-CH_2$ groups of the isopropenyl tail show a weak attraction to the closer $-CH_2$ groups in the cyclohexene ring. For axial conformers, there are larger isosurfaces showing the existence of weak attractive interactions involving the $-CH_2$ group of the isopropenyl substituent and the cyclohexene ring. The shapes of the isosurfaces are similar for all observed axial conformers, and consistent with non-directional dispersion interactions. A weak $C-H\cdots\pi$ hydrogen bond between one of the hydrogens of the isopropenyl $-CH_2$ group and the endocyclic double bond cannot be established because they are at long distances, exceeding 2.6 Å.

Conclusions

The conformational landscape of three structurally-related terpenoids has been systematically characterised from the analysis of their broadband rotational spectra in combination with quantum-mechanical calculations. The lower-lying Ax-a axial conformers have been detected for the first time, as well as the higher-energy Eq-a equatorial conformers. The latter have been found to totally relax in Ar and partially relax in Ne despite being separated by a low-height barrier from one of the other equatorial conformers. Our results illustrate the dependence of conformational relaxation on interconversion barriers and relative energies.

The experimental data has been used to benchmark a range of theoretical methods. MP2 and B3LYP-D3BJ levels of theory with the 6-311++G(d,p) basis set predict rotational constants closer to the experimental ones and hence better describe the conformations. Inclusion of semi-classical corrections in the B3LYP density functional to describe dispersion interactions is crucial to obtain structures and relative conformational abundances consistent with experimental observations for axial conformers. Grimme's dispersion correction including Becke-Johnson damping provides the best results.

Our data show that intramolecular dispersion interactions are relevant even in relatively small molecules and that their influence can significantly change the conformational landscape. The observation of axial conformers shows that dispersion forces partially compensate the energy penalty for having a substituent in an axial rather than equatorial position. These results, together with those reported for limonene oxide[36] and perillyl alcohol[46], and energy predictions for substituted cyclohexanes[50] imply that the stabilisation of axial conformers by dispersion interactions is widespread.

The different ability of the theoretical methods to account for dispersion results in different descriptions for axial and equatorial conformers. Specifically, there are larger discrepancies between theoretical and experimental rotational constants for axial conformers, and the conformational energy ordering changes among different methods. These discrepancies are still present when including anharmonic vibrational corrections, and they are larger than the 1% expected from recent benchmarking of several molecular data sets[11,38], indicating a poor description of intramolecular forces in axial conformers.

As molecular size increases intramolecular dispersion interactions are expected to play a larger role in shaping conformational preferences as more contact points would be possible. Improving the theoretical description of these interactions will be desirable to achieve a more accurate account of larger molecular systems. Rotational spectroscopy, with its ultra-precision in structural determination, should play a key role in providing high quality experimental data to benchmark theoretical models.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

1   M. F. Jarrold, *Phys. Chem. Chem. Phys.*, 2007, 1659–1671.

2   S. Tsuzuki, L. Schäfer, H. Gotō, E. D. Jemmis, H. Hosoya, K. Siam, K. Tanabe and E. Ōsawa, *J. Am. Chem. Soc.*, 1991, **113**, 4665–4671.

3   J. P. Wagner and P. R. Schreiner, *Angew. Chemie - Int. Ed.*, 2015, **54**, 12274–12296.

4   N. O. B. Lüttschwager and M. A. Suhm, *Soft Matter*, 2014, **10**, 4885–4901.

5   N. O. B. Lüttschwager, T. N. Wassermann, R. A. Mata and M. A. Suhm, *Angew. Chemie - Int. Ed.*, 2013, **52**, 463–466.

6   D. M. Hewett, S. Bocklitz, D. P. Tabor, E. L. Sibert, M. A. Suhm and T. S. Zwier, *Chem. Sci.*, 2017, **8**, 5305–5318.

7   P. R. Schreiner, L. V. Chernish, P. A. Gunchenko, E. Y. Tikhonchuk, H. Hausmann, M. Serafin, S. Schlecht, J. E. P. Dahl, R. M. K. Carlson and A. A. Fokin, *Nature*, 2011, **477**, 308–311.

8   A. A. Fokin, L. V. Chernish, P. A. Gunchenko, E. Y. Tikhonchuk, H. Hausmann, M. Serafin, J. E. P. Dahl, R. M. K. Carlson and P. R. Schreiner, *J. Am. Chem. Soc.*, 2012, **134**, 13641–13650.

9   A. A. Fokin, T. S. Zhuk, S. Blomeyer, C. Pérez, L. V. Chernish, A. E. Pashenko, J. Antony, Y. V. Vishnevskiy, R. J. F. Berger, S. Grimme, C. Logemann, M. Schnell, N. W. Mitzel and P. R. Schreiner, *J. Am. Chem. Soc.*, 2017, **139**, 16696–16707.

