MINI-REVIEW

The Hydrogen Bond and Beyond: Perspectives for Rotational Investigations of Non-Covalent Interactions†

Marcos Juanes,[a] Rizalina T. Saragi,[a] Walther Caminati,[b] Alberto Lesarri[a]*

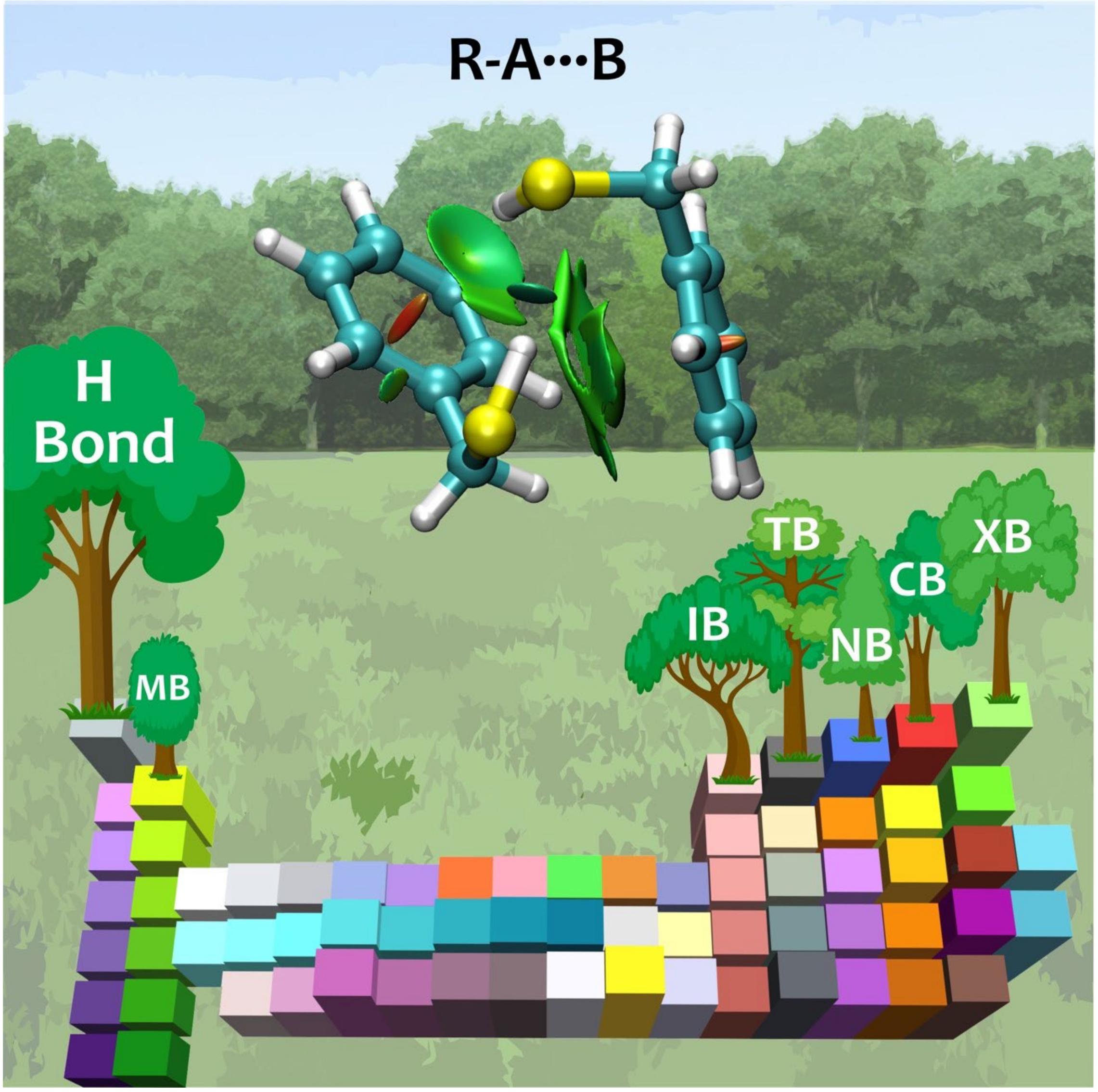
---

†This article is dedicated to Prof. Dr. Pablo Espinet on the occasion of his 70th birthday, for his contributions to Chemistry.

[a]Mrs. R. T. Saragi, Mr. M. Juanes, Prof. Dr. A. Lesarri, Departamento de Química Física y Química Inorgánica - IU CINQUIMA, Facultad de Ciencias, Universidad de Valladolid, 47011 Valladolid (Spain). E-mail: lesarri@qf.uva.es, Web: www.uva.es/lesarri
[b]Prof. Dr. W. Caminati, Dipartimento di Chimica "G. Ciamician", Università di Bologna, Via Selmi, 2, 40126 Bologna (Italy).

Frontispiece graphic:

(Production: see file attached corresponding to figure below)



Frontispiece text:

The forest of non-covalent interactions, dominated by the centenary hydrogen bond (HB), has more trees than expected. In the Minireview on page xx, Lesarri and co-workers outline the role played by supersonic-jet rotational spectroscopy to discern self-aggregation, molecular recognition and recently evidenced interactions like the halogen (XB), calchogen (CB), pnicogen (NB) or tetrel (TB) bonds. The empirical data obtained in the gas-phase are highly complementary to theoretical predictions and condensed phase observations, contributing to our understanding of intermolecular interactions.

Biographical sketches:

Marcos Juanes got a B.S.+M.S. Degree in Physics in 2014 at the University of Valladolid, which included a Erasmus stay in Physics and Astronomy at the University of Catania (Italy). Following a programming experience in the private sector, he is now pre-doctoral researcher at the Universidad de Valladolid. His research interests are focused in experimental methods in rotational spectroscopy and computational calculations.

Rizalina Tama Saragi got a Bachelor in Chemistry in 2014 at the Universitas Gadjah Mada (Yogyakarta, Indonesia) and a Master in Theoretical Chemistry and Computational Modelling in 2016 at the Universidad Autónoma de Madrid in Spain. She is presently a pre-doctoral researcher at the Universidad de Valladolid. Her research interests combine rotational spectroscopy and computational chemistry.

Walther Caminati got the "Laurea" in Chemistry at the Università di Bologna in 1970 (110/110 and laude), where he became Assistant, Associate and finally Full Professor of Physical Chemistry in 1990, compulsory retiring at the end of 2016. He spent 15 months at Harvard University with Prof. E. Bright Wilson (1978-1979), 10 months at ETH in Zurich with Prof. A. Bauder (1987) and, as "Invited Professor", 14 months (2004-2006) at the University of Valladolid with Prof. J. L. Alonso. He is interested in the study of large amplitude motions and non-covalent interactions in molecules and in small molecular clusters, by using experimental and theoretical methods, mainly rotational spectroscopy. He has been member of the Editorial Boards of Journal of Molecular Spectroscopy and Journal of Molecular Structure.

Alberto Lesarri was educated at the University of Valladolid, where he got a Ph.D. degree in Chemistry in 1991 under the supervision of Profs. José L. Alonso and Juan C. López. He worked as Chercheur Associé of the French CNRS at the Laboratoire de Spectroscopie Hertzienne (now PhLAM) in Lille with Prof. Jean Demaison in 1993 and he has been a visiting scientist at a number of international labs, most recently at the Leibniz Universität Hannover with Prof. Jens-Uwe Grabow. He holds a chair of Physical Chemistry in Valladolid since 2012. His research interests include experimental techniques in microwave and laser spectroscopy, with particular focus in biochemical molecules and noncovalent interactions.

Abstract: In the last decade experiment and theory have expanded our vision of non-covalent interactions, shifting the focus from the conventional hydrogen bond to new bridging interactions involving a variety of weak donor/acceptor partners. While most experimental data originates from condensed phases, the introduction of broadband (chirped-pulse) microwave fast-passage techniques has revolutionized the field of rotational spectroscopy, offering unexplored avenues for high-resolution studies in the gas phase. We present an outlook of hot topics for rotational investigations on isolated intermolecular clusters generated in supersonic jet expansions. Rotational spectra offer very detailed structural data, easily discriminating the isomeric or isotopic composition and effectively cancelling any solvent, crystal or matrix bias. The direct comparison with quantum mechanical predictions provides insight into the origin of the inter- and intra-molecular interactions with much greater precision than any other spectroscopic technique, simultaneously serving as test-bed for fine-tuning of theoretical methods. We present recent examples of rotational investigations around three topics: oligomer formation, chiral recognition and identification of halogen, calchogen, pnicogen or tetrel bonds. The selected examples illustrate the benefits of rotational spectroscopy for the structural and energetic assessment of inter-/intra-molecular interactions, which may help to move from fundamental research to applications in supramolecular chemistry and crystal engineering.

