



ARCHIVIO ISTITUZIONALE
DELLA RICERCA

Alma Mater Studiorum Università di Bologna
Archivio istituzionale della ricerca

Computational molecular spectroscopy

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:

Computational molecular spectroscopy / Barone, Vincenzo; Alessandrini, Silvia; Biczysko, Malgorzata; Cheeseman, James R.; Clary, David C.; McCoy, Anne B.; DiRisio, Ryan J.; Neese, Frank; Melosso, Mattia; Puzzarini, Cristina. - In: NATURE REVIEWS METHODS PRIMERS. - ISSN 2662-8449. - ELETTRONICO. - 1:1(2021), pp. 38.1-38.27. [10.1038/s43586-021-00034-1]

This version is available at: <https://hdl.handle.net/11585/867763> since: 2022-02-28

Published:

DOI: <http://doi.org/10.1038/s43586-021-00034-1>

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

(Article begins on next page)

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>).
When citing, please refer to the published version.

This is the final peer-reviewed accepted manuscript of:

Barone, V.; Alessandrini, S.; Biczysko, M.; Cheeseman, J. R.; Clary, D. C.; McCoy, A. B.; DiRisio, R. J.; Neese, F.; Melosso, M.; Puzzarini, C. Computational Molecular Spectroscopy. Nat Rev Methods Primers 2021, 1 (1), 1–27.

The final published version is available online at: <https://doi.org/10.1038/s43586-021-00034-1>.

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>)

When citing, please refer to the published version.

Computational Molecular Spectroscopy

Vincenzo Barone¹, Silvia Alessandrini¹

Malgorzata Biczysko²

James R. Cheeseman³

David C. Clary⁴

Anne B. McCoy⁵, Ryan DiRisio⁵

Frank Neese⁶

Mattia Melosso⁷, Cristina Puzzarini^{7,*}

¹ Scuola Normale Superiore, Piazza dei Cavalieri 7, Pisa, 56126, Italy

² International Centre for Quantum and Molecular Structures, Physics Department, Shanghai University, 99 Shangda Road, Shanghai, 200444 China

³ Gaussian Inc., 340 Quinnipiac St., Bldg. 40, Wallingford, Connecticut 06492-4050, United States

⁴ Physical and Theoretical Chemical Laboratory, University of Oxford, Oxford OX1 3QZ, United Kingdom

⁵ Department of Chemistry, University of Washington, Seattle, Washington 98195, United States

⁶ Max-Planck-Institut für Kohlenforschung, Kaiser Wilhelm-Platz-1, Mülheim an der Ruhr, Germany

⁷ Department of Chemistry "Giacomo Ciamician", University of Bologna, Via F. Selmi 2, 40126 Bologna, Italy

*Corresponding author: cristina.puzzarini@unibo.it

Abstract

Molecular spectroscopy techniques are unique tools to probe molecular systems non-invasively and investigate their structure, properties, and dynamics in different environments and physicochemical conditions. Different spectroscopic techniques and their combination can lead to a more comprehensive picture of investigated systems. However, the increasing sophistication of these experimental techniques makes it more and more complex and difficult to interpret the results without the help of computational chemistry. As a consequence, computational molecular spectroscopy has progressively changed from a highly specialized field to a general tool also employed by experimentally-oriented researchers. Computational spectroscopy, born as a branch of quantum chemistry for providing predictions of spectroscopic properties and features, evolved as an independent field. In this Primer, we focus on the characterization of medium-sized molecular systems by means of different spectroscopic techniques. We first provide essential information about the characteristics, accuracy and limitations of the available computational approaches, and select examples with the aim of illustrating general trends, that is outcomes of general validity that can be used for modeling spectroscopic phenomena. We emphasize the need for estimating error bars and limitations, coupling accuracy with interpretability, and discuss the results in terms of widely recognized chemical concepts.

[H1] 1. Introduction

Spectroscopy is the experimental way to study the electronic structure of a system, which is intimately connected to its molecular structure, chemical linkages, and reactivity. Molecular spectroscopy can probe any system in a non-invasive way, thus allowing the investigation of structure and properties in different environments and/or physicochemical conditions. The molecules addressed in this Primer fall into the category of medium-sized systems, which range in dimension from a dozen atoms (such as the smallest amino acid, glycine) to several tens of atoms (e.g. chlorophyll). Almost all possible environments will be considered: from gas phase to solution, to crystals.

Among the various spectroscopic techniques,¹⁻⁵ rotational spectroscopy is the most accurate and reliable source for structural information and dynamics of gas-phase molecules.⁶⁻¹² Similarly, vibrational spectroscopy permits the characterization of molecules in terms of conformation, chemical linkage, and mutual interactions among atoms and atomic charges modulated by the temperature and environmental effects. Indeed, while rotational spectroscopy is limited to the gas phase, vibrational spectroscopic techniques can also investigate condensed phases. For these reasons, vibrational spectroscopies (infrared, Raman, as well as their chiral counterparts) are commonly employed for characterizing the structure and dynamical behavior of molecular systems. Electronic spectroscopic techniques, in gas or condensed phases, deal with transitions between different electronic states, thus giving access to the characterization of the molecular system in excited electronic states.

Modern high-resolution experimental spectroscopy may involve the acquisition of spectra resolving hundreds, if not thousands of peaks, which is the case, for example, of **rotational [G]** and **ro-vibrational [G]** spectra of polyatomic, asymmetric molecules as well as electron spin resonance (**ESR [G]**) spectra of metalorganic complexes. This spectral overcrowding means the interpretation of high-resolution spectra without the help of quantum chemistry (QC) is a daunting if not impossible task. Indeed, computational spectroscopy, born as a branch of quantum chemistry for providing predictions of spectroscopic properties and features, evolved as an independent field. Currently, theoretical studies in the field of molecular spectroscopy play three roles: interpretation, complementarity, and prediction and support of experimental results. Computational spectroscopy exploits theoretical models, provides tools and computer codes, and validates procedures for the prediction, analysis, interpretation, and understanding of spectroscopic features, properties and/or phenomena. There are several aspects and reasons that contribute to make computational spectroscopy an unavoidable tool in the field of molecular spectroscopy. While there is no room for addressing them in all detail¹³⁻¹⁸, in the following we emphasize the topics we consider of primary importance.

In terms of spectral interpretation, spectroscopic experiments often need a broad computational investigation. For example, in order to analyze a recorded rotational or vibrational spectrum of flexible molecular systems, a computational conformational analysis as well as subsequent spectral predictions and simulations are necessary to understand which **conformers [G]** contribute and how. QC also helps identify which aspects of a given structure are responsible for a specific spectroscopic property. Computational studies can establish structure/property relationships as they allow the on or off switching of specific effects and the analysis of the impact of these changes on the simulated spectrum. To give an example, in organometallic complexes, there is a strong relationship between metal-ligand bond distances and **Mössbauer isomer shifts [G]**. Combining broad computational

91 studies with a focus on structure-property relationships can, for example, identify short-lived and
92 unstable species (in either ground or excited states).

93
94 In terms of complementarity, one of the goals of experimental spectroscopy is to understand the
95 structure and bonding in molecule, although what is actually measured are the frequencies of light
96 that are absorbed. Computational spectroscopy can act as a bridge between experiments and
97 underlying physical properties, as it provides the theoretical expressions linking observable
98 measurements and molecular properties. Computational and experimental spectroscopy can also
99 be used to benchmark each other.¹⁹ Experimental spectroscopy is extremely sensitive to the
100 electronic structure of a given system, and it is one of the best ways to verify the reliability and
101 accuracy of theoretical predictions and validate QC calculation results. In parallel, experimentally
102 accessible spectroscopic properties may be much more sensitive to molecular structure than total
103 energies, which are often not experimentally measurable.

104
105 In terms of prediction and support, the combination of theory and experiment provides
106 experimentally calibrated or experimentally guided insights into electronic structure and, hence,
107 can serve as a guide to the reactivity of systems. The prediction and interpretation of structural
108 properties and dynamic behavior of molecules is at the heart of a deeper understanding of their
109 stability and chemical reactivity. Furthermore, understanding electronic structure and how is
110 reflected in the spectroscopic properties can give insights into entire classes of compounds, rather
111 than only for individual molecules. Computational spectroscopy can also act as the link between
112 different experimental techniques that traditionally were analyzed separately, such as, for example,
113 infrared (IR), Raman, Resonance Raman, ultraviolet–visible absorption or fluorescence (as well as
114 their chiral counterparts), and electron magnetic resonance. QC computations yield direct
115 information on many properties of molecular systems, which can link the molecular properties
116 measured using different experimental techniques. Finally, while peak positions and intensities
117 provide information on the structure of the system, the spectral line-shape is related to dynamical
118 (e.g. fluctuation) aspects. As a consequence, vis-à-vis comparison between simulated and
119 experimental spectra also gives access to these features.

120
121 Figure 1 provides a schematic representation of the types of transitions involved in the
122 spectroscopies addressed in this Primer: rotational, vibrational and vibronic spectroscopy. These
123 techniques investigate the transitions between the corresponding energy levels. Together with
124 them, their chiral counterparts, the alternative approach for rotational and vibrational
125 spectroscopies denoted Diffusion Monte Carlo (DMC), and magnetic resonance spectroscopies will
126 be also considered. Figure 1 also allows us to point out the physical aspects underlying each
127 spectroscopic technique. For instance, rotational spectroscopy is related to the rotational motion
128 of the molecular system under consideration, and it can thus be carried out experimentally only in
129 the gas phase. Vibrational spectroscopy describes instead vibrational motion of the atoms within
130 the molecule, and it can be therefore exploited also in condensed phases. The approach mainly
131 followed in this Primer for obtaining the energy levels (DMC being the major exception) is based on
132 effective Hamiltonians and the resolution of the corresponding Schrödinger equation.

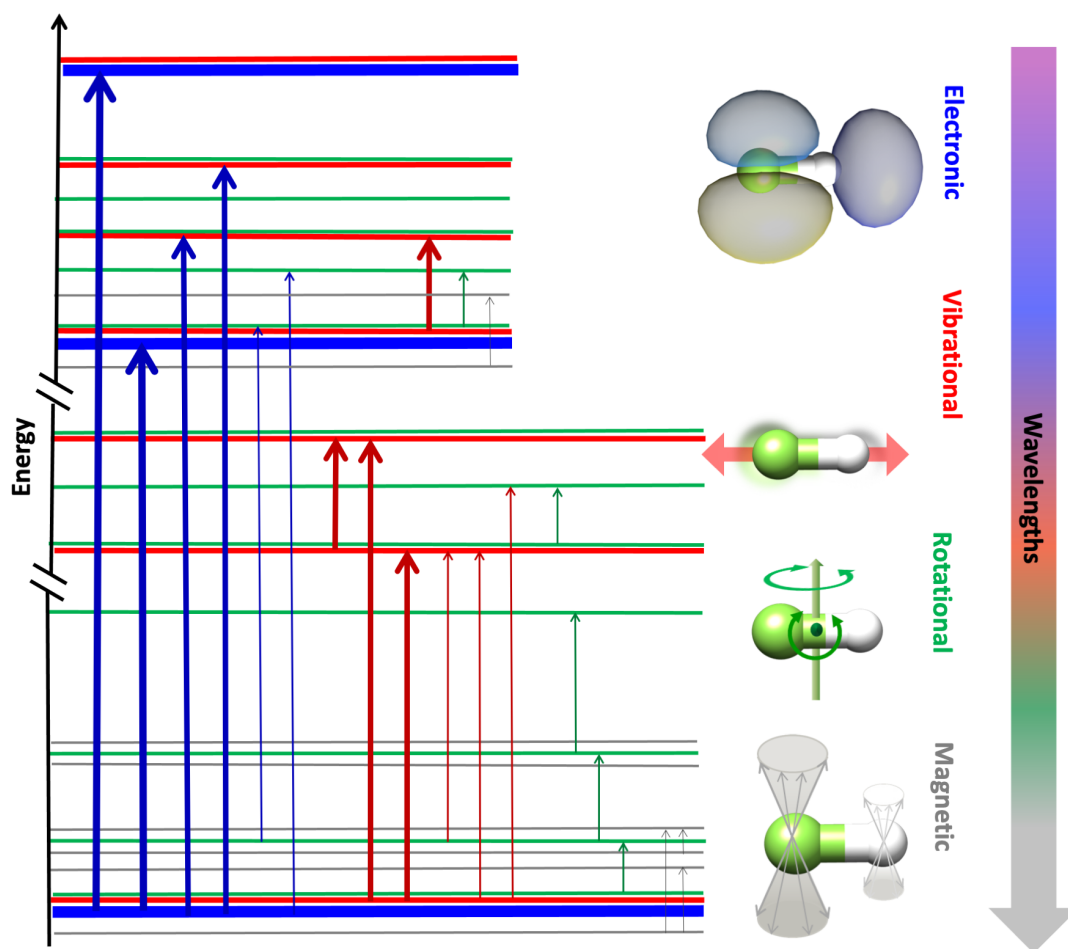


Figure 1. Schematic representation of the energy levels, obtained from the resolution of the opportune Schrödinger equation, and the types of possible transitions. Blue arrows denote the transitions involving a change in the electronic state (from left to right: from thicker to thinner, electronic, vibronic and rovibronic transitions). Red arrows denote the transitions involving different vibrational states (from left to right: vibrational and ro-vibrational transitions). Green arrows denote the transitions only involving rotational energy levels. Dark grey arrows denote the transitions between energy levels obtained from magnetic field splitting.

134

135

136

137

138

139

140

141

142

143

144

145

146

This Primer is organized as follows. The next section, titled Experimentation, provides the theoretical foundations and computational requirements of the spectroscopic techniques mentioned above. In the subsequent section, some specific results for these spectroscopic techniques are presented, like e.g. the derivation of structural information and the determination of the **absolute configuration** (AC) [G] of chiral molecules. The fourth section, devoted to applications, reports a selection of significant examples such as Astrochemical studies and the characterization of biomolecules and transition metal complexes. In the next two sections the issues of reproducibility and data deposition, and limitations and optimizations will be addressed, respectively. Finally, outlook and perspectives will be provided.

[H1] 2. Experimentation

In the framework of a Primer dedicated to computational spectroscopy, we translate the instrumentation, experimental design, and equipment to the language of the computational world and discuss the theoretical foundations, computational requirements, and codes. In this section, we start with the theory underlying the spectroscopic phenomena associated with molecular systems, attempting to keep the treatment of mathematical expressions as simple as possible. We then move to the computational requirements needed to reach the desired accuracy. We conclude the section with a schematic presentation of some representative computer codes that are currently employed in the field of computational spectroscopy.