10 S. T. Shipman, J. L. Neill, R. D. Suenram, M. T. Muckle and B. H. Pate, *J. Phys. Chem. Lett.*, 2011, **2**, 443–448.

11 S. Grimme and M. Steinmetz, *Phys. Chem. Chem. Phys.*, 2013, **15**, 16031–16042.

12 E. Gloaguen, B. De Courcy, J. P. Piquemal, J. Pilmé, O. Parisel, R. Pollet, H. S. Biswal, F. Piuzzi, B. Tardivel, M. Broquier and M. Mons, *J. Am. Chem. Soc.*, 2010, **132**, 11860–11863.

13 S. Grimme, S. Ehrlich and L. Goerigk, *J. Comput. Chem.*, 2011, **32**, 1456–1465.

14 C. Corminboeuf, *Acc. Chem. Res.*, 2014, **47**, 3217–3224.

15 S. Grimme, A. Hansen, J. G. Brandenburg and C. Bannwarth, *Chem. Rev.*, 2016, **116**, 5105–5154.

16 J. Hermann, R. A. DiStasio and A. Tkatchenko, *Chem. Rev.*, 2017, **117**, 4714–4758.

17 Y. Zhao and D. G. Truhlar, *Acc. Chem. Res.*, 2008, **41**, 157–167.

18 J. H. Kroll and J. H. Seinfeld, *Atmos. Environ.*, 2008, **42**, 3593–3624.

19 D. Pybus and C. Sell, Eds., *The Chemistry of Fragrances*, Royal Society of Chemistry, Cambridge, 2nd edn., 2006.

20 F. Partal Ureña, J. R. A. Moreno and J. J. López González, *Tetrahedron: Asymmetry*, 2009, **20**, 89–97.

21 F. Partal Ureña, J. R. Avilés Moreno and J. J. López González, *J. Phys. Chem. A*, 2008, **112**, 7887–7893.

22 G. G. Hoffmann, *J. Mol. Struct.*, 2003, **661**–**662**, 525–539.

23 J. R. A. Moreno, T. R. Huet and J. J. L. González, *Struct. Chem.*, 2013, **24**, 1163–1170.

24 J. R. Avilés Moreno, F. Partal Ureña, J. J. López González and T. R. Huet, *Chem. Phys. Lett.*, 2009, **473**, 17–20.

25 T. R. Huet, J.-R. Aviles Moreno, O. Pirali, M. Tudorie, F. Partal Ureña and J.-J. Lopez Gonzalez, *J. Quant. Spectrosc. Radiat. Transf.*, 2012, **113**, 1261–1265.

26 M. Mineyama and T. Egawa, *J. Mol. Struct.*, 2005, **734**, 61–65.

27 G. A. Garcia, L. Nahon and I. Powis, *Int. J. Mass Spectrom.*, 2003, **225**, 261–270.

28 C. J. Harding, E. Mikajlo, I. Powis, S. Barth, S. Joshi, V. Ulrich and U. Hergenhahn, *J. Chem. Phys.*, 2005, **123**, 234310.

29 C. J. Harding and I. Powis, *J. Chem. Phys.*, 2006, **125**, 234306.

30 T. Egawa, Y. Kachi, T. Takeshima, H. Takeuchi and S. Konaka, *J. Mol. Struct.*, 2003, **658**, 241–251.

31 D. Loru, M. A. Bermúdez and M. E. Sanz, *J. Chem. Phys.*, 2016, **145**, 074311–8.

32 D. Loru, I. Peña and M. E. Sanz, *J. Mol. Spectrosc.*, 2017, **335**, 93–101.

33 J. R. Avilés Moreno, F. Partal Ureña and J. J. López González, *Vib. Spectrosc.*, 2009, **51**, 318–325.

34 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09 Revis. E.01*, 2010.

35 H. M. Pickett, *J. Mol. Spectrosc.*, 1991, **148**, 371–377.

36 D. Loru, M. M. Quesada-Moreno, J. R. Avilés-Moreno, N. Jarman, T. R. Huet, J. J. López-González and M. E. Sanz, *ChemPhysChem*, 2017, **18**, 268.

37 N. Borho and Y. Xu, *Phys. Chem. Chem. Phys.*, 2007, **9**, 1324–1328.

38 S. Oswald and M. A. Suhm, *Phys. Chem. Chem. Phys.*, 2019, **21**, 18799–18810.

39 J. Kraitchman, *Am. J. Phys.*, 1953, **21**, 17–24.

40 C. C. Costain, *J. Chem. Phys.*, 1958, **29**, 864–874.

41 Z. Kisiel, *Spectrosc. from Sp.*, 2001, 91–106.

42 R. S. Ruoff, T. D. Klots, T. Emilsson and H. S. Gutowsky, *J. Chem. Phys.*, 1990, **93**, 3142–3150.

43 P. D. Godfrey and R. D. Brown, *J. Am. Chem. Soc.*, 1998,

Journal Name

ARTICLE

    120, 10724–10732.