Introduction

Non-covalent interactions (NCI) sustain molecular aggregation in biological, chemical and technological processes with a strikingly diverse array of interaction energies and geometries.[1,2,3] Diversity arises not only by the multiple combinatorial possibilities of different atomic groups, but also because of the fuzzy character of NCI, which, quite contrary to covalent bonds, admit broad and diffuse structural and energetic limits. The monograph by Gilli and Gilli[1] exemplifies that just the conventional O-H···O hydrogen bond can adopt a near continuous of bonding energies (4-120 kJ mol^{-1}) and O···O contacts (2.38 to 3.00 Å).

Moreover, in the last decade our vision of non-covalent forces has expanded considerably, moving from the conventional hydrogen bond[1] (HB) to a whole new palette of previously unanticipated donor-acceptor interactions.[2,3] First, the now centenary HB was redefined by IUPAC in 2011[4] to accommodate weak interactions like aliphatic donors[5] (C-H···O, C-H···N, etc), π acceptors[6] (C-H···π, N-H···π, etc), low-electronegativity donors[7] (S-H, P-H, etc) or H acceptors,[8] among others. Then, further developments in crystal engineering[3] catalyzed the IUPAC move to define the halogen bond[9] (XB) in 2013. In the XB the anisotropic electron distribution within halogen atoms makes terminal σ-hole[10] or lateral π-hole[11] regions new electrophilic attractors, turning common electron donors into acceptors.[12] The electrostatic argument was later generalized[13] to explain experimental observations into the new conceptual frames of calchogen bonds (CB),[14] pnicogen bonds[15,16] (NB), tetrel bonds[17,18] (TB), involving atoms of groups 14, 15, 16[19] or even coinage-metals[20] in R-A···B bridging interactions formally analogue to the HB or XB (R-H/X···B). Legon has noticed ironically that rotational[21,22,23] and vibrational[24,25] experiments existed for the new bonds long before they had a name, occasionally being called "*anti-hydrogen bond*".[26] This extension of the chemical discourse makes NCI more diverse and attractive than ever.

The experimental investigations of NCI are multitude. However, most of the empirical findings refer to condensed phases, usually from neutron/X-ray diffraction or spectroscopy (IR and NMR).[1,2,3] In consequence, the structural description of NCI, in particular the HB, is generally biased by matrix,[27] crystal[28] or packing effects.[29] Conversely, single-molecule structural techniques provide complementary information on the intrinsic intra- and intermolecular effects associated with weak long-range interactions, directly comparable to ab initio calculations. The most detailed single-molecule information originates from gas-phase high-resolution spectroscopy, in particular using jet-cooled expansions for the preparation of molecular adducts.[30]

Vibrational spectra are used as a defining element of the HB and XB,[4,9] yet the structural information obtained through the vibrational modes is indirect and often resolution-limited (10^{-1}-10^{-3} cm^{-1}), even when combined with mass- and conformer-specific IR/UV double-resonance laser techniques.[31] On the other hand rotational spectroscopy offers extreme frequency resolution (10^{-6}-10^{-7} cm^{-1}) and a direct structural route through the moments of inertia, at the cost of a much more complicated analysis. Traditionally used for small molecules,[32,33] the introduction of microwave broadband techniques by Pate[34,35,36] in 2007 has expanded exponentially the scope of rotational spectroscopy. Previous rotational investigations of NCI are collected in specific databases, like MOGADOC[37] or Novick's bibliography.[38] Presently, rotational spectroscopy sums about 1100 studies on weakly-bound complexes and an undetermined number on intramolecular HBs (Figure 1). This contribution, despite much smaller than crystallographic data, is usually overlooked.

In this minireview we will update on the current status of rotational investigations on NCI, covering three (personal) hot topics including oligomer formation, chiral recognition and identification of halogen, calchogen, pnicogen or tetrel bonds. We do not intend to present an in-depth appraisal, but to show how the introduction of broadband rotational spectroscopy has impacted the gas-phase investigations on NCI, offering unexpected possibilities. Because of space limitations and the much larger literature available elsewhere, computational investigations on NCI[1-3] are not discussed here.

Experimental methods: Broadband rotational spectroscopy

This report will focus on chirped-pulse Fourier transform microwave (CP-FTMW) techniques for supersonic jet molecular rotation spectroscopy.[34-36] CP-FTMW offers broadband acquisition (ca. 10 GHz) in a single experimental event, offering a true multiplexing advantage in the microwave region. Previous microwave studies mostly used the Balle-Flygare FTMW spectrometer[39] or molecular beam electric resonance[40] (MBER) spectroscopy. Chirped-pulse techniques are based in fast-passage microwave excitation, using a frequency modulated pulse covering the full GHz-size working band (typically 2-8 GHz or 8-18 GHz, Figure 2). The chirped pulse produces a transient excitation, resulting in a coherent polarization of all molecules in the jet with a permanent electric dipole moment. Since the excitation period should be shorter than the time scale for rotational decoherence the chirped pulse must be very short (μs), meaning that only fully-digital waveform generators are capable of band sweeping at ca. 10 GHz/μs. Unlike transform-limited pulses used in single-tone polarization, a chirped pulse decouples excitation bandwidth from pulse duration, reducing the power requirements for broadband excitation. In any case, the amplification needs are considerably larger (20W-1 kW) than in the resonator-assisted Balle-Flygare spectrometers. The transient spontaneous emission following excitation is collected by a digital oscilloscope (>25 GS/s), acquiring the full-band time-domain spectrum in each experimental cycle. A Fourier transformation finally produces the frequency domain spectrum. The perpendicular orientation of the molecular jet to the probing radiation reduces the time the molecules spend bathed in the radiation (compared to the coaxial expansion of the Balle-Flygare spectrometer) and determines the duration of the free-induction decay (typically 40 μs). The resulting spectral linewidths (FWHM) reach ca. 100 kHz. The operation efficiency can be improved using several excitation pulses per gas injection or multiple sample injectors or combined with other spectroscopic techniques.[41] The preparation of the supersonic jet is standard, seeding a diluted sample in a monoatomic carrier gas, which is expanded near-adiabatically through a pulsed solenoid valve. Molecular jets are cluster sources with very low internal energies (rotational temperatures ca. 2-5 K). Further technical details are found in the literature.[34,35,39] CP-FTMW spectrometers are now commercially available (BrightSpec).

Self-aggregation and oligomer formation

Adiabatic expansions allow the generation and isolation of weakly-bound clusters *à la carte*, with specific selection of chemical groups, molecular sizes and intermolecular interactions. Following the combination of rotational spectroscopy and supersonic jets a large number of intermolecular clusters were analyzed,[32,33] producing a wealth of information on van der Waals adducts,[42] HBs,[43] XBs,[44] and charge-transfer complexes,[45] generally neutrals, but also some radical and ion complexes.[46] However, most of the observed clusters were formed by a small number of constituent units, mostly dimers. In consequence, the observation of oligomers has been hampered except for the smallest molecules. The availability of broadband techniques has boosted both the cluster sizes and the complexity of the interacting molecules. As a result, structural and dynamical information on self-aggregation beyond dimers is becoming progressively available, providing experimental probes on aggregation patterns and intermolecular potential energy surfaces.

The clusters of triatomics and tetrahedral halocarbons are representative examples of small-molecule aggregation. For difluoromethane Caminati and Cocinero have resolved the rotational spectra from the trimer[47] and tetramer[48] up to the heptamer.[49] The presence of two hydrogen atoms activated by the electronegative halogens allows multiple weak C-H···F HBs between the aliphatic bonds and the two organic fluorine F-C groups on aggregation. The tetramer of Figure 3 shows a distorted rhomboid in which the monomers are individually oriented to produce bifurcated contacts between the C-H and F-C bonds, which forms the basis for the construction of the pyramidal pentamer and larger structures. The hexamer and heptamer are based in rhomboid and octahedral geometries. The increment in molecular size is accompanied by the formation of an extensive network of weak HBs, with the number of intermolecular contacts ($r_{C\text{-}H\cdots F}$<1.9

Å) passing from 14 in the tetramer to 30 in the heptamer and an increase in binding energies from dimer to heptamer of -17 to -151 kJ mol^{-1}.