[H2] 2.1. Theoretical foundations

The goal of computational spectroscopy is to couple accurate theoretical results with the interpretation of the experimental outcomes by using well-defined models. Theoretical analysis of spectroscopic phenomena is related to the transitions between the **energy levels [G]** (E_{mol}) of a given molecule (see Figure 1), which can be obtained from the solution of the corresponding Schrödinger equation:

$$\hat{H}_{mol}(\mathbf{r}, \mathbf{R})|\Psi(\mathbf{r}, \mathbf{R})\rangle = E_{mol}|\Psi(\mathbf{r}, \mathbf{R})\rangle \quad (\text{Equation 1})$$

where $\hat{H}_{mol}(\mathbf{r}, \mathbf{R})$ is the molecular **Hamiltonian [G]** (that is the Hamiltonian associated to the molecular system under consideration), with \mathbf{R} and \mathbf{r} being the **position arrays [G]** of the nuclei and electrons, respectively; $|\Psi(\mathbf{r}, \mathbf{R})\rangle$ is the **wave function [G]** denoting the state of the molecule. As Equation 1 is unsolvable for the majority of the molecular systems, approximations must be introduced in order to obtain energy levels. The **Born-Oppenheimer (BO) [G]** approximation²⁰ permits the separation of nuclei and electrons motions, thus leading to electronic and nuclear Schrödinger equations. Once nuclear and electronic motions are separated, a further approximation is required to simplify the nuclear Schrödinger equation. This is provided by the Eckart-Sayvetz conditions,^{21,22} which factors out the translational motion and minimizes the couplings between vibrations and rotations. One of the major consequences of the BO approximation is the definition of the concept of **potential energy surface (PES) [G]**, which is a function of the nuclear coordinates and provides the relationship between the electronic energy of a molecule (from the resolution of the electronic Schrödinger equation) and its geometry. Stable molecular structures (equilibrium structures) are minima on the PES. A mathematical description of the PES enters the Hamiltonian of the nuclear Schrödinger equation and, to simplify the treatment, it is often expressed in terms of force constants, which are the derivatives of the electronic energies with respect to nuclear coordinates evaluated at the minimum.

Here, we focus on the nuclear Schrödinger equation and, in the following, its resolution by means of perturbation theory techniques is presented. The advantage of perturbation theory is that it is generally accurate, and it is a powerful interpretative tool allowing a direct connection with the parameters that are used by experimentalists to fit their spectra. The most common approach for considering nuclear quantum effects and obtaining the energies and wave functions needed to study spectroscopic properties involves solving the time-independent Schrödinger equation:

$$\hat{H}_{vr}(\mathbf{R})|\Psi_{vr}(\mathbf{R})\rangle = E_{vr}|\Psi_{vr}(\mathbf{R})\rangle \quad (\text{Equation 2})$$

with the Watson Hamiltonian²³ \hat{H}_{vr} being the most widely used Hamiltonian for the description of the vibro-rotational motion of semi-rigid molecular systems. The Watson Hamiltonian is expressed in terms of the dimensionless **normal coordinates** [G] (q) and their conjugate momenta (\hat{p}) referred to the equilibrium geometry of the system within a reference frame (principal inertia system) centered in the center of mass and oriented in order to diagonalize the equilibrium **inertia tensor** [G] (Eckart-Seyvetz conditions):

$$\hat{H}_{vr} = \frac{1}{2} \sum_{\alpha, \beta} (\hat{J}_{\alpha} - \hat{\pi}_{\alpha}) \mu_{\alpha\beta} (\hat{J}_{\beta} - \hat{\pi}_{\beta}) + \frac{1}{2} \sum_r \omega_r \hat{p}_r^2 + V(q) - \frac{1}{2} \sum_{\alpha} \mu_{\alpha\alpha} \quad (\text{Equation 3})$$

where the q are linear combinations of the displacements of the Cartesian coordinates of the atoms. The harmonic wavenumber associated to the r -th normal coordinate is denoted by ω_r , and $\mu_{\alpha\beta}$ denotes an element of the inverse inertia tensor. \hat{J}_{α} is the rotational angular-momentum operator about axis α , and $\hat{\pi}_{\alpha}$ represents the α -th component of vibrational angular momentum. Since the exact form of the inverse molecular inertia tensor μ and the potential energy V are unknown, they are expanded as Taylor series with respect to q . A detailed account can be found in refs. ^{23,24}.

A different procedure is offered by a Hamiltonian-independent approach based on inverting the information contained in the experimental **spectroscopic transitions** [G] in order to derive the corresponding energy levels. After collecting all available (experimentally) measured transitions and selecting the most accurate data (i.e. those affected by the low errors), and compiling them into a database, spectroscopic networks are established in order to interconnect the energy levels. A spectroscopic network is a graph where the nodes are the energy levels and the links are the transitions. Inversion of the transitions through a weighted least-squares-type procedure results in the energy levels and associated uncertainties. The MARVEL (Measured Active Rotational-Vibrational Energy Levels) protocol in the field of ro-vibrational spectroscopy^{25,26} provides an illustrative example.

[H3] 2.1.1. Rotational Spectroscopy

To address rotational spectroscopy, the first step is the definition of a suitable Hamiltonian. The starting point is the Watson Hamiltonian, from which the rotational part should be extracted. To accomplish this, a **contact transformation** [G] is applied to the vibro-rotational Hamiltonian in Equation 2, and this leads to a block-diagonal effective Hamiltonian.²⁷ Each of these blocks is labelled in terms of the powers of q and \hat{p} , and powers of \hat{J} : the power of the former (vibrational) is referred to as n and that of the latter (rotational) to l . Thus, the vibro-rotational Hamiltonian is now indicated as \tilde{H}_{nl} . By retaining the pure rotational and centrifugal-distortion terms (i.e. all Hamiltonian terms with $n = 0$), the rotational Hamiltonian is obtained:

$$\tilde{H}_{rot} = H_{02} + \tilde{H}_{04} + \tilde{H}_{06} \quad (\text{Equation 4})$$

where \tilde{H}_{04} and \tilde{H}_{06} are the quartic and sextic centrifugal-distortion terms, and H_{02} is the rigid-rotor Hamiltonian:

$$H_{02} = \sum_i B_i^{eq} \hat{J}_i^2 \quad (\text{Equation 5})$$

where \hat{J}_i is the projection of the rotational angular momentum operator along the i -th inertial axis, and the B_i^{eq} terms represent the equilibrium rotational constants, which are inversely proportional

241 to the corresponding components of the inertia tensor (diagonal in the principal inertia system),
242 which in turn only depends on the equilibrium structure and the isotopic masses of the molecule
243 under consideration.²⁸ From a computational point of view, equilibrium rotational constants are
244 derived from geometry optimization, the computational procedure that leads to the identification
245 of the equilibrium structure. The accuracy of the equilibrium rotational constants therefore depends
246 on the accuracy of this procedure.

247
248 To provide a description of the rotational motion that adheres to the real world, it is mandatory to
249 go beyond the rigid-rotor approximation and include centrifugal distortion (\tilde{H}_{04} , \tilde{H}_{06} , and even
250 higher-order terms)^{27,28} in the treatment. In the expression of the centrifugal-distortion terms, the
251 opportune power of the rotational angular momentum operator (which is expressed by the
252 subscript of \tilde{H}) multiplies the centrifugal distortion constants. For the computational determination
253 of the latter, different approximations of the PES entering the Hamiltonian are required: the
254 **harmonic [G]** part for the quartics (\tilde{H}_{04}) and an **anharmonic description [G]** for the sextics (\tilde{H}_{06}).
255 The tilde-sign denotes the result from a Hamiltonian reduction (interested readers are referred
256 to^{27,29}). It has to be noted that the Hamiltonian of Eq. 4 applies to the semirigid-rotor approximation
257 case (where the term “semirigid” implies the treatment of centrifugal distortion) and do not take
258 the effect of molecular vibrations into account. For a more accurate and realistic treatment, the
259 terms describing the vibration-rotation interaction need to be incorporated. These lead to the
260 description of the dependence of the rotational and centrifugal constants on the vibrational
261 quantum numbers.

262
263 The interactions of the molecular electric and/or magnetic fields with the nuclear or electron (for
264 open-shell species) moments introduce additional terms in the rotational Hamiltonian,²⁸ and are
265 responsible for the hyperfine structure in rotational spectra (these aspects are detailed later in the
266 text). It should be noted that some of these hyperfine interactions are at the basis of magnetic
267 spectroscopies such as nuclear magnetic resonance (**NMR [G]**)³⁰ and ESR^{30,31} for interaction with
268 nuclear and electron moments, respectively. Although a detailed analysis of those spectroscopies is
269 outside the scope of the present primer, they play a central role in the study of biological molecules
270 and transition metal complexes in condensed phases.^{32,33}

271 272 **[H3] 2.1.2. Vibrational and Vibronic Spectroscopy**

273 The terms of the vibro-rotational Hamiltonian of concern to vibrational spectroscopy are

$$274 \tilde{H}_{vib} = H_{20} + \tilde{H}_{30} + \tilde{H}_{40} + D \quad (\text{Equation 6})$$

275
276
277 where the last term D incorporates high-order pure vibrational terms as well as those representing
278 the interaction with the rotational motion (the so-called Coriolis couplings appearing among the
279 latter terms).^{23,34} The **rigid-rotor harmonic-oscillator model [G]** corresponds to the first term (H_{20}),
280 and allows to compute wavenumbers (ω) and intensities of the **fundamental bands [G]** (one-quanta
281 transitions from the vibrational ground state) based on second (quadratic) derivatives of energy
282 (quadratic force constants) and first derivatives of properties (e.g. dipole moment for IR spectra or
283 scalar product of electric and magnetic moment for vibrational circular dichroism, **VCD**³⁵ **[G]**).

284
285 While a harmonic description of the PES entering the vibro-rotational Hamiltonian allows for a
286 simplified description of the vibrational motion, a more realistic picture of the PES requires including
287 anharmonic corrections. However, this complicates the resolution of the corresponding Schrödinger
288 equation, thereby often resorting to perturbation theory. **Vibrational perturbation theory to the**

289 **second order [G]** (VPT2)^{36,37} offers a very effective solution since the energy levels for all vibrational
290 states can be computed from well-defined combinations of Coriolis couplings together with third
291 and semi-diagonal fourth energy derivatives with respect to **normal modes [G]** (χ_{ii} and χ_{ij}), leading
292 to the anharmonic wavenumbers for fundamentals, **overtones [G]**, and **combination bands [G]**.³⁸

293
294
$$\Delta E_i(0 - 1) = \nu_i = \omega_i + 2\chi_{ii} + \frac{1}{2}\sum_{i \neq j} \chi_{ij} \quad (\text{Equation 7})$$

295
$$\Delta E_i(0 - 2) = 2\omega_i + 6\chi_{ii} + \sum_{i \neq j} \chi_{ij} = 2\nu_i + 2\chi_{ij} \quad (\text{Equation 8})$$

296
$$\Delta E_{ij}(0 - 1, 0 - 1) = \omega_i + \omega_j + 2\chi_{ii} + 2\chi_{jj} + 2\chi_{ij} + \frac{1}{2}\sum_{k \neq i, j} (\chi_{ik} + \chi_{jk}) = \nu_i + \nu_j + \chi_{ij}$$

297 (Equation 9)

298
299 In analogy, anharmonic intensities can be obtained by a **double-perturbative approach [G]** in which,
300 for both energy and property, the terms beyond the second and first derivatives, respectively, are
301 treated as perturbations, with the unperturbed reference being the harmonic oscillator
302 Hamiltonian. Computationally, this model requires second- and semi-diagonal third derivatives of
303 the suitable property, with appropriate equations being derived up to three-quanta transitions.^{35,39-}
304 41

305
306 The most common way to derive the anharmonic PES and property surface (PS **[G]**) required for
307 VPT2 computations is based on numerical differentiation of the analytical second derivatives of the
308 energy and the first derivatives of the properties.^{34,42,43} However, energies and/or gradients can be
309 employed in numerical procedures⁴² and, for some electronic structure methods, fully analytical^{44,45}
310 derivations have also been reported. When taking into account resonance effects and/or decoupled
311 large amplitude motions by reduced-dimensionality variational approaches, this model is a very
312 effective working-horse for spectroscopic studies, in particular when dealing with medium- to large-
313 sized molecules.^{34,35,39} The more so as vibro-rotational couplings can also be written in terms of
314 energy and rotational constant derivatives, without any additional electronic energy computation.⁴⁶
315 In this connection, effective analytical first and second derivatives of methods rooted into the
316 density functional theory (**DFT [G]**) together with general purpose vibrational perturbation
317 implementations and reduced dimensionality models are allowing for reliable yet feasible
318 anharmonic computations of vibrational (IR, Raman) spectra of large systems and also of their chiral
319 counterparts (for example VCD). Noted is that semi-diagonal third-energy derivatives with respect
320 to normal modes are sufficient to evaluate also first-order vibrational modulation effects on other
321 spectroscopic parameters (e.g. optical activity, hyperfine tensors, etc.).

322
323 Together with perturbative approaches, alternative methodologies are possible such as, e.g.
324 vibrational self-consistent field (VSCF),⁴⁷ vibrational configuration interaction (VCI),⁴⁸ or vibrational
325 coupled clusters (VCC).⁴⁹ However, despite recent efforts,⁵⁰ they remain much more difficult to
326 translate into black-box procedures to be used also by non-specialists.

327
328 Moving to vibronic spectroscopy (vibrational transitions between different electronic states, see
329 Figure 1), vibrational signatures of one-photon absorption (**OPA [G]**) and one-photon emission (**OPE**
330 **[G]**) spectra including chiroptical ones (e.g. electronic circular dichroism, **ECD [G]**) and resonance
331 regimes (Resonance Raman) are defined by the overlaps between vibrational wavefunctions of the
332 initial (*I*) and final (*F*) electronic states ($\langle \Psi_F(\tau) | \Psi_I(\tau) \rangle$).⁵¹ Small amplitude vibrations can be
333 effectively analyzed by harmonic models,^{52,53} which take into account the difference between the
334 normal modes description in the initial (q_I) and final (q_F) states by using the Shift vector, **K**, and the
335 Duschinsky rotation matrix,⁵⁴ **J**):

336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355

$$q_I = Jq_F + K \quad (\text{Equation 10})$$

Strong, bright electronic transitions can be simulated in terms of equilibrium transition dipole moments, d_{IF} (Franck-Condon approach^{55,56}), whereas inclusion of the transition dipole moment first derivatives with respect to normal coordinates becomes mandatory for forbidden or weakly-allowed transitions (Herzberg-Teller term⁵⁷):

$$[d_{IF}^{eq} \langle \Psi_F(\tau) | \Psi_I(\tau) \rangle]^{FC} + \left[\sum_n \frac{\delta d_{IF}^n}{\delta q} \langle \Psi_F(\tau) | \Psi_I(\tau) \rangle \right]^{HT} \quad (\text{Equation 11})$$

with the sum over n (in the second term) running over the $3N-6$ normal coordinates ($3N-5$ for linear molecules, N being the number of atoms of the molecule). Finally, for flexible molecular systems internal (in place of cartesian) coordinates must be employed whenever curvilinear effects cannot be neglected (as it is usually the case for low-frequency modes like, e.g., torsions, inversions or ring puckerings),^{58,59} and possibly also integrated with one-dimensional variational models for decoupled large amplitude motions⁶⁰. The considerations above are limited to those cases where the BO approximation applies. More advanced treatments, also including non-adiabatic contributions, are needed for more involved situations (e.g. near conical intersections).