44   S. Blanco, J. C. López, S. Mata and J. L. Alonso, *Angew. Chemie - Int. Ed.*, 2010, **122**, 9373–9378.

45   M. E. Sanz, A. Lesarri, M. I. Peña, V. Vaquero, V. Cortijo, J. C. López and J. L. Alonso, *J. Am. Chem. Soc.*, 2006, **128**, 3812–3817.

46   F. Xie, N. A. Seifert, M. Heger, J. Thomas, W. Jäger and Y. Xu, *Phys. Chem. Chem. Phys.*, 2019, **21**, 15408–15416.

47   E. R. Johnson, S. Keinan, P. Mori-Sánchez, J. Contreras-García, A. J. Cohen and W. Yang, *J. Am. Chem. Soc.*, 2010, **132**, 6498–6506.

48   R. Chaudret, B. De Courcy, J. Contreras-García, E. Gloaguen, A. Zehnacker-Rentien, M. Mons and J. P. Piquemal, *Phys. Chem. Chem. Phys.*, 2014, **16**, 9876–9891.

49   T. Lu and F. Chen, *J. Comput. Chem.*, 2012, **33**, 580–592.

50   R. Bjornsson and I. Arnason, *Phys. Chem. Chem. Phys.*, 2009, **11**, 8689–8697.
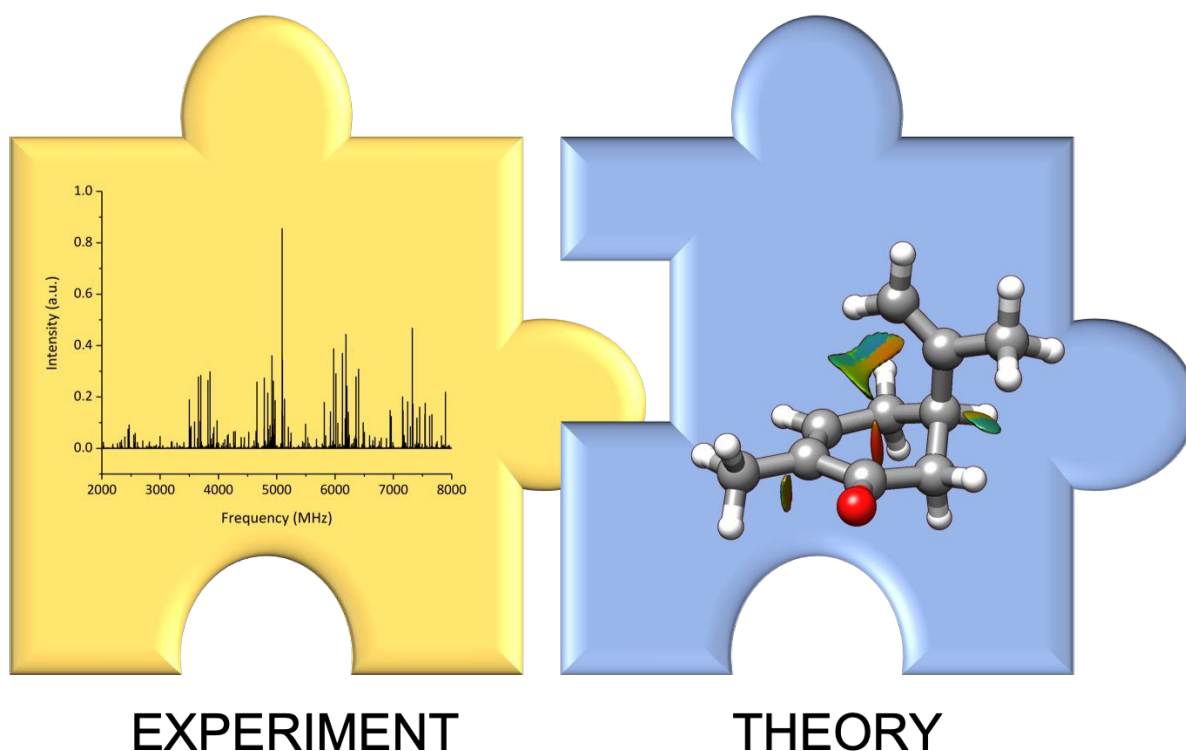
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Using rotational spectroscopy in combination with quantum chemistry calculations, we show that intramolecular dispersion forces stabilise the axial conformers of monoterpenoids, and that an accurate account of these interactions is challenging for theoretical methods.

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