The strong self-aggregation of water has been rotationally observed by Pate and is notorious because of its complicated isomerism, dynamical and cooperative effects and large molecular sizes, extending from the hexamer,[50,51] heptamer,[35] nonamer[52] and decamer[52] up to the pentadecamer $(H_2O)_{15}$.[53] These water clusters represent the transition from quasi-planar three-, four- and five-membered ring skeletons to tridimensional structures often based in stacking of the smaller rings or addition to prismatic heavy-atom structures, sometimes offering 3,[50] 5[52] or even 7[53] isomerization possibilities. More important, the non-rigidity within the O-H···O HB network is exposed by the presence of tunnelling splittings in the spectrum,[51] a feature resulting from low interconversion barriers between equivalent permutational isomers and which is only detectable through high-resolution rotational[50,51] or rovibrational[54] spectroscopy. As an example, the hyperfine doublings in the hexamer prism confirmed an unreported internal motion with geared and antigeared simultaneous rotations of pairs of water molecules, involving a concerted breaking of two hydrogen bonds in the adduct (Figure 4). Cooperative effects attributable to three-body effects were observed in the nonamer and decamer, with nearest-neighbor O···O distances varying from 2.65 to 2.90 Å (Figure 5).

For the planar formic acid the strong HBs involving the carboxylic group favored the observation of the oligomers up to the pentamer,[55] formed by two stacked sheets made of a near-planar trimer and dimer. The dimer should not be observable because of a lack of permanent dipole moment. However, the H→D asymmetric substitution generates a tiny dipole moment, which allowed the observation of the tunneling due to the concerted double proton transfer.[56] Trimers and tetramers have been observed by Xu on mono[57] and trifluorinated[58] ethanol, stabilized by a combination of hydroxyl O-

H···O hydrogen bonds and weak C-H···F interactions. For larger molecules, the trimers of phenol[59] and aniline[60] have been observed by the authors. Unlike the single isomer of $(\text{phenol})_3$, the weaker N-H···N HB in $(\text{aniline})_3$ is easily balanced with N-H···π and C-H···π HBs, increasing the possibilities for molecular aggregation and giving rise to three different isomers (Figure 6).

Molecular recognition and chiral detection

These experiments explore at molecular level the structural, dynamical and energetic features observed in the association of chiral molecules through NCI, with the ultimate goal of understanding the molecular basis for enantioselectivity and chiral amplification. Molecular recognition in the gas-phase has previously used spectroscopy, circular dichroism, mass and photoelectron spectrometry and chromatography.[61] The first experiments in supersonic jets used IR-UV or IR spectroscopy to obtain vibrational signatures[62] of the chiral bonding. These studies mostly used mono- or bifunctional alcohols to exploit the relatively strong O-H···O hydrogen bonds formed by the hydroxyl group. The basic strategy, common to other chiral separation techniques, is the formation of diastereomeric intermolecular complexes between the two enantiomers of a target compound and a chiral selector. A number of dimers have been studied by Howard, Caminati and Xu with rotational resolution, including either two monomeric species with permanent chirality, or molecules with transient chirality like those associated to the internal rotation of the hydroxyl group. The dimers of ethanol,[63] 2-fluoroethanol,[64] 2-butanol,[65] glycidol[66] and propylenoxide[67] were among the first tested, observing a facile formation of both homo- and heterochiral dimers (i.e., six isomers for the propylene oxide dimer), but minimal stereoselectivity. The fact that dimerization of propylene oxide is controlled by weak C-H···O interactions was exposed as an argument on the important role of weak HBs in chiral recognition, also noticed in vibrational studies.[68] Transient chirality associated to OH stereomutation in alcohols is quenched on formation of hydrogen bonded diastereomeric interactions with other chiral species (either permanent or transient), forming permanently chiral species. Examples include the dimers of ethanol,[69] 2-fluoroethanol,[70] 2,2,2-trifluoroethanol[71] and glycidol[72] with propylenoxide or dimethyloxirane. These works can provide experimental isomer abundances which, on assumption of a conformational distribution close to equilibrium, can be compared with the predicted chiral energies. The predicted relative energies between homo- and heterochiral complexes (chirodiastaltic energy) are small (i.e., -0.16 to 1.28 kJ mol^{-1} in 2-fluoroethanol···propylene oxide[70]), pointing to a "limited selectivity".[70] Moreover, stereospecific relative energies are model dependent and not always reproducible with theory, underlining that "it is quite challenging to capture such subtle energy difference accurately with current ab initio methods".[72] Actually, inclusion of zero-point energies or BSSE corrections may change the stability order, as sub-kJ/mol accuracy may be required.[69, 73] In one of the few cases claiming extreme chirality synchronization, a strong preference for the homochiral diastereoisomer in the 2,2,2-trifluoroethanol dimer, the rotational reanalysis found the missing dimer, with abundances homo:hetero=1:0.1 (equivalent to an energy difference of 1.1 kJ mol^{-1} at a conformational temperature of 60 K).[73] In other example of transient axial chirality in the anesthetic sevoflurane,[74] two homo- and heterochiral isomers were detected for the dimer, stabilized by a combination of a primary C-H···O and C-H···F HBs (Figure 7). The observed population ratio homo:hetero=1.3:1 suggested practically no stereoselectivity, as expected for the similar topologies of the intermolecular interactions in both species.

The formation of weakly-bound intermolecular clusters between a chiral species and an enantiopure chiral resolving agent (tag molecule) has been recently proposed as an appropriate method to determine both the absolute configuration and enantiomeric excess by rotational spectroscopy.[75,76]

Calchogen, pnicogen and tetrel bonds

As mentioned in the introduction, the last ten years have seen a flurry of theoretical results unveiling new forms of donor-acceptor NCI.[2,3] In particular, it has been noticed that electronegative elements in Groups 14, 15 and 16 can establish attractive directional interactions (R-A···B) involving calchogen, pnicogen or tetrel atoms. Consensus exists towards a consistent terminology using the electrophilic atom to name these interactions, to distinguish from the cases where they participate as nucleophilic electron donors.[19,77] XB/CB/NB/TBs are explained as result of interactions with σ- and π-hole regions, and, similarly to the HB, they include a combination of attractive electrostatic, polarization, charge transfer, and dispersion forces, though their specific relative influence is still debatable.[2] Rotational spectroscopy can contribute to recognize, identify and characterize these interactions, simultaneously offering comparison with more common HBs and between gas and condensed phases, where most of previous information was obtained.[78] Among the initial rotational studies on HBs[43] some neutral heterodimers were early recognized as unfitting to HB patterns, as in the S···N, [21] N···C[23] and C···Br[24] interactions reviewed by Legon.[26] Specific searches for XB/CB/NB/TBs are now appearing at slow pace. These investigations are mostly directed to: 1) interrogate and differentiate the structures corresponding to the XB/CB/NB/TBs, 2) evaluate the interaction energy in the context of other NCI and 3) contribute to establish the origin of the NCI forces. XBs are the most studied interactions in the gas phase, as initiated by Legon on dihalogens[44] and continued by a series of chlorofluorocarbon heterodimers analyzed by Caminati involving Cl···F,[79] Cl···O,[80,81] Cl···N[82] or Cl···C[83] interactions. These dimers allowed discerning strong dynamical effects due to internal rotation within the dimers, together with structural information (r_0(Cl···F)= 2.995[79] Å, r_0(Cl···O)=3.048 Å[81], r_0(Cl···N)= 3.081-3.090 Å[82]) and binding data (MP2 dissociation energies from -1.8 kJ mol^{-1} in $CF_3Cl\cdots FCH_3$[79] to -10.2 kJ mol^{-1} in $CF_3Cl\cdots$pyridine.[84] Additionally, $CF_3I\cdots B$ dimers were observed systematically stronger than the corresponding chlorine species, evidencing that heavier halogens exhibit stronger XBs.[83]

The CBs detected rotationally involve sulfur dioxide or carbon disulfide as electrophile and a small number of n- or π-electron donors, including among others N_2,[85] CO,[86] $(CH_3)_2O$,[87] $N(CH_3)_3$[88] and NH_3.[89] As an example, Grabow and Barone recently examined calchogen-calchogen interactions between sulfur dioxide and dimethylsulfide (DMS).[90] The analysis of $DMS\cdots SO_2$ confirmed the stacked geometry in Figure 8, with one of the lone-pairs of the Lewis base oriented to the σ-hole in SO_2 and the methyl groups confronting the oxygen atoms, indicative of secondary $C\text{-}H\cdots O$ interactions. The $S\cdots S$ distance was determined as 2.947(3) from semiexperimental calculations, with a CBS extrapolated interaction energy of 23.5 kJ mol^{-1}. Noticeably, the (^{33}S) nuclear quadrupole coupling constants and the potential barrier for the internal rotation of the methyl group in DMS are consistent with a partial charge transfer in the dimer from DMS to SO_2, as confirmed with NBO and NOCV/CD methodologies. The origin of the NCI forces was examined with a SAPT energy decomposition,[2,74, 91] indicating the electrostatic term is by far the largest contributor (Table 1).