A sketch of the main spectroscopic techniques, which can be reliably simulated in this framework is given in Figure 2, while for additional tutorial and review see refs.^{34,61,62}

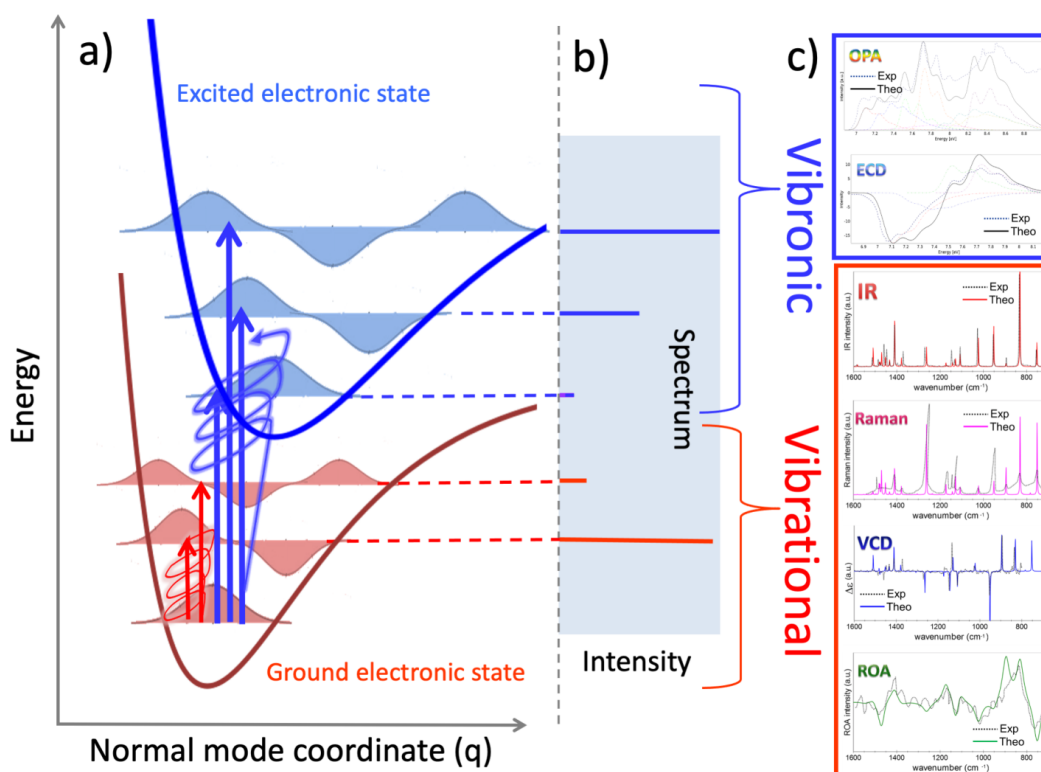


Figure 2. General theoretical framework for vibrational and vibronic spectroscopies, and their chiral counterparts. Panel (a): schematic representation of the ground (red) and excited (blue) electronic state PESs, vibrational energy levels and wavefunctions. The energy scale underestimate gap between the two electronic states. Straight arrows represent transitions from the vibrational ground state: vibrational (red; IR and Raman) and vibronic (involving both states, blue; OPA). Circled arrows stand for the interaction with circularly polarized light corresponding to VCD (red), ROA (red) and ECD (blue) spectroscopies. Panel (b): schematic representation of resulting vibrational and vibronic line positions and corresponding intensities. Panel (c): examples of simulated and experimental spectra from refs.^{17,35}.

[H3] 2.1.3. Chiral Spectroscopy

The chiral spectroscopic techniques addressed in this Primer are limited to optical rotation (OR), ECD and VCD, as well as Raman optical activity (ROA [G]). OR and ECD arise from the differential refraction and absorption, respectively, for left and right circularly polarized light and are associated with electronic transitions. Optical rotatory dispersion (ORD [G]) is the wavelength dependence of the OR. VCD and ROA arise from the differential absorption and scattering, respectively, for left and right circularly polarized light and are associated with vibrational transitions. The approximations and models related to the vibrational wavefunctions and their overlaps are the same as described in the previous section (2.1.2).

ORD is determined by the electric dipole – magnetic dipole polarizability, which is computed using linear response methods as implemented in different QC software packages.⁶³⁻⁶⁵ Specifically, QC programs report the specific rotation at each incident frequency in units of degrees $\text{dm}^{-1} (\text{g/mL})^{-1}$, which can then be compared directly with the experiment. ECD and VCD are determined by the dipole and rotational strengths of electronic or vibrational transitions, respectively, which are related to the scalar products of the electric dipole and magnetic dipole transition moments. For VCD, these are computed using linear response methods at either the harmonic^{1,66,67} or anharmonic³⁵ level. The experiments measure the differential absorbance for left and right circularly polarized light, which is typically converted to the differential molar extinction coefficient $\Delta\epsilon$ (in units of $\text{M}^{-1} \text{cm}^{-1}$), which is related to the absorbance through Beer's Law⁶⁸. Since experimental band-shapes of VCD spectra are most frequently Lorentzian while the experimental band-shapes of ECD spectra tend to be Gaussian, the appropriate line-shape function [G] is added to the calculated $\Delta\epsilon$. For more detail and the relevant conversions, the reader is referred to^{1,66,69} for VCD and^{69,70} for ECD.

ROA is determined by electric, magnetic, and quadrupole polarizability transition moments of vibrational transitions that are computed using linear response methods at either the harmonic^{67,71,72} or anharmonic³⁵ level. In the far-from-resonance theory, where the exciting laser radiation is far from the lowest allowed electronic excited state, ROA intensity differences are determined by three tensor invariants constructed as linear combinations of products of these polarizability tensors.^{1,69,73,74} Depending on the choice of polarization modulation and scattering geometry, several forms of ROA are obtained, although the most common is back scattered circular polarization denoted as SCP(180). QC programs report the ROA scattering activities for a particular experimental setup, which are then converted to a differential scattering cross section which includes a factor of $(\nu_{inc} - \nu_i)^4$, where ν_{inc} and ν_i are the wavenumbers for the incident frequency and mode i , respectively^{69,75,76} Since experimental band shapes are typically Lorentzian, calculated spectra are plotted using the Lorentzian line-shape function. As absolute ROA intensities are not typically measured, it is common practice to label the intensity differences as $I_R - I_L$, as is done for the experimental spectra.

[H3] 2.1.4. Diffusion Monte Carlo (DMC)

An alternative to conventional time-independent computational approaches to rotational and vibrational spectroscopy is offered by propagation of the time-dependent Schrödinger Equation as

$$|\Psi(\tau)\rangle = \sum_n c_n e_n^{-\tau(E_n - V_{\text{ref}})} |\phi_n\rangle \quad (\text{Equation 12})$$

where $|\phi_n\rangle$ is an eigenstate of the Hamiltonian, with energy E_n ⁷⁷⁻⁸⁶ and $\tau = it/\hbar$. When we propagate an arbitrary wave function in imaginary time, at long times the leading contribution to

404 the wave function will be the ground state. Further, if $V_{\text{ref}} = E_0$, the amplitude of the wave function
 405 will remain constant. The advantage of DMC approaches over conventional approaches comes in
 406 the representation of the wave function. In the simplest implementation of diffusion Monte Carlo,
 407 $|\Psi(\tau)\rangle$ is represented by an ensemble of localized functions, $g(\mathbf{x} - \mathbf{x}_i)$,

408

$$409 \langle \mathbf{x} | \Psi(\tau) \rangle = \sum_i w_i(\tau) g(\mathbf{x} - \mathbf{x}_i) \quad (\text{Equation 13})$$

410

411 At each time step in the simulation, each of the components of each of the \mathbf{x}_i is displaced by a
 412 random value based on Gauss-random distributions, where the distribution for the j th atom has a
 413 width of $\sqrt{\frac{\Delta\tau}{m_j}}$, where m_j represents the corresponding mass. After the atoms are displaced, the
 414 potential energy is evaluated, and the weight $w_i(\tau)$ is adjusted according to

415

$$416 w_i(\tau + \Delta\tau) = e^{(V(\mathbf{x}_i) - V_{\text{ref}})\Delta\tau} w_i(\tau) \quad (\text{Equation 14})$$

417

418 This relatively simple algorithm provides a Monte Carlo sampling of the ground state wave function
 419 for the molecule of interest based on the provided potential surface as well as the ground state
 420 energy. By propagating the ensemble forward in time we can obtain the information required to
 421 generate the ground state probability amplitude.^{84,87} Such information allows us to explore how the
 422 molecule samples the potential and evaluate, for example, rotational constants for obtaining
 423 rotational spectra. Finally, energies and wave functions for rotation or vibrationally excited states
 424 can be obtained using this approach by imposing a nodal structure for these states.^{86,88,89} The major
 425 advantage of DMC over more conventional approaches is that it allows a way to explore the role of
 426 nuclear quantum effects in systems where the ground state wave function is delocalized among
 427 multiple local minima on the potential surface. These are situations where approaches, like
 428 perturbation theory, become less effective.

429

430

431 [H2] 2.2. Software for computational spectroscopy

432 Some available QC packages together with their potentialities and main features are provided in
 433 Table 1.

Table 1. Selection of common software packages for computational spectroscopy applications: QC methodologies and main spectroscopic features.		
Software package	Methodology	Spectroscopic applications
CFOUR http://www.cfour.de/ [academic]	CC theory / MP2 (analytic 2 nd derivatives) CC composite schemes	Rotational spectroscopy: all parameters Vibrational spectroscopy: VPT2 NMR/ESR spectroscopies: all parameters
Gaussian https://gaussian.com/ [commercial]	DFT/TD-DFT/MP2 (analytic Hessians) CCSD(T) energies QM/QM'/MM/PCM	Rotational spectroscopy: all parameters Vibr. Spectroscopy: IR, Raman, VCD, ROA Electr. Spectroscopy: UV-Vis, ECD, RR, RROA NMR/ESR spectroscopies: all parameters
Molpro https://www.molpro.net/ [commercial]	CC and explicitly correlated CC Multireference methods DFT/TD-DFT	Rot. Spectroscopy: equilibrium rot. constants Vibrational Spectroscopy: VSCF/VCI
NWCHEM https://nwchemgit.github.io/ [academic]	CC theory energies MP2 analytical gradients DFT/TD-DFT QM/MM COSMO/SMD/VEM	Rot. spectroscopy: equilibrium rot. constants Vibration spectroscopy: VSCF energies Electr. Spectroscopy: UV-Vis NMR: shielding tensors and indirect spin-spin coupling

ORCA https://orcaforum.kofo.mpg.de/app.php/portal [academic]	CC and explicitly correlated CC Local correlation methods Multireference methods DFT/TD-DFT QM/MM, Embedding schemes Implicit solvation	Rot. Spectroscopy: equilibrium rot. constants Vibr. Spectrosc.: IR, Raman, res. Raman, NRVS Electr. Spectroscopy: UV-Vis, ECD, MCD, Fluorescence, Phosphorescence, Band shapes NMR/ESR spectroscopies: all parameters X-ray absorption/emission, RIXS, Mössbauer
QChem http://www.q-chem.com/ [commercial]	CC theory (ground and excited states, spin-flip methods), MP2/ADC schemes (energies and gradients) DFT/TD-DFT QM/MM PCM	Rot. spectroscopy: equilibrium rot. constants Vibrational spectroscopy: IR/Raman, anharmonic energies TOSH, VPT2, VCI Electronic Spectroscopy: UV-Vis, RR
PSI4 http://www.psicode.org [academic]	CC /MP2 CCSD(T) gradients CC/MP2 composite schemes for energies, gradients and Hessians DFT/TD-DFT Solvent via external codes	Spectrosc. constants for diatomics from PES fit Rot. spectroscopy: equilibrium rot. constants Vibrational spectroscopy: harmonic models, Electronic Spectroscopy: UV-Vis, OR

434

435

[H2] 2.3. Computational requirements

436

The computational requirements strongly depend on the type of spectroscopic technique under consideration and the accuracy specifically required.

437

438

439

440

441

442

443

444

445

446

447

448

449

450

451

452

453

454

455

456

457

458

459

460

461

462

463

464

In the case of rotational and vibrational spectroscopies, the leading properties to be accurately computed are the equilibrium rotational constants (which means equilibrium structure determinations) and the harmonic frequencies (which implies harmonic force-field evaluations), respectively. To obtain accurate results, one has to put effort on the electronic structure calculations, the key point being to reduce as much as possible the errors due to the truncation of both basis set (one-electron error) and wavefunction (N-electron error). To achieve this goal, composite schemes have been set up: these evaluate the contributions important to reach high accuracy at the best possible level and then combine them through the additivity approximation (see, e.g., refs. ⁹⁰⁻¹⁰²). These usually involve the **coupled-cluster (CC) theory [G]** ¹⁰³ and in particular the **CC single and double excitations and a perturbative treatment of triples (CCSD(T)) [G]** method¹⁰⁴, which is often denoted as the “gold standard” for accurate calculations. On the other hand, the introduction of explicitly-correlated (F12) treatments¹⁰⁵ allows for partially recovering the one-electron error without extrapolation techniques. The development of local-correlation treatments based on pair natural orbital (**PNO [G]**)^{106,107} allows instead for improving the scaling of coupled cluster treatments with the number of electrons.

From a computational point of view, going beyond the rigid-rotor harmonic-oscillator approximation increases the complexity and the cost of electronic structure calculations, thus requiring a reduction of the level of theory for the electronic computations as well as the introduction of approximations for the solution of the nuclear problem. Concerning the former issue, **global-hybrid or double-hybrid density functionals**¹⁰⁸⁻¹¹⁰ **[G]** provide an optimal alternative to low-cost ab initio methodologies such as the Møller-Plesset theory to second order (MP2)¹¹¹, while VPT2 offers a powerful tool for the latter. The definition of hybrid coupled cluster/density functional theory (CC/DFT) models, employing anharmonic corrections and/or property predictions beyond the electric dipole moment from DFT, have been shown to represent nearly optimal compromises between feasibility and accuracy.^{35,112,113}

465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512

However, application of DFT approaches to computational spectroscopy studies requires careful benchmarking of all the required properties. Unfortunately, most of the benchmark studies reported so far have been focused on the accuracy of energetic properties, for selected equilibrium structures,¹¹⁴⁻¹¹⁷ whose conclusions cannot be directly transferred to assess the accuracy of wider regions of the PES (1) or other properties (2).^{62,118-120} Concerning the issue 1, flexible systems (like, e.g., most biomolecules) are governed by flat potential energy surfaces, whose behavior cannot be described in terms of the well-separated energy minima within nearly-harmonic basins, which have been considered in most benchmarks. Focusing on point 2, the interpretation of important spectroscopic techniques requires properties (e.g. magnetic dipole moments for chiroptical techniques), whose computation has -however- not yet been validated in a comprehensive way. Moreover, often second and higher analytical derivatives (of energy and properties) are not implemented for some of DFT models, hampering their application in computational spectroscopy studies. As a matter of fact, only a limited number of functionals and basis sets have been benchmarked for geometric structures,¹²⁰⁻¹²⁶ anharmonic vibrational frequencies,^{62,118,119,126,127} and other spectroscopic properties.^{119,126} The situation is less advanced for excited electronic states, but the first benchmark studies going beyond vertical excitation energies have been reported^{128,129}. Moreover, the recent implementation of analytical TD-DFT Hessians allows more efficient VPT2 computations for excited electronic states of medium- to large-sized molecules.¹³⁰ A more reliable, but much more computationally expensive alternative to DFT is offered by highly accurate Equation-of-Motion-CC (EOM-CC [G])¹³¹. Nevertheless, despite the successful applications of these approaches, multireference (MR) methods¹³² cannot be avoided whenever **nondynamic (static) correlation [G]** is important. Indeed, MR methods being based on wave functions described by the linear combination of several electronic configurations are able to well address strong correlation effects. We note in passing that modern linear or low-order scaling local correlation methods (based on MP2 or CCSD(T)) have found increasing use in quantum chemistry and also in theoretical spectroscopy¹³³⁻¹³⁵ However, a more detailed description of these aspects is out of the scope of this Primer.

The most generally applicable methods in transition-element theoretical spectroscopy (see section 4.3) are based on traditional¹⁸ or more recent (e.g. **density matrix renormalization group [G]**, DMRG¹³⁶) multireference wavefunction based theories. These methods can now be routinely applied to larger molecules (100-200 atoms). While they have been used extensively in form of, for example, complete active space perturbation theory to second order (**CASPT2 [G]**)^{137,138} or N-electron valence state perturbation theory to second-order (**NEVPT2 [G]**)¹³⁹, severe limitations still exist that will provide incentive for method developers for decades to come. A more thorough description of these approaches and their strengths and weaknesses is outside the scope of this Primer.

A non-exhaustive summary of the computational evaluation of spectroscopic parameters is provided in Table 2, where - for each spectroscopic technique considered in this Primer - the (best) accuracy obtainable, the type of computation required as well as the level of theory and the affordable dimension of the system are collected. Noted is that this table is based on analytical derivative techniques, which means that further extensions in terms of properties and levels of theory can be reported.

[bH1] Table 2. QC methodologies for the evaluation of spectroscopic parameters and associated accuracy.					
Spectroscopy	Spectroscopic parameters	Accuracy	QC calculations	QC methodology & feasible number of atoms	
				Wave function	DFT
Magnetic	<ul style="list-style-type: none"> Chemical Shifts Spin-Spin Coupling g-tensor Zero-Field splitting Hyperfine coupling Quadrupole coupling Magnetizability 	Moderate; Variable for different nuclei	Response property calculation for imaginary and triplet perturbations	CCSD(T) < 10 Local CCSD(T) <200 (Local) MP2 < 200 HF < 1000	GGA < 2000 Hybrid < 1000 Double hybrid < 100
Nuclear	<ul style="list-style-type: none"> Mössbauer NRVS 	10 ⁻⁹ eV <10%	Isomer shift, Quadrupole splittings, low-energy vibrational modes	CCSD <10 DLPNO-CCSD < 100	DFT < 1000
Rotational	<ul style="list-style-type: none"> Rotational constants Equilibrium Vibrationally corrected 	<0.1% - 0.5% 0.1% - 2%	Geometry optimization (minimum of the PES) Anharmonic force field (2 nd and 3 rd energy deriv.)	Composite schemes < 30 MP2 < 20 CCSD(T) < 10	Hybrid > 100 Double-hybrid < 100 Hybrid < 100 Double-hybrid < 20
	<ul style="list-style-type: none"> Centrifugal (quartic) distortion constants 	<1%	Harmonic force field	Composite schemes < 15	Hybrid <30 Double-hybrid < 20
Vibrational	<ul style="list-style-type: none"> Vibrational freq. Harmonic 	1-20 cm ⁻¹	Harmonic force field	Composite schemes < 15 MP2 < 20 CCSD(T) < 10	Hybrid < 400 Double-hybrid < 50 Hybrid < 50 Double-hybrid < 20
	<ul style="list-style-type: none"> Anharmonic (VSCF/ VCI/ VPT2) 	1-10 cm ⁻¹	Anharmonic contributions (3 rd + 4 th energy derivatives)		
	<ul style="list-style-type: none"> IR/Raman intensities Harmonic Anharmonic 	10 km mol ⁻¹ 5 km mol ⁻¹	dipole mom./polarizability: 1 st der. wrt to nucl. coord. dipole mom./ polarizability: 2/3 der. wrt to nucl. Coord	Composite schemes < 15 MP2 < 20 CCSD(T) < 10	Hybrid < 100 Double-hybrid < 50 Hybrid < 50 Double hybrid < 20
	<ul style="list-style-type: none"> VCD/ROA intensities Harmonic Anharmonic 	10-30%	Magnetic moments: 1 st der. wrt to nucl. coord. Magnetic moments: 2/3 der. wrt to nucl. coord.		Hybrid < 100 Hybrid < 50
Vibronic	<ul style="list-style-type: none"> Electronic energy 	0.1 -0.5 eV	Initial - final state energy difference between	MRCI, ADC EOM-CCSD <50 DLPNO-STEOM-CCSD < 150	TD-DFT < 200 TDA < 2000
	<ul style="list-style-type: none"> Ground state equilibrium structure, normal modes and frequencies 	(see Rotational and Vibrational)			
	<ul style="list-style-type: none"> Excited electronic state equilibrium structure 	0.02-0.1 Å	Geometry optimization (minimum of the PES)	ADC(2) <50 EOM-CCSD, CC3 <15	TD-DFT < 100 TDA < 200
	<ul style="list-style-type: none"> Excited electronic state normal modes and Harmonic frequencies Anharmonic frequencies 	30 cm ⁻¹ 10 cm ⁻¹	Harmonic force field (analytical or numerical differentiation of analytical gradient) Anharmonic contributions (3 rd + semi-diag. 4 th deriv.)	EOM-CCSD < 20 MRCI, EOM-CCSD < 6	TD-DFT < 100 TDA < 200 TD-DF T <20
	<ul style="list-style-type: none"> OPA/OPE/ECD 	0.2 eV	Electric and/or magnetic transition moment	EOM-CCSD, CC3 < 15	TD-DFT < 100 TDA < 200
	<ul style="list-style-type: none"> FC/HT 	0.05 eV	Transition moment derivatives		TD-DFT < 100
X-ray	<ul style="list-style-type: none"> K-edge absorption L-edge absorption K-beta emission RIXS 	1 eV 10% relative intensity	Excitation energies Multipole transition moments	EOM-CCSD < 20 MRCI < 10 NEVPT2 < 200 (RO-)CIS < 1000	TD-DFT < 1000

[H1] 3. Results

In this section a few spectroscopic techniques have been selected to provide examples of how to process, treat and interpret spectroscopic data, specifically for spectroscopies involving rotational and vibrational motions.

[H2] 3.1. Rotational Spectroscopy for structural information

Despite the fact that rotational spectroscopy is the technique of choice for structural determinations, such derivations are seldom straightforward. Indeed, extracting geometrical parameters from the experimental information (rotational constants) is hampered by the number of data (rotational constants) actually available and vibrational effects.⁶ The fruitful interplay of high-resolution spectroscopy and QC allows for overcoming such difficulties, thereby exploiting a semiexperimental approach.

The semiexperimental approach leads to equilibrium structures (i.e., by definition, the geometries corresponding to minima on the PES) by least-squares fitting the structural parameters to the semiexperimental equilibrium rotational constants ($B_{i,e}^{SE}$), which are determined by subtracting the computed vibrational corrections ($\Delta B_{i,0}^{calc}$) from the experimental (vibrational) ground-state rotational constants ($B_{i,0}^{exp}$):⁶

$$B_{i,e}^{SE} = B_{i,0}^{exp} - \Delta B_{i,0}^{calc} = B_{i,0}^{exp} + \frac{1}{2} \sum_n \alpha_i^n \quad (\text{Equation 15})$$

where i denotes the principal inertial axis (a, b or c; so that $B_{i=a} = A$); the α_i^r are the so-called vibration-rotation interaction constants and the sum is taken over all fundamental vibrational modes n .²⁸ As evident from Eq. 15, resorting to equilibrium rotational constants allows to get rid of vibrational effects (via the subtraction of the vibrational corrections). To overcome the limitation of the number of experimental data (for a given isotopologue, there are at most three rotational constants), different isotopic species are considered. In fact, these share the same equilibrium structure because, within the BO approximation, the PES of a given molecule is isotope independent. At the same time, they have different equilibrium rotational constants (because they depend on the equilibrium structure and on the isotopic masses), thus increasing the amount of experimental data. A sufficient number of isotopic species is required to have enough information for a complete structural determination (i.e. to have more data than geometrical parameters). This procedure is graphically described in Figure 3. Vice versa, high-level QC calculations allow accurate predictions of the rotational parameters¹⁴⁰ to be used for planning, guiding, and interpreting experiment.³⁴ Such an interplay can be enhanced by exploiting graphical tools able to visualize, compare and manipulate spectra as well as to handle their assignment.¹⁴¹

While these accomplishments are well established for small to medium-sized, semi-rigid molecules (such as those shown in Figure 3), the situation is more involved for larger (and usually less rigid) molecular systems. In recent years, thanks to the introduction of laser ablation vaporization¹⁴² and broadband⁹ techniques, the targets of spectroscopic studies have been shifting towards flexible molecules as well as non-covalent molecular complexes involving more than two molecules, both categories being characterized by a large number of closely spaced energy minima (conformers or isomers), all contributing to the overall spectrum. Therefore, a correct analysis of the latter requires the knowledge of the rotational spectra of all isomers and/or conformers present in the gas-phase mixture. Then, by weighting each contribution according to its population, the overall rotational

561 spectrum is obtained. Therefore, an incomplete account of conformers [G] can easily generate an
 562 unsatisfactory modeling; the situation is similar to the case of a wrong equilibrium structure
 563 determination when considering a semi-rigid molecule. To overcome these difficulties, powerful
 564 unsupervised techniques (such as machine learning algorithms) for the exploration of the degrees
 565 of freedom associated to the large amplitude motions are required.¹⁴³
 566

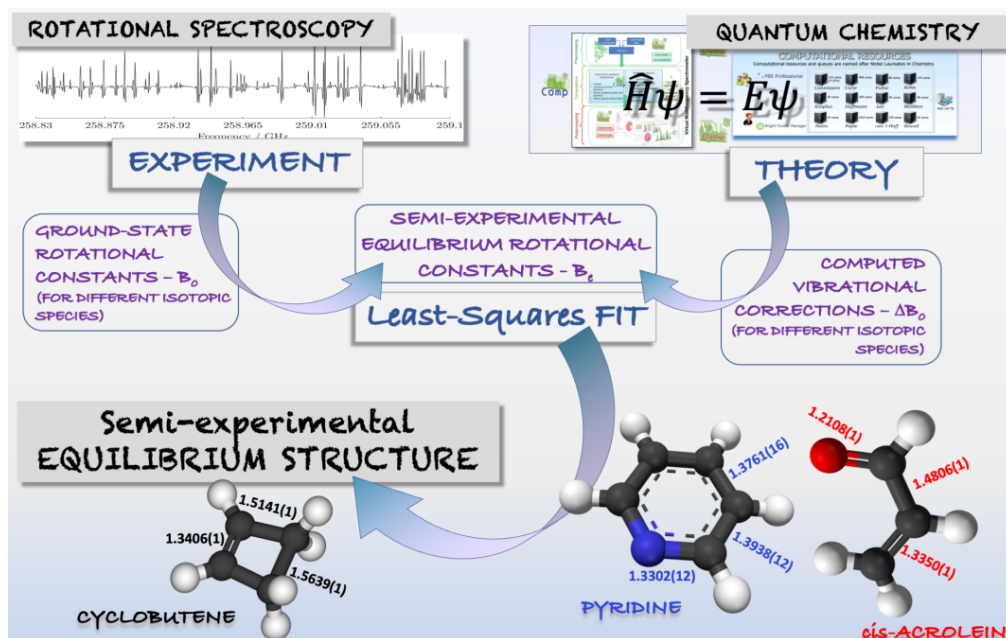


Figure 3. Schematic representation of the interplay of experiment and theory in rotational spectroscopy for the determination of molecular structure. Experimental vibrational ground-state rotational constants are computationally corrected for vibrational effects. The resulting semi-experimental equilibrium rotational constants for different isotopic species allow for the determination of the equilibrium structure.

567
 568 **[H2] 3.2. Vibrational/vibronic spectroscopy of flexible systems**
 569

570 The simplest approach to vibrational spectroscopy is based on the double harmonic approximation,
 571 which employs quadratic and linear approximations for the PES (for transition frequency) and PS
 572 (for intensity), respectively. This tool is available in several electronic structure QM codes, and it
 573 becomes extremely efficient whenever analytical energy second derivatives and property gradients
 574 are available. Mechanical (PES) and electric/magnetic (PS) anharmonicities can be introduced by
 575 means of perturbative^{34,35,39-41,43} or variational^{34,47,48,144-146} time-independent (TI) approaches. The
 576 first route, despite some limitations (e.g. the proper treatment of large amplitude motions, LAMs
 577 [G]), allows for a general and robust simulation of spectral line-shapes and vis-à-vis comparisons
 578 with experimental outcomes.^{35,39-41,61} Integration of both models within a general platform
 579 simultaneously allows the correct treatment of small amplitude motions [G] (SAMs) and LAMs¹⁴²
 580 Spectral simulation, analysis, and comparison with experiment can be greatly facilitated by
 581 dedicated graphical tools like, e.g., the Virtual Multifrequency Spectrometer (VMS).⁶¹
 582

583 In TI models, structures and properties of energy minima and their local environments are employed
 584 in variational or perturbative formalisms mostly exploiting the Watson Hamiltonian³⁴ (given in
 585 Equation 3 and discussed in section 2.1). In time-dependent (TD) approaches, classical or semi-
 586 classical dynamics simulations are performed over the whole PES and the corresponding PS.¹⁴⁷⁻¹⁴⁹
 587 The two approaches (TI and TD) offer complementary information and the selection of the most
 588 appropriate strategy depends on several factors, including the environment (e.g. TI models are more

589 suitable for isolated molecules and TD ones for condensed phases), the effective mass governing
590 the motion (e.g. classical TD models are more effective for large masses), and other effects. For
591 flexible molecular systems, harmonic models based on curvilinear coordinates⁵⁸ should be used; for
592 systems with several low-lying conformers/tautomers, appropriate averaging of individual spectra
593 must be performed. Analogously to rotational spectroscopy, the presence of several low-lying
594 conformers/tautomers can tune the overall spectrum, thus requiring appropriate conformational
595 searches and weighting of the spectra of the most stable structures by the corresponding Boltzmann
596 populations.¹⁵⁰ In the case of solutions, for innocent solvents (that is solvents that do not establish
597 specific interactions like, e.g., hydrogen bonds), solvatochromic effects can be incorporated at a
598 negligible cost by means of the polarizable continuum model (PCM [G])³⁴, while - in more complex
599 cases - at least solvent molecules in the cybotactic [G] region must be explicitly included.¹⁵¹

600

601 Moving to vibronic spectroscopy, absorption or emission electronic spectra are the envelopes of
602 specific vibrational levels of the initial and final electronic states. However, most of the current
603 computations still employ rough phenomenological models in which vertical transition energies are
604 broadened by empirical Gaussian or Lorentzian functions. Moreover, the analysis of experimental
605 data is often based on the assumption that the peak maxima are related to the so-called 0-0
606 transition (transition between vibrational ground states of initial and final electronic state).
607 However, it is impossible to know *a priori* which vibronic transition will be most intense, as it
608 depends on the largest overlap of vibrational wavefunctions. Therefore, realistic simulations must
609 take into account vibrational effects. In the Franck-Condon approximation the transition dipole
610 moment (Eq. 11) is considered constant (i.e. nuclear-coordinate independent) in harmonic TI (sum-
611 of-state)⁵² or TD (path-integral)⁵³ approaches. The simplest formulation, based on one-dimensional
612 vibrational overlaps between (a possibly reduced number of) identical normal modes for the
613 different electronic states, is still employed in several studies and is also exploited in the
614 prescreening procedure for more sophisticated TI computations.⁵¹ While more accurate, direct
615 nuclear dynamics simulations are prohibitive for large systems and, as such, the most advanced
616 models employing highly accurate potential energy and property surfaces (PES and PS) can only be
617 applied to small-sized molecules.¹⁴⁴⁻¹⁴⁶ Integration of TI and TD models within a general platform
618 allows at the same time simulations of highly resolved spectra (including band assignments) and full
619 convergence of spectra at finite temperatures. For more complex, flexible systems several
620 approximate yet sufficiently accurate approaches have been proposed^{34,152-154} for both vibrational
621 and vibrationally-resolved electronic spectra.