A few pnicogen bonds involving nitrous oxide have been examined rotationally.[26] Recently Spada, Tasinato and Puzzarini reported the dimer of nitroethane-trimethyl amine in Figure 9, bound by a directional $N\cdots N$ interaction (calculated at $r_{N\cdots N}$=3.044 Å) and weaker $C\text{-}H\cdots O$ and $C\text{-}H\cdots N$ HBs.[92] In this case electrostatic and dispersion terms were found comparable, with an interaction energy of -24 kJ mol^{-1}. A limited charge transfer between the two nitrogen atoms was predicted with the NOCV/CD method.

Conclusions

The introduction of CP-FTMW methods represents an unprecedented technical jump, advancing the capabilities of rotational spectroscopy to handle complex spectral problems, as illustrated with the study of NCI interactions involved in molecular aggregation, chiral recognition or new donor-acceptor interactions. Simultaneously, the results illustrate the challenges and limitations for future studies.

Rotational investigations can provide empirical data on NCI highly complementary to other spectroscopies and theoretical predictions, in particular conformational composition and accurate molecular structures. Other advances not treated here, in particular chirality detection,[75,76,93] will also impact the field in the near future. However, present day analyses are still limited to relatively small and simplified models. Appreciation of molecular recognition models, the role of molecular flexibility and the balance of NCI, including cooperative and competitive effects, will require the systematic examination of larger, more realistic molecular systems. The progress toward detailed structural characterization of large clusters will come from a combination of advances in microwave instrumentation and double-resonance techniques,[34,35,39, 94] automated computer analysis[95] and molecular modelization.[1-3] In particular, the synergy of broadband rotational spectroscopy and supporting quantum mechanical predictions will be crucial for future analyses. Ultimately, questions associated to the physical nature, energetics and influence of NCI will find an answer in the convergence of empirical and predictive data, contributing to developments in applications in supramolecular Chemistry and crystal Engineering and outlining the role of molecular rotation spectroscopy as spectral tool and computational benchmark.

Acknowledgements

Financial support from the MINECO-FEDER (CTQ2015-68148-C2-2-P) is gratefully acknowledged. We thank Prof. Dr. Ibon Alkorta (IQM-CSIC, Madrid) for critically reading the manuscript.

Conflict of interest

The authors declare no conflict of interest.

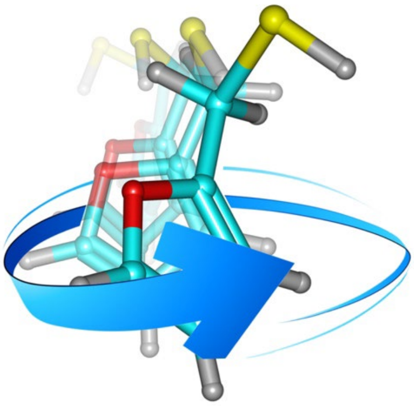
Keywords:

Non-covalent interactions, Rotational Spectroscopy, Molecular Aggregation, Chiral Recognition, Calchogen Bonds, Pnicogen Bonds

Entry for the Table of Contents:

MINIREVIEW

Rotating molecules: We review the role of rotational spectroscopy to investigate non-covalent interactions, using mass- and interaction-specific molecular aggregates generated and isolated in a supersonic jet expansion. We provide examples of recent investigations using halogens, calchogens and pnictogens as electrophile partners in R-A···B interactions.



Rotational Spectroscopy

*M. Juanes, R. T. Saragi, W. Caminati, A. Lesarri**

Page No. – Page No.

The Hydrogen Bond and Beyond: Perspectives for Rotational Investigations of Non-Covalent Interactions

REFERENCES

[1] G. Gilli, P. Gilli, *The Nature of the Hydrogen Bond*, IUC-Oxford Univ. Press, Oxford, **2009**.
[2] S. Scheiner (Ed.), *Noncovalent Forces*, Springer Int. Pub., Heildeberg, **2015**.
[3] J. J. Novoa (Ed.), *Intermolecular Interactions in Crystals: Fundamentals of Crystal Engineering*, Royal Soc. Chem., London, **2018**.
[4] E. Arunan, G. R. Desiraju, R. A. Klein, J. Sadlej, S. Scheiner, I. Alkorta, D. C. Clary, R. H. Crabtree, J. J. Dannenberg, P. Hobza, H. G. Kjaergaard, A. C. Legon, B. Mennucci, D. J. Nesbitt, *Pure Appl. Chem.* **2011**, *83*, 1619-1636, and *Pure Appl. Chem.* **2011**, *83*, 1637-1641.
[5] G. R. Desiraju, *Acc. Chem. Res.* **1996**, *29*, 441-449.
[6] M. Nishio, M., Hirota, Y. Umezawa, *The CH$\cdots\pi$ interaction*, Wiley-VCH, New York, **1998**.
[7] O. Takahashi, Y. Kohno, M. Nishio, *Chem. Rev.* **2010**, *110*, 6049-6076.
[8] V. I. Bakhmutov, *Dihydrogen bonds: Principles, Experiments and Applications*, Wiley, Hoboken, NJ, **2008**.
[9] G. R. Desiraju, P. S. Ho, L. Kloo, A. C. Legon, R. Marquardt, P. Metrangolo, P. Politzer, G. Resnati, K. Rissanen, *Pure Appl. Chem.* **2013**, *85*, 1711−1713.
[10] T. Clark, M. Hennemann, J. S. Murray, P. Politzer, *J. Mol. Model.* **2007**, *13*, 291-296.
[11] J. S. Murray, P. Lane, T.Clark, K. E. Riley, P. Politzer, *J. Mol. Model.* **2012**, *18*, 541-548.
[12] a) G. Cavallo, P. Metrangolo, R. Milani, T. Pillati, A. Priimagi, G. Resnati, G. Terraneo, *Chem. Rev.* **2016**, *116*, 2478-2601. b) P. Metrangolo, G. Resnati (Eds.), Halogen Bonding I, Springer Int. Pub., Heildelberg, 2015.
[13] a) J. S. Murray, P. Lane, T. Clark, P. Politzer, *J. Mol. Model.* **2007**, *13*, 1033-1038 b) J. S. Murray, P. Lane, P. Politzer, *Int. J. Quantum Chem.* **2007**, *107*, 2286-2292. c) J. S. Murray, P. Lane, P. Politzer, *J. Mol. Model.* **2009**, *15*, 723-729. d) J. S. Murray, P. Lane, T. Clark, K. E. Riley, P. Politzer, *J. Mol. Model.* **2012**, *18*, 541-548.
[14] R. Minyaev, V. I. Minkin, *Can. J. Chem.* **1998**, *76*, 776-778.
[15] S. Zahn, R. Frank, E. Hey-Hawkins, B. Kirchner, *Chem. Eur. J.* **2011**, *17*, 6034.
[16] S. Scheiner, *J. Chem. Phys.* **2011**, *134*, 094315.
[17] A. Bauzá, T. J. Mooibroek, A. Frontera, *Angew. Chem. Int. Ed.* **2013**, *52*, 12317.
[18] D. Mani, E. Arunan, *Phys. Chem. Chem. Phys.* **2013**, *15*, 14377-14383.
[19] G. Cavallo, P. Metrangolo, T. Pillati, G. Resnati, G. Terraneo, *Cryst. Growth Des.* **2014**, *14*, 2697.
[20] A. C. Legon, N. R. Walker, *Phys. Chem. Chem. Phys.* **2018**, *20*, 19332-19338.
[21] E. J. Goodwin, A. C. Legon, *J. Chem. Phys.* **1986**, *85*, 6828-6836.
[22] K. R. Leopold, G. T. Fraser, W. Klemplerer, *J. Chem. Phys.* **1984**, *80*, 1039.
[23] M. S. Ngari, Y. Xu, J. Jäger, *J. Mol. Spectrosc.* **1999**, *197*, 244.
[24] Y. P. Peng, S. W. Sharpe, S. K. Shin, C. Wittig, R. A. Beaudet, *J. Chem. Phys.* **1992**, *97*, 5392.
[25] A. C. Legon, A. P. Suckley, *Chem. Phys. Lett.*, **1989**, *157*, 5.
[26] A. C. Legon, *Phys. Chem. Chem. Phys.* **2017**, *19*, 14884-14895.
[27] O. M. Wilkin, N. Harris, J. F. Rooms, E. L. Dixon, A. J. Bridgeman, N. A. Young, *J. Phys. Chem. A* **2018**, *122*, 1994.
[28] T. Steiner, *Angew. Chem. Int. Ed.* **2002**, *41*, 48-76
[29] J. Zhang, P. Chen. B. Yuan, W. Ji, Z. Cheng, X. Qiu, *Science* **2013**, *342*, 611.
[30] M. Becucci, S. Melandri, *Chem. Rev.* **2016**, *116*, 5014-5037.
[31] J.-P. Schermann, *Spectroscopy and Modelling of Biomolecular Building Blocks*, Elsevier, Amsterdam, **2008**.
[32] W. Caminati, J.-U. Grabow, in *Frontiers and Advances in Molecular Spectroscopy*, Elsevier, Amsterdam, **2018**, chap. 17, pp. 569-598.
[33] W. Caminati, J.-U. Grabow, in *Frontiers of Molecular Spectroscopy*, Elsevier, Amsterdam, **2009**, chap. 15, pp. 455-552.
[34] S. T. Shipman, B. H. Pate, in *Handbook of High Resolution Spectroscopy*, ed. M. Quack and F. Merkt, Wiley, New York, **2011**, pp. 801–828.
[35] C. Pérez, S. Lobsiger, N. A. Seifert, D. P. Zaleski, B. Temelso, G. C. Shields, Z. Kisiel, B. H. Pate, *Chem. Phys. Lett.* **2013**, *571*, 1-15.
[36] G. B. Park, R. W. Field, *J. Chem. Phys.* **2016**, *144*, 200901-1/10.
[37] J. Vogt, N. Vogt, R. Rudert, E. Popov, S. Schlagenhauf, K. Deutzmann, R. Kramer, *Struct. Chem.* **2015**, *26*, 1725-1727.
[38] S. E. Novick, *Bibliography of Rotational Spectra of Weakly Bound Complexes*, **2016**, available at: https://wesfiles.wesleyan.edu/home/snovick/SN_webpage/vdw.pdf
[39] J.-U. Grabow, in *Handbook of High Resolution Spectroscopy*, ed. M. Quack and F. Merkt, Wiley, New York, 2011, pp. 723–800.