622

623 [H3] 3.2.1 The MI-IR spectrum of glycine

624 A step-by-step route from the starting harmonic computations to the final realistic simulated
625 spectra is presented in Figure 4 for glycine (H₂NCH₂COOH), the simplest amino acid. Glycine is
626 characterized by conformational flexibility due to the rotation along three single bonds: N-C, C-C
627 and C-O. The small size of the molecule allows for a full theoretical exploration of its conformational
628 space, which confirmed the presence of eight local minima,^{113,120,155} labelled by roman numbers
629 referring to their stability order, with "p,n" describing the planarity or non-planarity of the
630 backbone, and "c,g,t" the cis, gauche or trans orientation of the lone-pair(N)-N-C-C, N-C-C-O, and C-
631 C-O-H dihedrals.

632

633 The six most stable conformers have been studied by means of Fourier transform infrared (FTIR)
634 spectroscopy with three of them detected under the same experimental conditions.¹⁵⁶⁻¹⁵⁸ Figure 4
635 compares the computed spectra with FTIR results for glycine deposited in a low-temperature matrix.
636 The most intense experimental bands can be identified based on the harmonic spectrum of the most

637 stable conformer Ip. An improvement (a more realistic spectrum) is obtained by including
 638 anharmonic corrections to band positions and intensities, with the consequent appearance of
 639 several new bands (non-fundamental transitions). The best agreement with experiment is obtained
 640 once the contributions from IIn and IIIp conformers, weighted for their Boltzmann populations, are
 641 added. Fully anharmonic spectra allow to distinguish between low-intensity bands related to non-
 642 fundamental transitions of the most abundant conformer (not present at harmonic level) and the
 643 fundamental transitions of the less abundant ones (see ref. ¹¹³ for detailed discussion and analysis).
 644

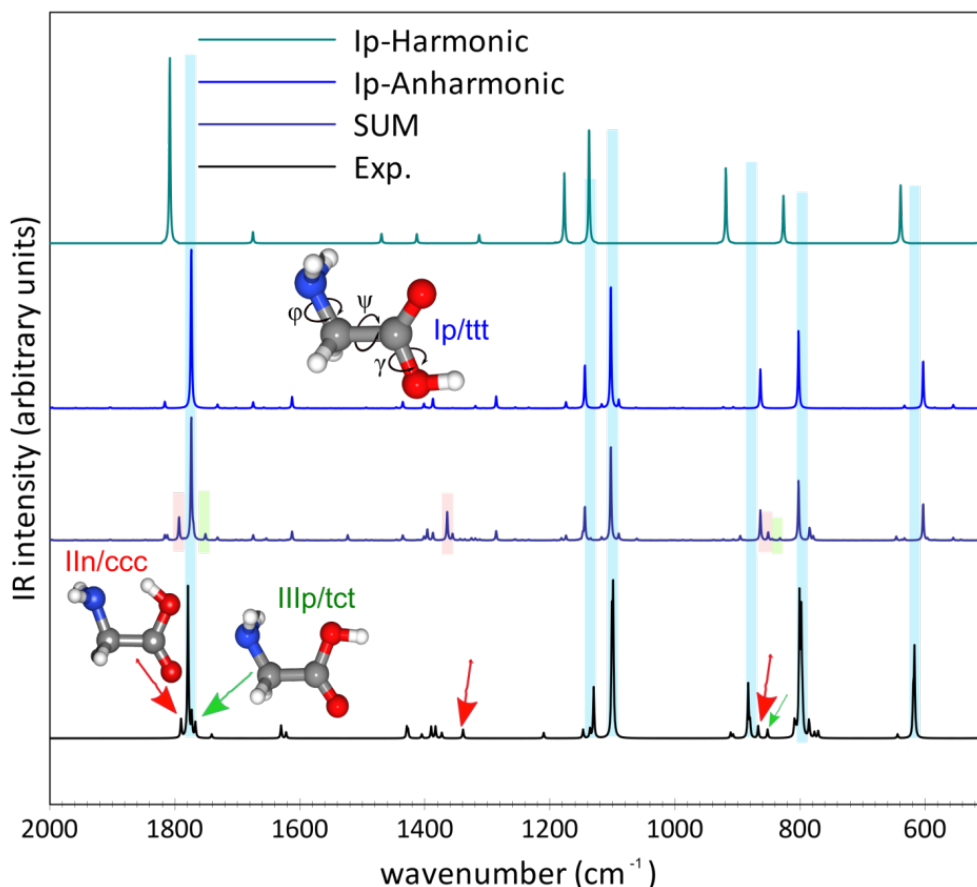


Figure 4. Computed¹¹³ and experimental¹⁵⁷ MI-IR spectra of glycine. Simulated harmonic and anharmonic theoretical spectrum of the most stable Ip conformer together with the final spectrum resulting from the sum of the contributions of Ip/ttt, IIn/ccc and IIIp/tct conformers, weighted for their relative abundances, at 410 K (temperature of the sample preparation), also assuming the conformational cooling of less stable conformers.

645

646 [H3] 3.2.2 Vibronic spectrum of chlorophyll-a

647 In general terms, vibronic spectra simulations are necessary to distinguish different contributions
 648 to the spectrum line-shape from different electronic transitions, conformers, or other species
 649 possibly present in the experimental mixture, for instance as photoproducts.¹⁵⁹ As an example, the
 650 UV-vis spectrum of chlorophyll-a in methanol solution (Figure 5) has been simulated considering
 651 environmental effects by means of hybrid implicit/explicit solvent model with the two methanol
 652 molecules coordinating the Mg ion and the bulk solvent effects accounted for using the PCM (see
 653 ref. ¹⁶⁰ for the details, and ref. ¹³⁵ for the gas-phase spectrum simulation).
 654

655 The spectra of chlorophylls are traditionally described in terms of four bands, based on the
 656 simplified four-orbital Gouterman model:¹⁶¹ two low-energy Q-bands and two high energy Soret (B)
 657 bands. The additional x/y labeling, according to the direction of their polarization within a
 658 macrocycle plane,¹⁶² can also (as in this case) be used. The top panel demonstrates how the set of

659 vibronic transitions defines the asymmetric shape of the lowest energy $S_1 \leftarrow S_0$ transition, which
 660 cannot be well described by the simplest vertical energy approach, irrespective of the applied
 661 broadening. This transition dominates the Qy band, but gives also a significant contribution to the
 662 Qx one. The final spectrum, which can be directly compared with the experimental one in the whole
 663 UV-vis range, is obtained from the single $S_x \leftarrow S_0$ ($x=1-8$) transition contributions. Simulation of
 664 vibronic spectra allows for the unequivocal assignment of the main spectral features, showing that
 665 the line shape is dominated by two pairs of overlapping transitions: $S_1 \leftarrow S_0$ and $S_2 \leftarrow S_0$ being the first
 666 pair and $S_3 \leftarrow S_0$ $S_4 \leftarrow S_0$ the second one. These pairs give rise to the Qy/Qx and By/Bx bands,
 667 respectively.
 668

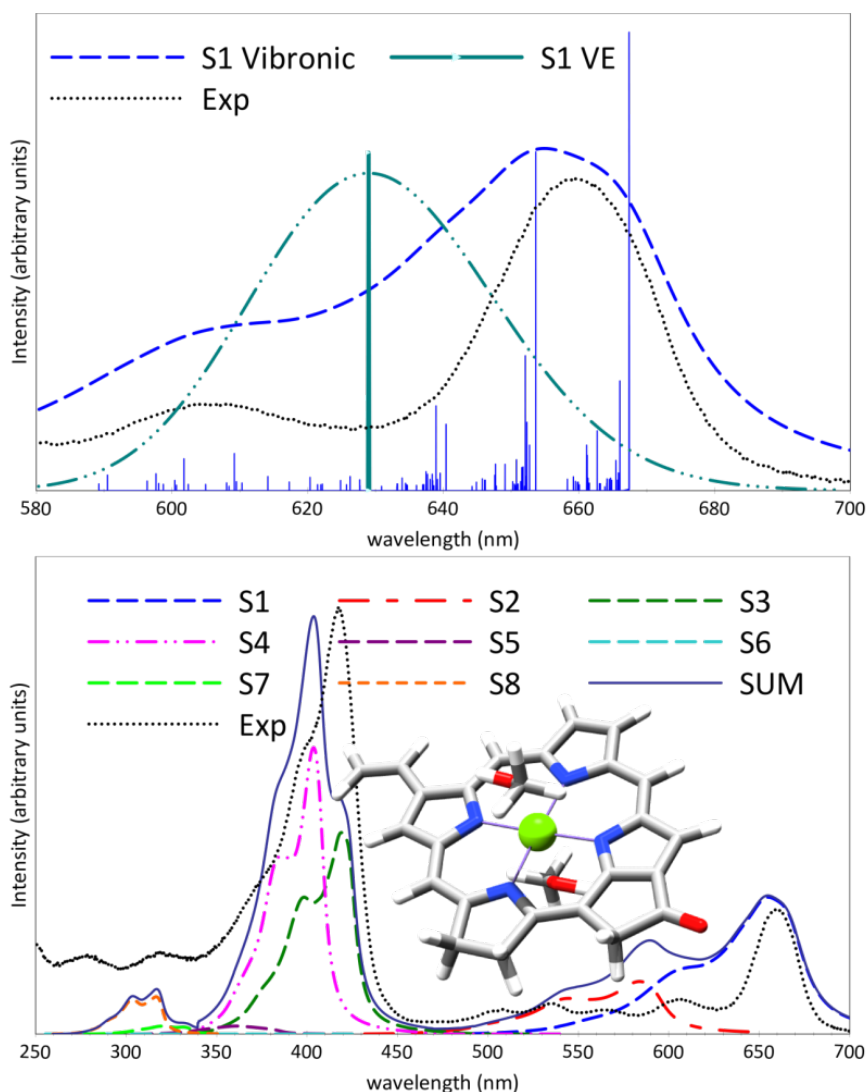


Figure 5. Computed¹⁶⁰ and experimental¹⁶³ UV-vis spectrum of chlorophyll-a in methanol. Simulated theoretical spectra: (top panel) $S_1 \leftarrow S_0$ (Q_y) transition simulated by the vertical approximation (VE) and vibronic spectrum; (bottom panel): absorption spectrum in the 250-700 nm range obtained as sum of vibronic spectra of the first 8 lowest single electronic transitions. All theoretical spectra are red-shifted by 450 cm^{-1} (about 20 nm). Theoretical stick spectra have been convoluted by Gaussian functions with a half-width at half maximum (HWHM) of 500 cm^{-1} (VE) or Lorentzian functions with a HWHM of 250 cm^{-1} (Vibronic).

669

670

671

[H2] 3.3. Molecular vibrations from diffusion Monte Carlo

672

For molecules that undergo large amplitude vibrations, many insights can be obtained from knowledge of how the ground state wave function samples the potential surface, and how this is affected by isotopic substitution. DMC provides an approach that is well-suited to exploring ground

673

674

675 state properties of molecules showing LAMs. The power of the DMC approach comes from the fact
676 that the wave function is represented by an ensemble of localized functions (or **walkers [G]**) as
677 described by Eq. (12). This allows for studies of systems that are not well-approximated by a simple
678 zero-order (harmonic) description (like, e.g., torsions around simple bonds or ring puckerings). This
679 comes at the cost that, generally, only one state can be calculated at a time, making the approach
680 well-suited for studies that focus on the ground state wave function and associated properties
681 including vibrationally averaged rotational constants.

682
683 In DMC, at each step in the simulation, a reference energy is evaluated using⁸⁶

$$684 \quad V_{\text{ref}} = \bar{V}(\tau) - \alpha \left(\frac{N_w(\tau)}{N_w(0)} \right) \quad (\text{Equation 16})$$

686
687 where the first term provides the ensemble average of the potential energy, and the second term
688 adjusts the value of V_{ref} to ensure a nearly constant ensemble size throughout the simulation. Once
689 the ensemble has equilibrated, the time averaged value of V_{ref} provides the zero-point energy of
690 the system of interest.

691
692 It is important to recognize that this value fluctuates throughout the simulation, as is illustrated for
693 $\text{H}^+(\text{H}_2\text{O})_2^{164}$ in panels A-C in Figure 6. These plots show the evolution of V_{ref} for three different
694 combinations of time increments ($\Delta\tau$) and ensemble sizes (N_w), where all simulations are
695 propagated over the same total time. Generally, the size of the fluctuations of V_{ref} decreases as N_w
696 or $\Delta\tau$ increases, thus improving the quality of the results, but also increasing the computational
697 time. Additionally, the size of these fluctuations can be tuned by changing the value of α . For the
698 plots shown in black in panels A-C of Figure 6, $\alpha = 0.5/\Delta\tau$. In panel C, we explore how the value of α
699 affects the sizes of the fluctuations in V_{ref} . As is seen, when $\alpha = 0.5$, the fluctuations are largest, and
700 as α is decreased to 0.1 or smaller, the size of these fluctuations remains roughly the same on the
701 scale of this plot. On the other hand, if we focus on a smaller range of propagation times, we find
702 that decreasing α removes the highest frequency fluctuations, while a low-frequency oscillation of
703 V_{ref} remains (see lower panel of Supplementary Figure 2 in the Supplementary Information). In
704 selecting α , one strives to identify a value where the high frequency oscillations of V_{ref} occur
705 between roughly three and ten time steps. This choice lessens the correlation of V_{ref} between
706 subsequent time steps without increasing the magnitude of the fluctuations of V_{ref} . Several tests
707 confirmed that $\alpha = 0.5/\Delta\tau$ generally yields good results in this regard.^{84,165,166}

708
709 The numbers shown in panel B provide the **zero-point energy [G]** that is obtained by averaging V_{ref}
710 over different ranges of τ . The numbers in parentheses represent the standard deviation among
711 five independent simulations that were performed using these parameters. As seen, the evaluated
712 energy is relatively insensitive to how long the averaging is over, but the standard deviations are
713 about half as large when V_{ref} is averaged over more than 10 000 a.u. of time. The evaluated zero-
714 point energies for nine different combinations of ensemble sizes and time increments are compared
715 in panel D. We note that the smallest N_w has the greatest uncertainty in its zero-point energy, and
716 when one uses both the smallest N_w and the largest $\Delta\tau$, the simulation yields a zero-point energy
717 that is inconsistent with the benchmark calculation (dotted line with grey shading). The larger
718 ensembles provide zero-point energies that agree with the benchmark results for all three time
719 increments. However, as with the fluctuations of V_{ref} , the statistical uncertainties in the reported
720 zero-point energies decrease for smaller $\Delta\tau$ and for larger ensembles, so a compromise must be
721 made between accuracy and computational time.