[40] T. R. Dyke, B. J. Howard, W. Klemperer, *J. Chem. Phys.* **1972**, *56*, 2442-2454.

[41] S. M. Fritz, B. M. Hays, A. O. Hernandez-Castillo, C. Abeysekera, T. S. Zwier, *Rev. Sci. Instrum.* **2018**, *89*, 093101-1/8.

[42] Y. Xu, J. van Wijngaarden, W. Jaeger, *Int. Rev. Phys. Chem.* **2005**, *24*, 301-338.

[43] A. C. Legon, *Chem. Soc. Rev.* **1990**, *19*, 197-237.

[44] a) A. C. Legon, *Angew. Chem. Int. Ed.* **1999**, *38*, 2686-2714. b) A. C. Legon, *Phys. Chem. Chem. Phys.* **2010**, *12*, 7736-7747.

[45] K. R. Leopold, M. Canagaratna, J. A. Phillips, *Acc. Chem. Res.* **1997**, *30*, 57-64.

[46] a) b) Y. Oshima, Y. Endo, *Chem. Phys. Lett.* **1996**, *256*, 635-640.

[47] S. Blanco, S. Melandri, P. Ottaviani, W. Caminati, *J. Am. Chem. Soc.* **2007**, *129*, 2700-2703.

[48] G. Feng, L. Evangelisti, I. Cacelli, L. Carbonaro, G. Prampolini, W. Caminati, *Chem. Commun.* **2014**, *50*, 171.

[49] C. Calabrese, L. Evangelisti, I. Uriarte, B. H. Pate, E. J. Cocinero, Comm. B7.2, *25th Int. Conf. High Res. Mol. Spectroscopy*, **2018** Bilbao (Spain).

[50] C. Pérez, M. T. Muckle, D. P. Zaleski, N. A. Seifert, B. Temelso, G. C. Shields, Z. Kisiel, B. H. Pate, *Science* **2012**, *336*, 897-901.

[51] J. O. Richardson, C. Pérez, S. Lobsiger, A. A. Reid, B. Temelso, G. C. Shields, Z. Kisiel, D. J. Wales, B. H. Pate, S. C. Althorpe, *Science*, **2016**, *351*, 1310-1313.

[52] C. Pérez, D. P. Zaleski, N. A. Seifert, B. Temelso, G. C. Shields, Z. Kisiel, B. H. Pate, *Angew. Chem. Int. Ed.*, **2014**, *53*, 14368-14372

[53] C. Pérez, D. P. Zaleski, N. A. Seifert, B. H. Pate, Z. Kisiel, B. Temelso, G. C. Shields, S. T. Shipman, I. Finnerman, Comm. TH06, *25th OSU Int. Symp. Mol. Spectroscopy*, **2013** Columbus (Ohio, USA).

[54] a) K. Liu, M. G. Brown, C. Carter, R. J. Saykally, J. K. Gregory, D. C. Clary, *Nature* **1996**, *381*, 501–503. b) W. T. S. Cole, J. D. Farrell, D. J. Wales, R. J. Saykally, *Science* **2016**, *352*, 1194-1197.

[55] J. L. Neill, Doctoral Dissertation, University of Virginia, **2011**.

[56] W. Li, L. Evangelisti, Q. Gou, W.Caminati, R. Meyer, *Angew. Chem. Int. Ed.*, **2019**, *58*, 859 –865.

[57] a) J. Thomas, X. Liu, W. Jäger, Y. Xu, *Angew. Chem. Int. Ed.* **2015**, *54*, 11711-11715. b) N. A. Seifert, J. Thomas, W. Jäger, Y. Xu, *Phys. Chem. Chem. Phys.* **2018**, *20*, 27630-27637.

[58] J. Thomas, N. A. Seifert, W. Jäger, Y. Xu, *Angew. Chem. Int. Ed.* **2017**, *56*, 6289-6293.

[59] N. A. Seifert, A. L. Steber, J. L. Neill, C. Pérez, D. P. Zaleski, B. H. Pate, A. Lesarri, *Phys. Chem. Chem. Phys.* **2013**, *15*, 11468-11477.

[60] C. Pérez, I. León, A. Lesarri, B. H. Pate, R. Martínez, J. Millán, J. A. Fernández, *Angew. Chem. Int. Ed.* **2018**, *57*, 15112-15116

[61] A. Zehnacker (Ed.), *Chiral Recognition in the Gas Phase*, CRC Press, Boca Raton FL, **2010**.

[62] a) A. Zehnacker, *Int. Rev. Phys. Chem.* **2014**, *33*, 151-207. b) A. Zehnacker, M. Suhm, *Angew. Chem. Int. Ed.* **2008**, *47*, 6970-6992.

[63] a) J. P. I. Hearn, R. V. Cobley, B. J. Howard, *J. Chem. Phys.* **2005**, *123*, 134324-1-7. b) D. Loru, I. Peña, M. E. Sanz, *J. Mol. Spectrosc.* **2017**, *335*, 93-101.

[64] X. Liu, N. Bohro, Y. Xu, *Chem. Eur. J.* **2009**, *15*, 270-277.

[65] A. M. King, B. J. Howard, *Chem. Phys. Lett.* **2001**, *348*, 343-349.

[66] A. Maris, B. M. Giuliano, D. Bonazzi, W. Caminati, *J. Am. Chem. Soc.* **2008**, *130*, 13860-13861.

[67] Z. Su, N. Borho, Y. Xu, *J. Am. Chem. Soc.* **2006**, *128*, 17126-17131.

[68] D. Scuderi, K. Le Barbu-Debus, A. Zehnacker, *Phys. Chem. Chem. Phys.* **2011**, *13*, 17916-17929.

[69] N. Borho, Y. Xu, *Angew. Chem. Int. Ed.* **2007**, *46*, 2276-2279.

[70] N. Bohro, Y. Xu, *J. Am. Chem. Soc.* **2008**, *130*, 5916-5921.

[71] J. Thomas, W. Jäger, Y. Xu, *Angew. Chem. Int. Ed.* **2014**, *126*, 7405-7408.

[72] J. Thomas, F. X. Sunahori, N. Borho, Y. Xu, *Chem. Eur. J.* **2011**, 17, 4582-4587.

[73] J. Thomas, Y. Xu, *J. Phys. Chem. Lett.* **2014**, *5*, 1850-1855.

[74] N. A. Seifert, C. Pérez, J. L. Neill, B. H. Pate, M. Vallejo-López, A. Lesarri, E. J. Cocinero, F. Castaño, *Phys. Chem. Chem. Phys.* **2015**, *17*, 18282-18287.

[75] B. H. Pate, L. Evangelisti, W. Caminati, Y. Xu, J. Thomas, D. Patterson, C. Pérez, M. Schnell, in *Chiral Analysis: Advances in Spectroscopy, Chromatography and Emerging Methods* (Second Edition), Ed.: P. L. Polavarapu, chap. 17, pp. 679-729, Elsevier, Amsterdam, **2018**, and references therein.

[76] S. R. Domingos, C. Pérez, M. Schnell, *Ann. Rev. Phys. Chem.* **2018**, *69*, 499-519.

[77] A IUPAC 2016-18 terminology Project for CB/PB/TB has not concluded at the time of writing, see www.iupac.org/project/2016-001-2-300.

[78] A. Bauzá, D. Quiñonero, P. M. Deyá, A. Frontera, *CrysEngComm* **2013**, *15*, 3137-313.

[79] Q. Gou, L. Spada, E. J. Cocinero, W. Caminati, *J. Phys. Chem. Lett.* **2014**, *5*, 1591-1595.

[80] L. Evangelisti, G. Feng., Q. Gou, J.-U. Grabow, W. Caminati, *J. Phys. Chem.* **2014**, *118*, 579-582.

[81] Q. Gou, G. Feng, L. Evangelisti, M. Vallejo-López, L. Spada, A. Lesarri, E. J. Cocinero, W. Caminati, *Chem. Eur. J.* **2015**, *21*, 4148-4152.
[82] G. Feng, L. Evangelisti, N. Gasparini, W. Caminati, *Chem. Eur. J.* **2012**, *18*, 1364-1368.
[83] W. Caminati, L. Evangelisti, G. Feng, B. M. Giuliano, Q. Gou, S. Melandri, J.-U. Grabow, *Phys. Chem. Chem. Phys.* **2016**, *18*, 17851-17855.
[84] Q. Gou, W. Caminati, private communication, **2019**.
[85] Y. D. Juang, M. A. Walsh, A. K. Lewin, T. R. Dyke, *J. Chem. Phys*. **1992**, *97*, 832-840.
[86] F. J. Lovas, M. K. Sprague, *J. Mol. Spectrosc.* **2015**, *316*, 49-53.
[87] J. J. Oh, K. W. Hillig II, R. L. Kuczkowski, *Inorg. Chem*. **1991**, *30*, 4583-4588.
[88] J. J. Oh, M. S. LaBarge, J. Matos, J. W. Kampf, K. W. Hillig, R. L. Kuczkowski, *J. Am. Chem. Soc.* **1991**, *13*, 4732-4738.
[89] E. Gougoula, C. Medcraft, I. Alkorta, N.R. Walker, A. C. Legon, *J. Chem. Phys*. 2019, **150**, 084307-1-8.
[90] D. A. Obenchain, L. Spada, S. Alessandrini, S. Rampino, S. Herbers, N. Tasinato, M. Mendolicchio, P. Kraus, J. Gauss, C. Puzzarini, J.-U. Grabow, V. Barone, *Angew. Chem. Int. Ed.* **2018**, *57*, 15822-15826.
[91] M. Juanes, A. Lesarri, R. Pinacho, E. Charro, J. E. Rubio, L. Enríquez, M. Jaraíz, *Chem. Eur. J.* **2018**, *25*, 6564-6571.
[92] W. Li, L. Spada, N. Tasinato, S. Rampino, L. Evangelisti, A. Giulandi, P. G. Cozzi, S. Melandri, V. Barone, C. Puzzarini, *Angew. Chem. Int. Ed*. **2018**, *57*, 13853-13857.
[93] a) D. Patterson, M. Schnell, J. M. Doyle, *Nature*, **2013**, *497*, 475-478. b) J.-U. Grabow, *Angew. Chem. Int. Ed*. **2013**, *52*, 11698-11700. c) C. Pérez, A. L. Steber, S. R. Domingos, A. Krin, D. Schmitz, M. Schnell, *Angew. Chem. Int. Ed.* **2017**, *129*, 12686-12691.
[94] K. N. Crabtree, M.-A. Martin-Drumel, G. G. Brown, S. A. Gaster, T. M. Hall, M. C. McCarthy, *J. Chem. Phys.* **2016**, *144*. 124201-1/12.
[95] a) D. F. Plusquellic, R. D. Suenram, B. Maté, J. O. Jensen, A. C. Samuels, *J. Chem. Phys*. **2001**, *115*, 3057-3067. b) N. A. Seifert, I. A. Finneran, C. Perez, D. P. Zaleski, J. L. Neill, A. L. Steber, R. D. Suenram, A. Lesarri, S. T. Shipman, B. H. Pate *J. Mol. Spectrosc*. **2015**, *312*, 13-21. c) C. Western, B. E. Billinghurst, *Phys. Chem. Chem. Phys.* **2017**, *19*, 10222-10226. d) L. Yeh, L. Satterthwaite, D. Patterson, 2019, in press.

Figure 1. Rotational studies of intermolecular clusters, as collected in MOGADOC [37]. *(Production note: This drawing combines a background image with MS-Word labels and arrows, so this is the original version*)

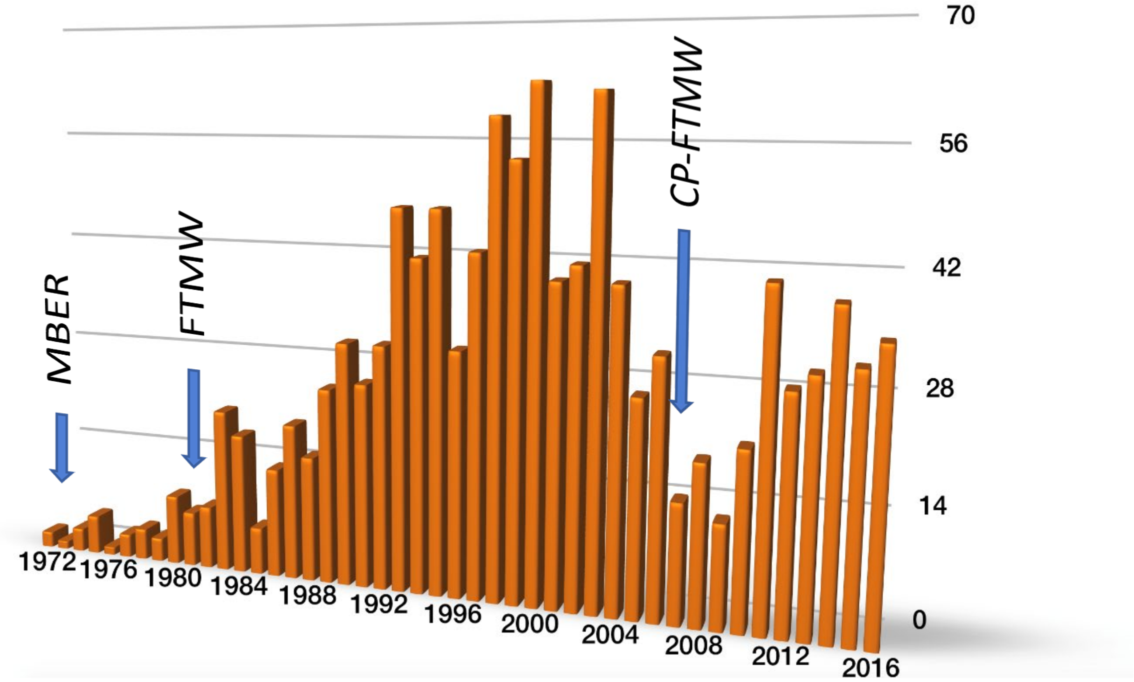


Figure 2. A simplified block diagram of a 2-8 GHz chirped-pulsed Fourier transform microwave (CP-FTMW) spectrometer, after Pate [34,35]. The operation principle can be extended to the millimeter-wave region.