722

723 In addition to the zero-point energies, DMC provides a powerful tool for obtaining projections of
 724 the ground state probability amplitude onto a desired coordinate. This is achieved by propagating
 725 the ensemble of walkers over a short period of **imaginary time** [G], τ_{DW} , and identifying the fraction
 726 of the ensemble at $\tau + \tau_{DW}$ that is traced to a particular walker in the ensemble at τ . This number
 727 is proportional to the value of the wave function at the coordinates of the walker at τ ,^{84,87} allowing
 728 us to use Monte Carlo integration to generate the desired projection of the probability amplitude,
 729 Ψ^2 . This approach is used to obtain the projection of the ground state probability amplitude onto
 730 the Δr (see inset in panel E), and the resulting distributions are shown in the panel E of Figure R4
 731 for several values of τ_{DW} . As it is hard to differentiate among these results, the mean values of Δr ,
 732 along with the standard deviation, are shown as functions of τ_{DW} in panel F. The convergence of
 733 the results can be estimated by the results reported in this panel, which compares the computed
 734 values against independently obtained values of these quantities based on symmetry ($\langle \Delta r \rangle$, black
 735 dotted line) or an alternative way to obtain expectation values ($\sigma_{\Delta r}$, green dotted line).^{83,167}
 736
 737 Extensions to DMC that enable the study of excited state energies and wave functions have been
 738 developed,^{86,168-170} although a discussion of these is beyond the scope of the present Primer.
 739

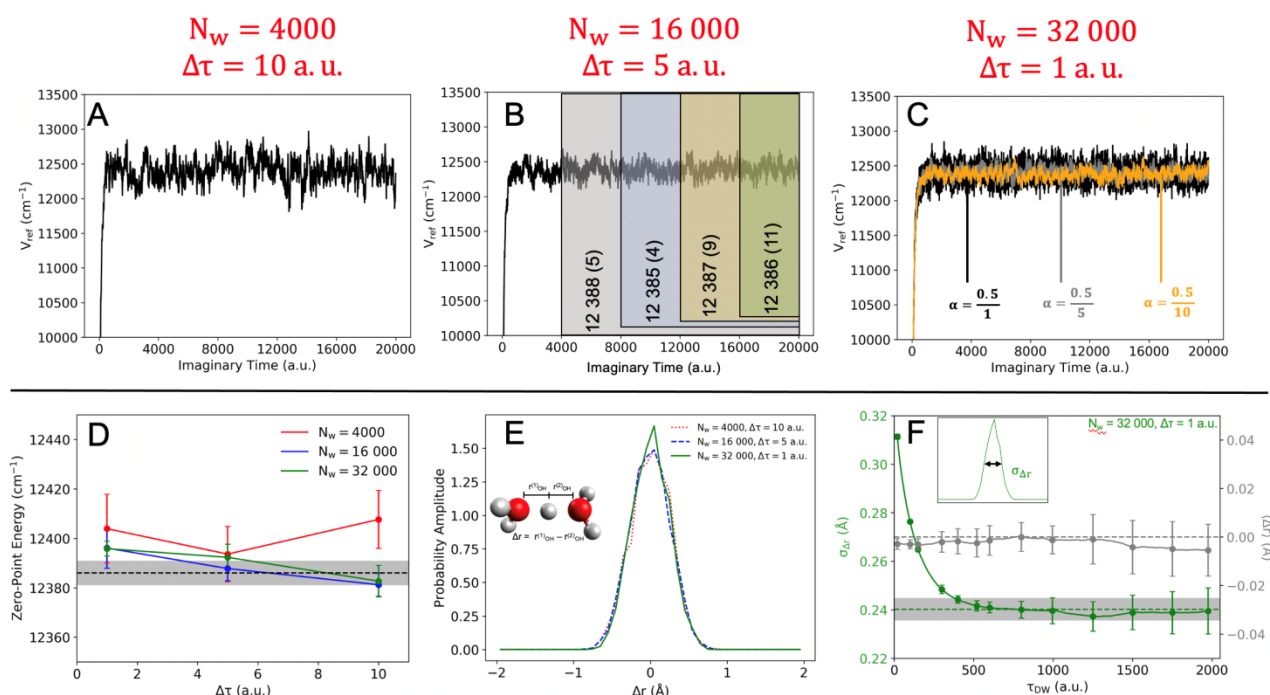


Figure 6: (A)-(C) The value of V_{ref} plotted as a function of imaginary time, obtained from DMC simulations using (A) $N_w=4000$ and $\Delta\tau=10$ a.u.; (B) $N_w = 16000$ and $\Delta\tau=5$ a.u.; and (C) $N_w = 32000$ and $\Delta\tau=1$ a.u.. In panel B, we also show how the evaluated zero-point energy depends on how long V_{ref} is averaged. These values are also tabulated in the Supplementary Information (Supplementary Tables 1 to 3). In Panel C, we also explore how the size of the α -parameter (see equation above) affects the magnitude of the fluctuations in V_{ref} . (D) The calculated zero-point energy is plotted as a function of the time increment for ensemble sizes ranging from 4000 (red) to 3200 (green) walkers, and compared to the results obtained using $N_w = 20000$ and a time increment of 10 a.u. (black line, where grey shading indicates a 5 cm⁻¹ uncertainty in that value). (E) Projections of Ψ^2 onto Δr (see inset) as a function of ensemble size based on a calculation where the number of descendants is evaluated after $\tau_{DW} = 520$ a.u. (F) The expectation value (grey) and standard deviation of Δr , plotted as a function of τ_{DW} . The dotted grey and green lines provide reference values of 0 Å for the average and 0.240 Å for the standard deviation. While the average value of Δr can be determined by symmetry, the standard deviation is obtained using an adiabatic DMC calculation.^{83,167} All error bars and uncertainties reflect the standard deviations among five independent DMC simulations.

740

[H2] 3.4. Determination of absolute configurations

The chiral spectroscopic techniques considered here (ORD, ECD, VCD and ROA) play a fundamental role in the determination of **absolute configuration (AC)** [G]. As spectra for enantiomers are mirror images, the AC can be determined by comparing the calculated spectra with the experimental ones. In the simplest case, in order to determine the AC using the methods mentioned above, the spectra of the two enantiomers are calculated and compared to the experimental spectrum of one of the enantiomers, (+) or (-). The calculated spectrum in best agreement with the experimental spectrum defines the AC of the experimental enantiomer. As an example, the experimental and calculated VCD spectra for (+)-camphor and (1R,4R)-camphor are shown in Figure 7a. Given the quantitative agreement between the calculated and experimental spectra, the AC of (+)-camphor is assigned to be 1R,4R. Since these are enantiomers, it follows that (-)-camphor is (1S,4S).

Each of these chiral spectroscopies can be applied individually or in combination.¹⁷¹⁻¹⁷⁶ The advantage of using multiple methods is that they provide complementary information, which is useful in distinguishing diastereomers with multiple chiral centers, as one method may not be able to distinguish particular stereocenters. Specifically, Polavarapu et al.¹⁷¹ found that ORD, ECD and VCD were individually unable to unambiguously assign the AC of Hibiscus and Garcinia acids, each containing two chiral centers. However, a combination of VCD with either ECD or ORD was able to correctly assign the AC of both molecules. Similarly, Hopman et al.¹⁷⁶ found that VCD and ROA, but not ECD, were able to correctly assign the AC of Synoxazolidinone, a marine antibiotic compound containing two chiral centers and one asymmetrically substituted double bond, resulting in a total of eight possible stereoisomers. A recent study by Bogaerts et al.¹⁷⁴ on Artemisinin, an anti-malaria drug containing seven chiral centers, found that even though ROA and VCD could independently assign the correct stereochemistry, the combination of these two methods resulted in an even stronger unambiguous AC assignment (VCD and ROA spectra shown in Figure 7b,d).

For molecules containing multiple chiral centers and whose diastereomers predict similar spectra, the harmonic approximation, which is routinely used for VCD and ROA, may not be sufficient in providing a reliable AC assignment. This is the case for Diplopyrone, a phytotoxic monosubstituted tetrahydropyranpyran-2-one, containing four chiral centers, two of which were previously unassigned.¹⁷³ In addition, this molecule possesses several low-energy conformers, further complicating the analysis of the spectra as discussed in section 3.2. In this case, ECD was not able to distinguish between the four possible diastereomers and the diastereomers predicted very similar harmonic VCD spectra. However, VCD spectra computed at the anharmonic level (Figure 7f) were sufficiently close to experiment to allow for a confident assignment of the two unknown chiral centers.

The comparison of calculated and experimental spectra is an important part of the assignment of AC. Although this comparison can be performed visually, different approaches exist to remove bias and to quantify the degree of similarity. All of these methods rely on the calculation of a spectral overlap between the experimental and predicted spectra.^{172,174} Another approach involves the analysis of the dissymmetry factor, the ratio of $\Delta\epsilon$ and ϵ .^{69,175,177} Another measure of the reliability of the calculated vibrational spectra is the concept of robust modes, first developed for VCD¹⁷⁸ and later extended to ROA.¹⁷⁹ In this approach, a mode is determined to be robust if the rotational strength or scattering activity will not change sign due to small perturbations in either experiment or calculation.

788
789
790
791
792
793

Although the primary utility of the chiroptical vibrational methods is to produce the spectra shown in Figure 7, additional information can be extracted which can help in the analysis and interpretation of the results. These include examining the vibrational transition current density associated with a molecular vibration^{180,181} for VCD and computing atomic contribution patterns and group coupling matrices¹⁸² for ROA.

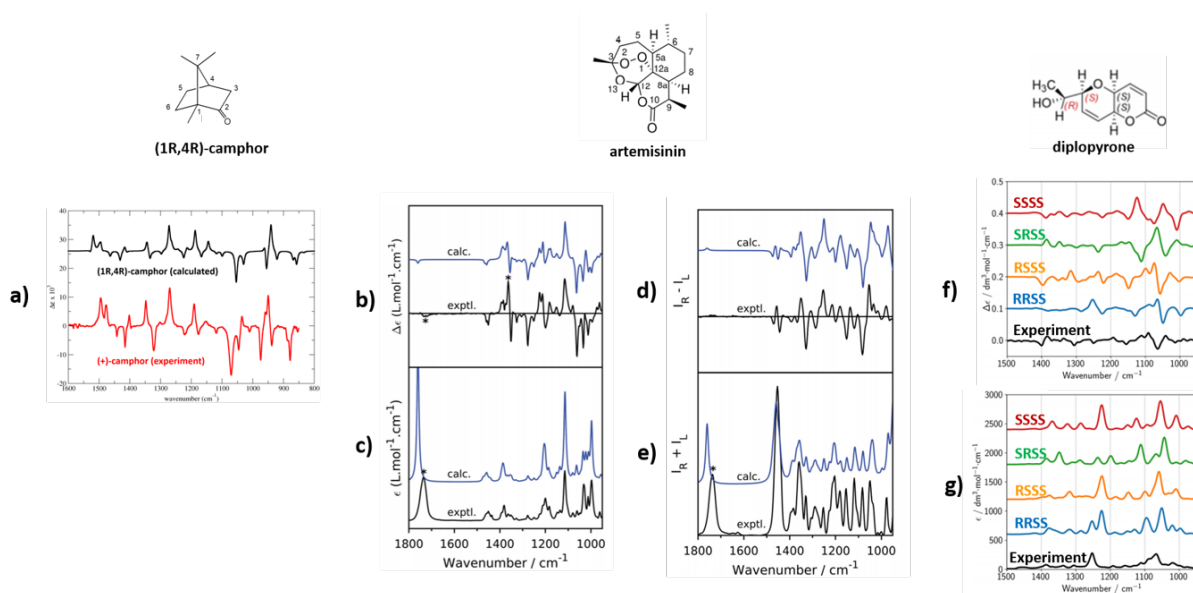


Figure 7: Computed and experimental VCD and ROA spectra for the determination of AC. (a) Comparison of calculated and experimental VCD spectra for (1R,4R)-camphor and (+)-camphor, respectively. Calculated spectra are plotted using the Lorentzian lineshape function using a HWHM of 4 cm^{-1} . Experimental data, originally from ref⁶⁶, kindly provided by Frank Devlin (USC). (b-e) Comparison of calculated and experimental VCD (b) and IR (c) and ROA (d) and Raman (e) spectra for artemisinin. Calculated spectra are plotted using the Lorentzian lineshape function using a HWHM of 5 cm^{-1} for VCD/IR and 8 cm^{-1} for ROA/Raman. Figure taken from¹⁷⁶. For a molecule containing seven chiral centers there would, in principle, be $2^7 = 128$ diastereomers, but since two of the chiral centers are fixed (via the endoperoxide bridge) this number is reduced to $2^6 = 64$. However, half of these are enantiomers so that conformational analysis and spectra calculations were performed for a total of 32 diastereomers. (f-g). Comparison of calculated anharmonic and experimental VCD (f) and IR (g) spectra for (+)-diplopyrone ((+)-6-[(1R)-1-hydroxyethyl] 2,4a(S),6(S),8a(S) tetrahydropyran[3,2-b]pyran-2-one). Calculated spectra are plotted using the Lorentzian lineshape function, using a HWHM of 8 cm^{-1} . Figure taken from¹⁷³.

794
795

796 [H1] 4. Applications

797
798 As done for the results section, a limited selection of possible applications is reported to provide
799 significant examples of the potential of computational molecular spectroscopy, the examples being
800 selected from the spectroscopies addressed in this Primer. However, the list of possible applications
801 is too long for being even simply enumerated here.

802 [H2] 4.1. Astrochemistry

803 The role of spectroscopic techniques in the study of the interstellar medium (ISM) has grown rapidly
804 in the last few decades, with rotational spectroscopy playing a critical role. Most of the
805 understanding of the ISM – the gas and dust existing in the space between the stars of a galaxy –
806 comes from Earth-based spectroscopic observations. Atoms and molecules in the gas phase
807 constitute 99% of the ISM's mass, while the remaining mass is composed of silicate and carbonate
808 grains.¹⁸³ At the low temperatures of the ISM, gas-phase particles emit radiation whose frequency
809 spans from the gigahertz to the terahertz domains. Physically, the quanta emitted corresponds to
810 the transitions between rotational energy levels of molecules. Thus, each molecule can be identified
811 through its peculiar fingerprints - i.e., its rotational transitions.¹⁸³ With these molecules being
812 ubiquitous in the ISM, the chemical composition - as well as the physical properties and the
813 evolutionary stage of interstellar objects - can be derived from radioastronomical observations.¹⁸⁴
814 The laboratory data needed to guide the latter and to discover new interstellar species are provided
815 by rotational-spectroscopy laboratory studies,¹⁸⁵ which are increasingly supported and
816 complemented by QC computations.¹⁴⁰

817
818 The search for interstellar complex organic molecules (i-COMs, i.e. species containing at least six
819 atoms and composed of carbon, hydrogen, oxygen, and/or nitrogen¹⁸⁶ can be assisted by the
820 Minimum Energy Principle (MEP), which states that “the most stable isomer of a given chemical
821 formula is always the most abundant in the ISM”.¹⁸⁷ A computational study of the relative stability
822 of different isomeric (structural or conformational) species allows the screening of potentially
823 observable molecules. In the case of conformers, the energy difference among the various
824 conformers can be as small as a few kJ/mol, and the size of the electric dipole moment becomes an
825 important parameter worth computing (the intensity of rotational transitions scales with the square
826 of the dipole moment component that allows the transition). The combination of the MEP and the
827 magnitude of the electric dipole moment enables the straightforward identification of the most
828 likely detectable i-COMs.