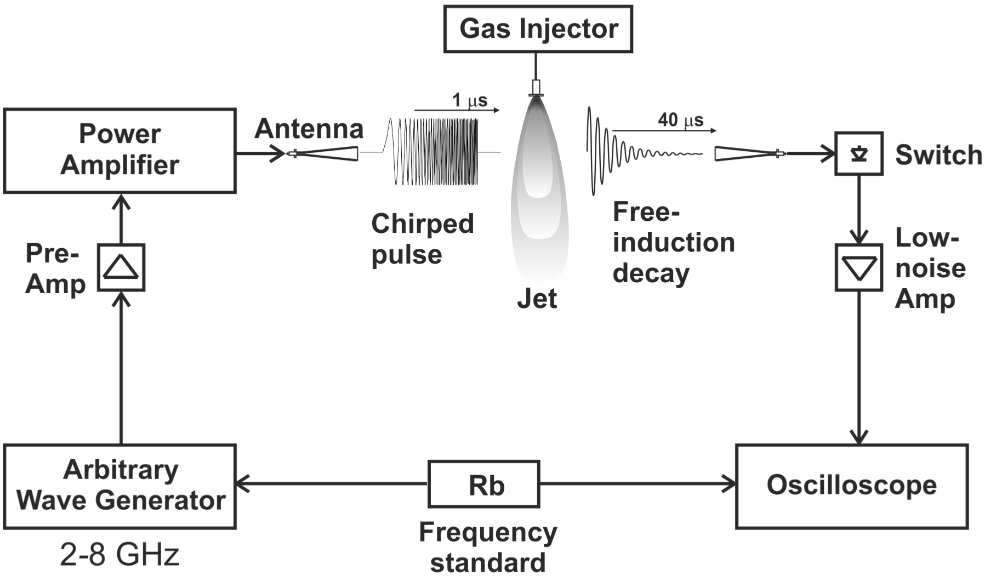


Figure 3. A network or bifurcated C-H···F HBs produce a rhomboid structure for the difluoromethane tetramer. Reprinted with permission from ref. [48] (copyright RSC).

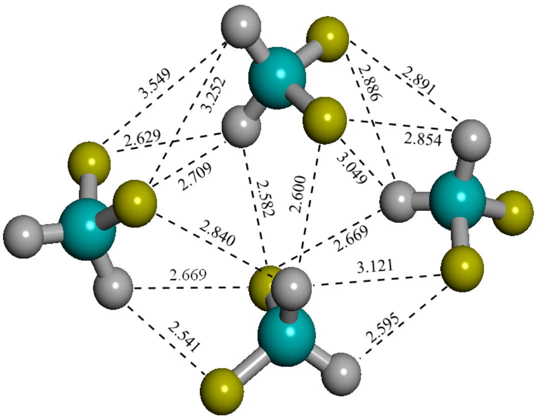


Figure 4. Antigeared (A) and geared (B) instanton tunneling pathways [48] in the water hexamer prism, together with variation of the potential energy along the instanton paths (C). Reprinted with permission from ref. [51] (copyright AAAS).

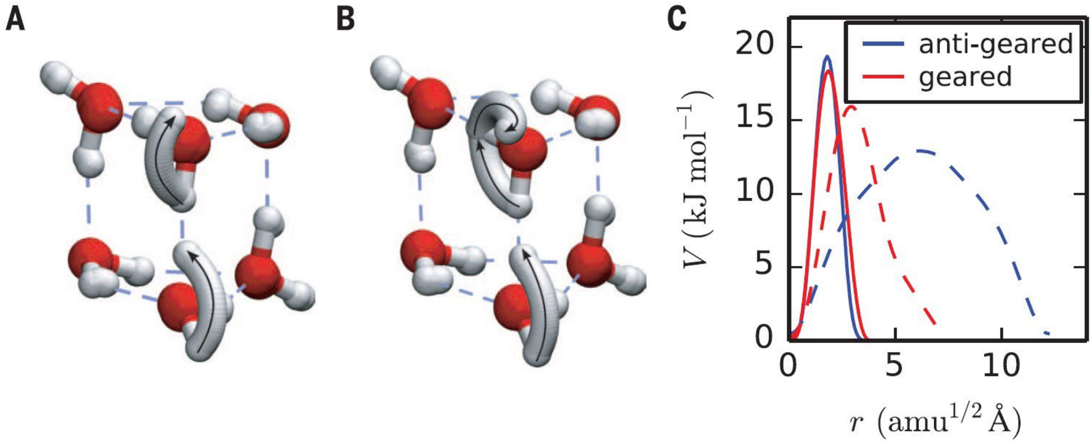


Figure 5. Structures of several isomers of the water nonamer and decamer determined from a full ^{18}O isotopic substitution, with experimental distances (bold top values) compared to RI-MP2 predictions (shorter distances in red). Reprinted with permission from ref. [52] (copyright Wiley-VCH).