829
830 Once the species of interest is recognized, computational spectroscopy guides the experimental
831 study by providing accurate predictions of the rotational parameters to be used for simulating their
832 spectra.^{141,188} Despite the potential accuracy that can be reached by such calculations,¹⁴⁰ this is
833 generally insufficient for directly guiding astronomical searches and/or assignments. However, in
834 some cases, QC predictions can assess the detection of new astrochemical species, as is the case
835 with the cyanobutadiynyl anion, C_5N^- .¹⁸⁹ Due to the difficulty of producing this species, no laboratory
836 study of its rotational spectrum has been reported to date. Nonetheless, C_5N^- has been discovered
837 in the envelope of a carbon-rich star thanks to the pinpoint match between astronomical
838 observations and predictions based on high-level coupled-cluster calculations.¹⁹⁰

839
840 The analysis of astronomical spectra can provide new information; however, the help of QC
841 calculations is often needed. To give a specific example, the investigation of the hyperfine structure
842 of the rotational spectrum is fundamental to gaining information on column densities, which provide
843

844 a measure for molecular abundances. The hyperfine structure in rotational spectra is due to
 845 interactions between the molecular electric and/or magnetic fields and the nuclear moments. The
 846 most important of these interactions is that between the molecular electric-field gradient and the
 847 electric quadrupole moment of nuclei (with the latter being present when the nuclear spin is greater
 848 than 1/2). Among the magnetic interactions, the weak magnetic field generated by the end-over-
 849 end rotation of a molecule interacts with the nuclear magnetic moments, thus producing a slight
 850 magnetic split or shift of the lines (with nuclear magnetic moments being present when the nuclear
 851 spin is non-null). These two interactions are referred to as nuclear quadrupole coupling and spin-
 852 rotation interaction, respectively; in addition, dipolar spin-spin interactions among different nuclear
 853 spins may also arise. In the case of molecular ions, the resolution of experiment is usually limited by
 854 the impossibility of reducing the working pressure inside the cell (because of the ion-production
 855 process),¹⁹¹ thus leading to the partial or even non-resolution of hyperfine structures, as shown in
 856 Figure 8. Interstellar lines are instead very narrow. Therefore, when required, one can resort to QC
 857 calculations to accurately predict the hyperfine structure of astronomical spectra: the quantitative
 858 accuracy obtainable with state-of-the-art QC calculations is demonstrated in Figure 8. Another
 859 significant example is offered by CF^+ ,¹⁹² for which the hyperfine structure of the astronomical
 860 (rotational) spectrum was assigned using the computed hyperfine parameters.
 861

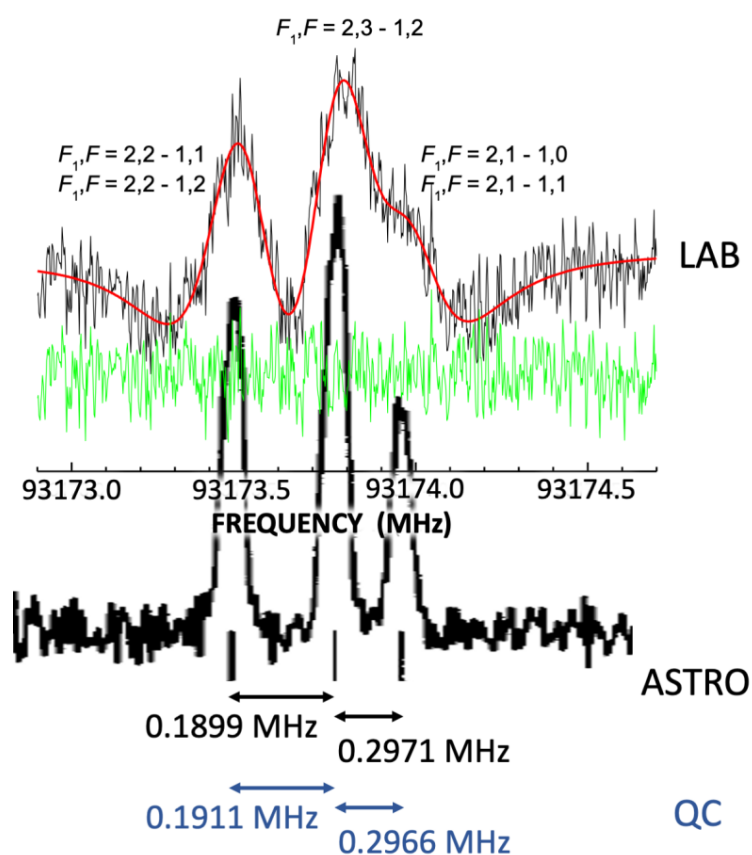


Figure 8. Comparison of a portion of the laboratory (LAB)¹⁹¹ and astronomical (ASTRO, low-mass cloud core L1512 in Taurus¹⁹³) spectrum of the first rotational transition ($J = 1 - 0$, with J being the rotational quantum number) of the diazenylium cation (N_2H^+). The actual comparison is between the red LAB spectrum (resulting from the line profile analysis of recorded spectrum in black, with the green trace being the corresponding residual) and the ASTRO counterpart, with the hyperfine splittings also reported. These are compared with the computed (QC) values.
 The hyperfine structure is due to the presence of two nuclear quadrupolar nuclei, the nitrogens. The quantum numbers F_1 and F arise from the coupling schemes $F_1 = J + I_{N1}$ and $F = F_1 + I_{N2}$, respectively, with I being the nuclear spin quantum number (=1 for nitrogen).

863 Finally, an appropriate modeling of the ISM demands the computation of collisional rate coefficients
864 for interstellar molecules by the most abundant species, i.e. hydrogen and helium (denoted as
865 collider). Interstellar species are often far from a local thermodynamic equilibrium (LTE) condition.
866 Therefore, the collisions occurring between the molecule under consideration and molecular
867 hydrogen (or atomic helium) significantly affect the population of rotational levels of the former
868 and thus have an impact on the rotational transitions observed with radioastronomy.¹⁹⁴ In turn, the
869 derivation of collisional data requires the computation of the PES of the molecule-collider with high
870 accuracy.

871

872 [H2] 4.2. Weakly bound clusters and biomolecules

873 A wide and expanding application of computational spectroscopy is the calculation of spectra for
874 weakly bound clusters and biomolecules. In its broadest sense this includes magnetic and electronic
875 spectroscopy^{195,196} but here we will confine comments to vibrational spectroscopy with applications
876 mainly to the near and far infrared region of the spectrum.

877

878 Advances in high resolution infrared spectroscopy of small van der Waals molecules have stimulated
879 very good agreement between theory and experiment.¹⁹⁷ This work started with rare gas atoms
880 attached to diatomic molecules¹⁹⁸ but has been extended to larger weakly bound clusters involving
881 polyatomic molecules¹⁹⁹. Clusters involving water molecules have received particular attention due
882 to the importance of water throughout the sciences.²⁰⁰ Water dimer is a key system and highly
883 accurate fully dimensional potential energy surfaces have been produced from sophisticated *ab*
884 *initio* procedures.²⁰¹ These potentials have been used in converged calculations of vibrational states
885 using appropriate basis functions for the different degrees of freedom and full-dimensional
886 Hamiltonians with variational procedures. This has led to excellent agreement between theory and
887 experiment for the spectra in the far infrared region of the water dimer.²⁰²

888

889 This advance is important as the PES for water dimer forms the main component of potentials for
890 larger water clusters, as the only supplements needed are fairly simple three- and four-body
891 interactions between the different water molecules.²⁰³ More challenging is the accurate calculation
892 of the ro-vibrational states of water clusters larger than the dimer, as conventional basis set
893 methods with variational procedures then quickly become unwieldy. However, alternative
894 procedures have been applied for larger water clusters that can calculate quite accurately some
895 parameters of experimental interest, such as the rotational constants of the lowest vibrational
896 states of clusters of different geometries, and tunneling splittings of vibrational states arising from
897 identical minima on the potential energy surfaces. In this way diffusion DMC,²⁰⁴⁻²⁰⁶ instanton,²⁰⁷ and
898 path integral²⁰⁸ procedures have been applied effectively on clusters up to (H₂O)₈ and have allowed
899 detailed comparison with far infrared and microwave experiments.

900

901 The general importance of water in biology has meant that clusters of water with molecules of
902 biological interest have been the subject of numerous calculations.²⁰⁹ Methods such as DMC can
903 also be applied to calculate structures of geometric isomers of biomolecules and the associated
904 rotational constants.²¹⁰ QC calculations of infrared spectra for complexes such as uracil-water have
905 shown the importance of hydrogen bonding and anharmonic effects in these systems.²¹¹
906

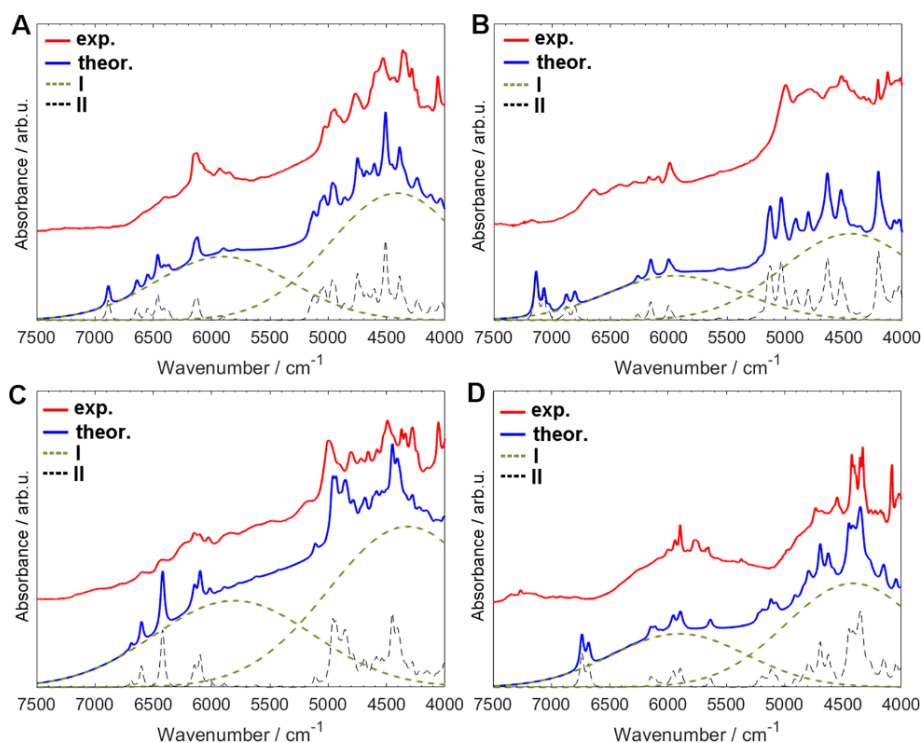


Figure 9. Experimental and calculated near infrared spectra of crystalline (A) adenine; (B) cytosine; (C) guanine; (D) thymine in the 4000–7500 cm^{-1} region.²¹²

907

908

909

910

911

912

913

914

915

916

917

918

919

920

921

922

[H2] 4.3. Spectroscopy of *d*- and *f*-elements

923

924

925

926

927

The spectroscopy of *d*- and *f*-elements introduces new experimental and theoretical challenges that are not easily met. At the heart of the challenges associated with these elements is the fact that they can exist in a variety of oxidation states that lead to spectroscopically well-defined d^n and f^n configurations (n =number of electrons in the *d*- or *f*-shell).

928

929

930

931

932

933

934

Given the high effective nuclear charge experienced by the *d*- or *f*-electrons, the corresponding orbitals are compact. Hence, compared to the strong bonds formed between main group elements, the *d*- and *f*-elements bind comparatively weakly through their orbitals to the surrounding ligands. Thus, the ligand environment induces limited **orbital splittings [G]**. This has been exploited very fruitfully in the phenomenological model of **crystal field theory [G]** (CFT²¹⁵). In CFT, the *d*- or *f*-electrons are treated as free ions perturbed by an electrostatic field created by the surrounding ligands. While quantitatively unrealistic, the theory captures essentials of *d*-(*f*-) element electronic

935 structure. Thus, the combination of a partially filled *d*- or *f*-shell and limited ligand field splittings
 936 leads to a series of low-lying electronic states formed from distributing *n*-electrons between the
 937 available orbitals and at the same time couples their spins in all possible ways to a resulting net total
 938 spin. On top of the complexity arising from a large variety of **multiplets [G]** comes the fact that *d*-
 939 and *f*-elements are heavy. Hence, the effects of relativity become much more prominent in these
 940 compounds and whenever there are unpaired electrons, a treatment of the spin-orbit-coupling (**SOC**
 941 **[G]**) becomes mandatory for theoretical spectroscopy.¹³ The electronic complexity is necessarily
 942 also reflected in the observed spectra. Throughout the range of available techniques ranging from
 943 hard X-rays (10^4 eV) down to microwaves and radiowaves (10^{-11} - 10^{-9} eV)) the spectra typically show
 944 a high amount of spectral crowding due to the multitude of final states that can be reached in the
 945 respective spectroscopic transitions. In addition, the spectra are difficult to interpret because of the
 946 complexity of the electronic states that are involved and consequently, they require a high amount
 947 of expertise to be interpreted correctly.
 948

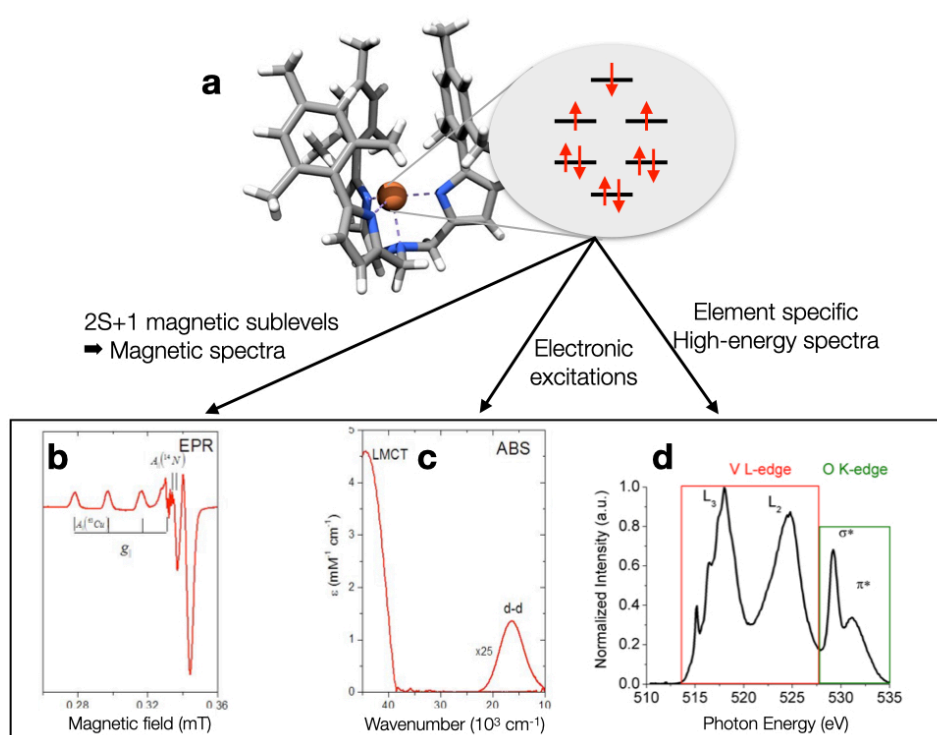


Figure 10. The complex arrangements of electrons in partially filled *d*- and *f*-shells give rise to a wide variety of spectroscopic phenomena that are challenging to model with high-accuracy by quantum chemistry. The geometric structure (panel **a**: left, grey=carbon, white=hydrogen, blue nitrogen, brown=transition metal) imposes a distinctive splitting of the molecular orbitals that are based on the transition metal *d*-orbitals (panel **a**: right). The distribution of the *n* electrons in a d^n configuration gives rise to a multitude of electronic states that can be probed with optical or magnetic spectroscopy (panels **b-d**). Among these, the most prominent ones are EPR (**b**), absorption (**c**) and X-ray absorption (**d**) spectra. EPR spectroscopy probes the net electron spin caused by the unpaired electrons of the electronic ground state. ABS probes transitions of electrons between valence orbitals, including the metal *d*-based orbitals. X-ray spectroscopy probes excitations from deep core electrons on the transition metal center(s) into the empty or half-filled valence orbitals. Since the core levels vary systematically along the periodic table, this provides a highly sensitive element specific probe of the system under investigation.