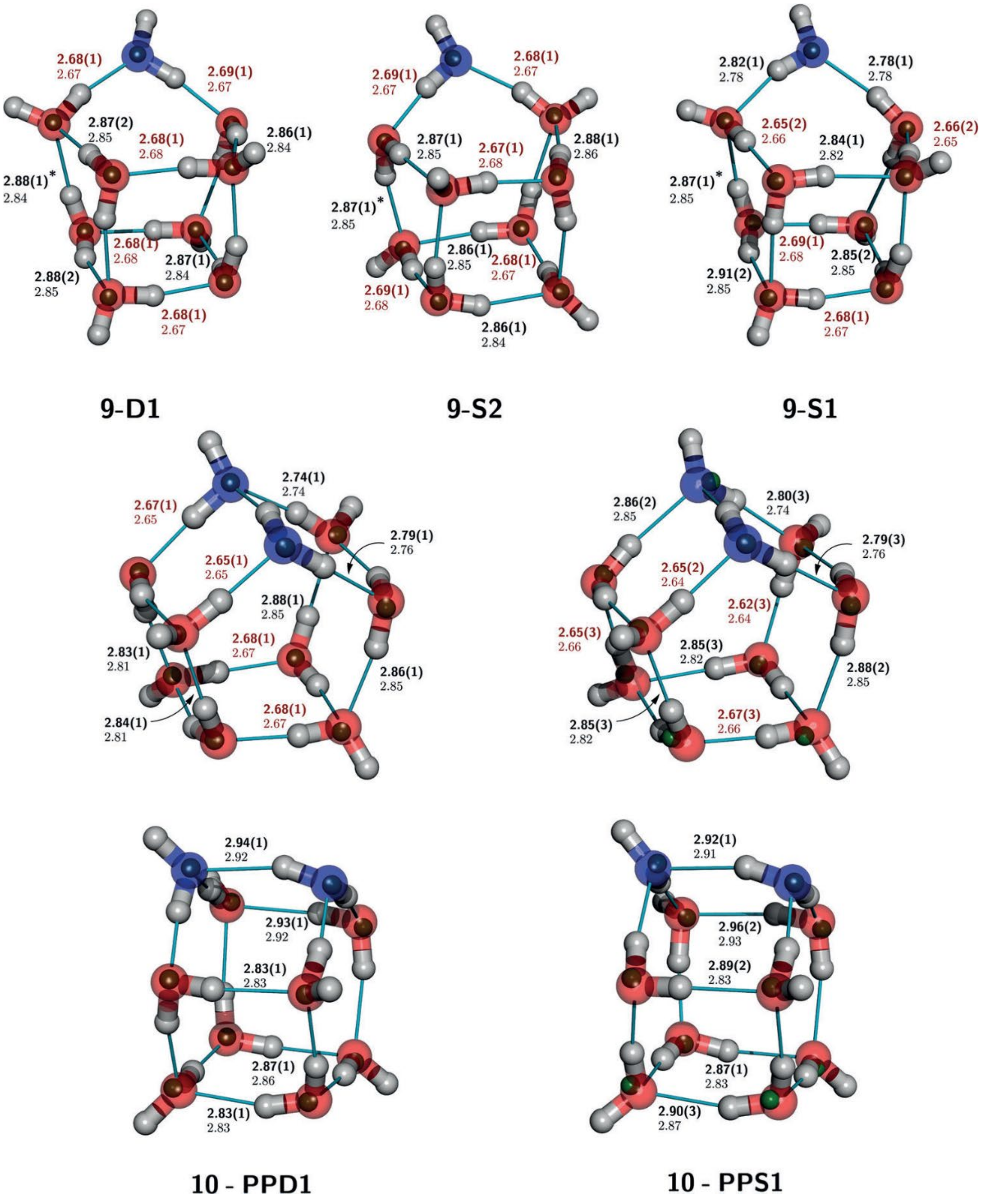


Figure 6. The three isomers of the aniline trimer, with intermolecular interactions mapped with NCI Plots (HBs in blue, weak stabilizing interactions in green). Reprinted with permission from ref. [60] (Copyright Wiley-VCH).

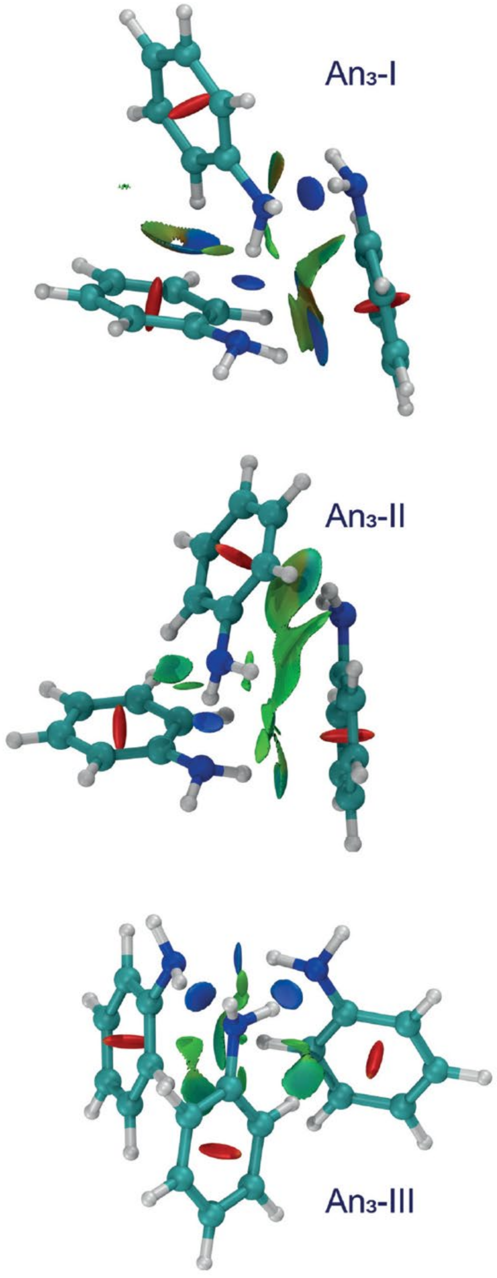


Figure 7. C-H···O and C-H···F HBs freeze the transient axial chirality in the sevoflurane dimer, producing distinct heterochiral (left) homochiral (right) diastereoisomers. Reprinted with permission from ref. [74] (Copyright RSC).

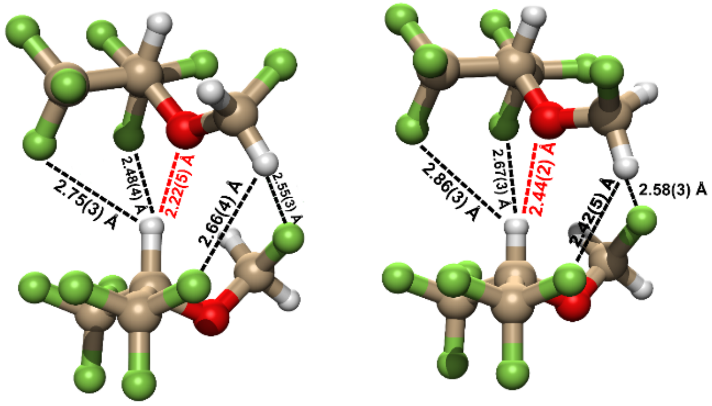


Figure 8. The S···S calchogen bond in the dimer of dimethyl sulfide with sulfur dioxide. Reprinted with permission from ref. [90] (copyright Wiley-VCH).

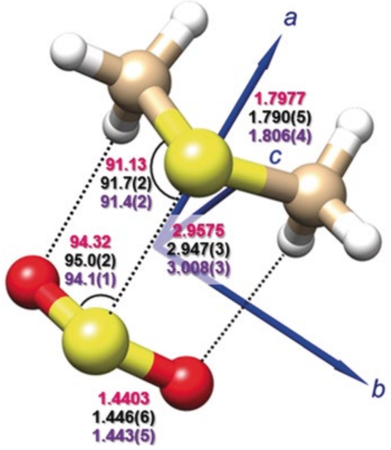


Figure 9. The N···N pnicogen bond in the dimer of trimethyl amine with nitroethane and charge-transfer diagrams. Reprinted with permission from ref. [92] (Copyrigth Wiley-VCH).

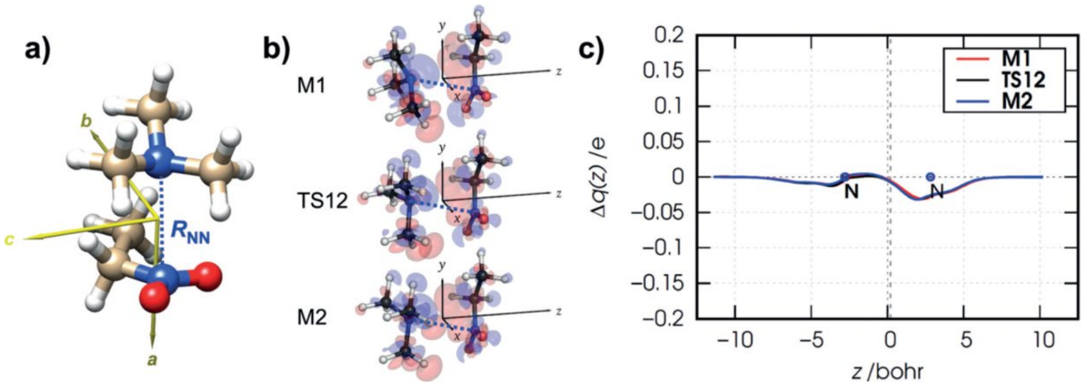


Table 1. The physical forces acting in NCI illustrated with a (SAPT) binding energy decomposition [2] for several heterodimers dominated by electrostatic, dispersion or mixed intermolecular interactions.

	$\Delta E_{\text{Electrostatic}}$	$\Delta E_{\text{Induction}}$	$\Delta E_{\text{Dispersion}}$	$\Delta E_{\text{Exchange}}$	ΔE_{Total}
$(H_2O)_2$[a]	-37.0	-9.0	-5.3	29.4	-21.8
$(H_2S)_2$ [a]	-12.9	-4.4	-5.2	18.0	-4.5
Dimethylsulfide···SO_2[b]	-71.5	-39.4	-41.6	121.7	-30.7
Nitroethane-$N(CH_3)_3$[c]	-29.4	-7.3	-31.1	39.8	-27.9
Sevoflurane-benzene[a]	-36.9	-10.5	-37.0	59.4	-25.0
Pyridine-CH_4[a]	-17.9	-4.1	-42.0	46.1	-17.8

[a]Ref. [91]. [b]Ref. [90]. [c]Ref. [92].