949
 950 The complex electronic multiplets in the presence of relativistic effects are not easily reproduced
 951 even in a semi-quantitative way by the available QC methods.²¹⁶⁻²¹⁸ In those cases where there are
 952 (near-) orbital degeneracies (as readily predicted by CFT), there may not be a **single Slater**

953 **determinant [G]** that is an appropriate starting point for the description of the electronic ground
954 state. In such a case, all single-reference determinant based methods (including DFT) fail to describe
955 the electronic structure of either the ground or the excited states correctly. Typically, not even the
956 number of reachable final states tend to be correct.^{13,17} Thus, DFT has many serious shortcomings
957 in the field of theoretical *d*- and *f*-element theoretical spectroscopy. These shortcomings were
958 highlighted in some reviews over a decade ago and stand unchanged today.^{13,17,219}

959
960 The occurrence of a rich multiplet structure together with the prominence of relativistic effects,
961 opens up rich opportunities for experimental spectroscopy (Figure 10). Magnetic low-energy
962 spectroscopies, such as NMR and ESR, can probe the magnetic sublevels of the electronic ground
963 state multiplets, while modern magnetometry is extensively used to study the magnetic properties
964 of *d*- and *f*-elements for molecular magnetism. Electronic spectroscopies including UV/vis, CD and
965 magnetic CD (**MCD [G]**) or resonance Raman spectroscopies provide in-depth insights into the
966 electronic structure of these species. Finally, since there are typically only a few atoms of a given
967 element present in the compound, element specific techniques like Mössbauer or X-ray
968 absorption/emission spectroscopies are very widely used.¹⁷ All of these methods provide detailed
969 fingerprints of the geometric and electronic structure of the systems under investigation.
970 Importantly, each one of these techniques is sensitive to different geometric and electronic
971 structure details. Thus, there is a host of experimentally available electronic structure information.
972 However, in order to develop the full information content of these spectra, it is inevitable to turn to
973 quantum chemistry for spectral interpretations. A successfully carried out study results in
974 experimentally calibrated electronic structure level insight of the investigated species, be they
975 stable entities or reaction intermediates. As discussed elsewhere, this leads to insights that can not
976 be obtained from the pure calculation of total energies^{220,221}

977

978 [H3] 4.3.1. Case study of magnetic Co(II) tetrathiolates

979 Coordination complexes of Co(II) ions (d^7 configuration) have been known in coordination chemistry
980 since its cradle days and have been routinely characterized with magnetic measurements like **SQUID**
981 **[G]**, EPR or MCD spectroscopy. It is well-known that in an approximately tetrahedral environment
982 the ground state has a total spin of $S=3/2$. A cursory look at the ion $[\text{Co}(\text{S-Ph})_4]^{2-}$ also reveals nothing
983 particularly special. However, this changed dramatically when Long and coworkers reported that
984 this ion show slow magnetic relaxation at zero magnetic field. This is the signature of the very
985 thought-after single-molecule magnet (SMM) behaviour.²²² What is particularly exciting is that
986 $[\text{Co}(\text{S-Ph})_4]^{2-}$ was the first mononuclear compound to show this behavior where for several decades
987 it was believed that only large, oligonuclear transition metal clusters could show SMM properties
988 (see²²³).

989

990 A careful study of the magnetic properties of two different salts containing $[\text{Co}(\text{S-Ph})_4]^{2-}$ coupled to
991 quantum chemical calculations were subsequently reported.^{224,225} Quite surprisingly, only the $[\text{Co}(\text{S-Ph})_4](\text{P}(\text{Ph})_4)_2$
992 was showing SMM behavior, while $[\text{Co}(\text{S-Ph})_4](\text{N}(\text{Et})_4)_2$ did not. The careful
993 experimental investigation showed that this is due to the Co(II) ion $\text{P}(\text{Ph})_4$ having a large and
994 negative zero-field splitting (**ZFS [G]**), while in the $\text{N}(\text{Et})_4$ salt, the ZFS is small and positive. The
995 magnetic properties of both structures were reproduced with excellent accuracy through
996 CASSCF/NEVPT2 calculation with inclusion of spin-orbit coupling (SOC). Furthermore, the method
997 of Ab Initio Ligand Field Theory (**AILFT [G]**) allowed for the ligand field parameters to be deduced
998 from the large-scale wavefunction based ab initio calculations. They revealed that the origin of the
999 radically different behavior is a subtle distortion that renders Co(II)-ion in the $\text{P}(\text{Ph})_4$ salt to be in an
1000 elongated tetrahedral environment, while in the $\text{N}(\text{Et})_4$ salt, it is in a compressed tetrahedral

1001
1002
1003
1004
1005
1006
1007
1008
1009
1010

structure. The changes in the d-orbital splitting pattern are then sufficient to cause the dramatic switch of magnetic properties, as predicted by ligand field theory. Quite fascinatingly, the origin of the dramatically different behavior can thus be traced back to weak intermolecular interactions in the second coordination sphere of the cobalt. These insights opened up the avenue for many further investigations on Co(II) complexes (e.g. ²²⁶). This study (summarized in Figure 11) is one demonstration that a large body of complex and initially puzzling experimental observations can be quantitatively interpreted in a unified manner through large-scale multireference *ab initio* calculations. Moreover, the results of these calculations can be translated concisely into a familiar chemical language through the AILFT procedure.

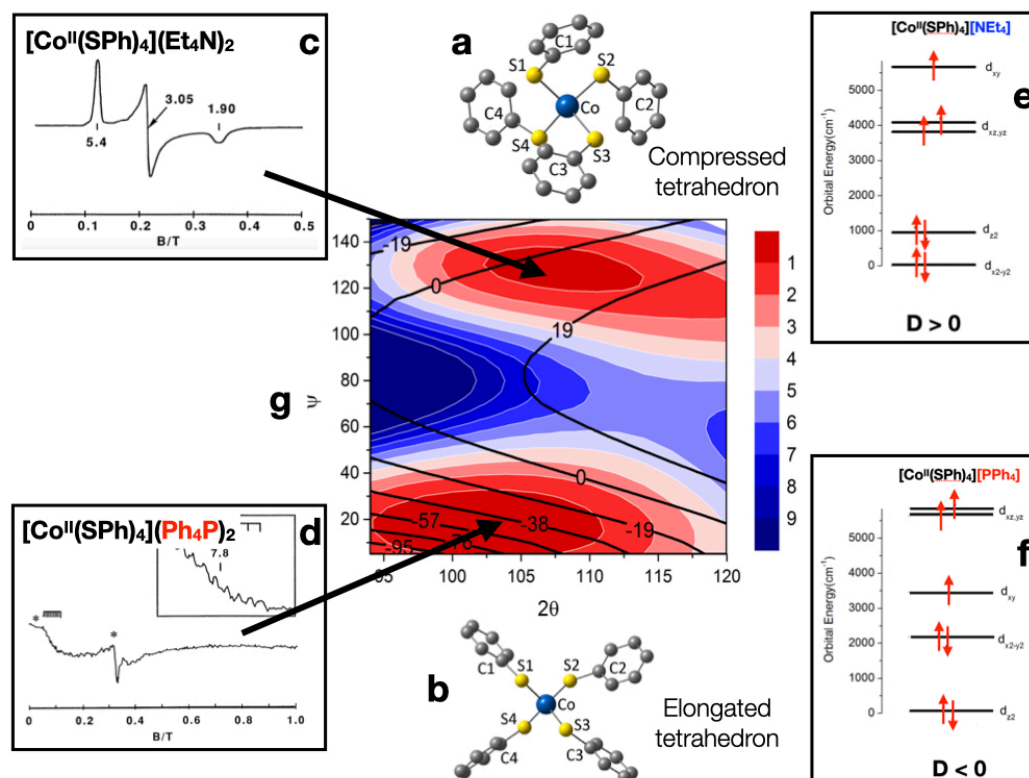


Figure 11. Panels **a,b**: the two structures of $[\text{Co}(\text{S-Ph})_4]^{2-}$ found in the $(\text{Et}_4\text{N})_2$ and $(\text{Ph}_4\text{P})_2$ salts reflecting compressed and elongated tetrahedra respectively. Panels **c,d**: the radically different EPR spectra of the two species demonstrating their very different electronic structures. Panels **e,f**: the effective d-orbital splitting patterns deduced from CASSCF/NEVPT2 calculations for the two structures effectively explaining the origin of the very different D-values. Panel **g**: Potential energy and property surface (ZFS-value) for two key angles describing the distortion into flattened and elongated tetrahedra in $[\text{Co}(\text{S-Ph})_4]^{2-}$. There are two shallow minima associated with qualitatively different D-values as reflected in their ESR spectra (**a,b**) and readily understood from quantum chemical calculations (**c,d**).

1011
1012
1013
1014
1015
1016
1017
1018
1019

1020 [H1] 5. Reproducibility and data deposition

1021
1022 Here we discuss different levels at which the issue of data reproducibility and deposition can be
1023 examined.

1024
1025 The first level is the definition of a general standard for the inputs and outputs (I/O) of electronic
1026 structure codes; this was discussed, for instance, in the MOLSSI workshop
1027 (<https://molssi.org/2019/08/19/molssi-workshop-rovibrational-molecular-spectroscopy/>). Indeed,
1028 we have been witnessing an increasing number of large-scale international and interdisciplinary
1029 collaborations, which often involve shared infrastructures and multi-user facilities, resulting in
1030 massive amounts of data. To enhance these collaborations, there is a strong need to integrate and
1031 standardize computational codes starting from a common syntax and/or language. An example in
1032 this direction is provided by the VMS project,⁶¹ which aims at integrating several spectroscopic
1033 techniques and providing a user-friendly interface to different QC programs (see, e.g., the module
1034 dedicated to rotational spectroscopy¹⁴²).

1035
1036 The second level is the compilation and management of highly accurate results for small (2-4 atoms)
1037 molecules, which can rival the corresponding experimental data.³⁴ Outside this narrow size range,
1038 theoretical models and computational procedures for computational spectroscopy are always
1039 based on approximations and assumptions, which need to be correctly recognized in the
1040 applications to realistic systems. Thus, small molecules can represent suitable fragments for
1041 benchmarking less refined methods and defining transferable correction factors for fragments of
1042 larger molecules.²²⁷ The latter paves the way toward the set-up of public databases of molecular
1043 structures and spectroscopic properties. One example is provided by the database of semi-
1044 experimental equilibrium structures (derived as described in section 3.1) available at
1045 <https://smart.sns.it/molecules/>.

1046
1047 The third level concerns the lines to be followed for the spectroscopic characterization of large
1048 systems, which are of increasing interest to different scientific communities. The available results
1049 for an adequate number of medium-sized systems should be organized in sets of comparable
1050 accuracy by clustering techniques employing widely accepted general criteria. For some properties
1051 (essentially energies), the general definition of platinum, gold and silver standards²²⁸ is more or less
1052 accepted. These definitions are based on the accuracy provided. For example, CCSD(T) calculations
1053 extrapolated to the complete basis set limit define the gold standard. The silver standard provides
1054 the best approximation to the gold standard at a reduced computational cost, while the platinum
1055 standard improves the gold one by adding further corrections (such as higher-order coupled cluster
1056 terms). However, such standards have not been developed for most spectroscopic properties, and
1057 for them the situation is thus more challenging. For instance, fully quantitative results for high-
1058 resolution spectroscopic techniques like rotational spectroscopy are still out of reach even for semi-
1059 rigid tri- and tetra-atomic systems,²²⁹ the required computations being unaffordable. However, new
1060 methods based on the **template approach [G]** possibly coupled with the machine-learning appear
1061 quite promising.^{227,230} To give an example, in the field of vibrational spectroscopies, some
1062 methodologies (such as VPT2 treatments based on an anharmonic description of the PES at a
1063 suitable level of theory³⁴) can reach an accuracy within 10 cm⁻¹ and are also applicable to large-sized
1064 systems with the help of linear scaling^{231,232} and reduced dimensionality²³³ techniques. In this
1065 connection, the compilation and management of databases (as mentioned for the second level for
1066 large molecules) is a task of current interest in the field. More work in this direction should be
1067 performed with compilations of spectroscopic parameters for molecules including heavy elements

1068 and for different spectroscopies. The situation is instead more involved for spectroscopic transition
1069 intensities, where the definition of widely accepted standards is still missing. Another important
1070 issue when dealing with large systems is their flexibility, which requires the implementation of
1071 effective approaches to search for the energetically low-lying structures (i.e. conformers or
1072 isomers).¹⁵⁰ In fact, a key point toward data/spectra reproducibility is the understanding of which
1073 of these conformers or isomers contribute to the overall spectroscopic signal. However, we are still
1074 far from any general definition of classes of methods/models achieving a desired accuracy.

1075
1076 Focusing on an integration of the levels 2 and 3, an interesting option would be to simulate and
1077 store overall spectra in place of databases collecting lists of spectroscopic parameters. Another step
1078 forward would be the set-up of compilations that combine results of different spectroscopies having
1079 comparable accuracies in view of their use to assist the experimental work, which more and more
1080 rests on the integrated use of different techniques.

1081
1082 A transversal issue is the role of environmental effects (e.g. solvent), which should be analyzed for
1083 different properties and/or solvents, thus allowing for the use of the most appropriate model for
1084 the specific case under consideration. Indeed, when the spectroscopic investigation is carried out in
1085 solution or, more generally, in condensed phase, data reproducibility requires the proper account
1086 of environmental effects. For instance, polarizable continuum models³⁴ can be employed to
1087 describe innocent solvents at a negligible additional cost with respect to the corresponding
1088 simulation in vacuo. Such a model can be improved by incorporating a reduced number of explicit
1089 solvent molecules in the treatment,¹⁵¹ provided that they occupy well-defined positions and are
1090 quite strongly bonded to the solute. In this respect, topological models for the automatic definition
1091 of the number and position of strongly bonded solvent molecules are under active development²³⁴
1092 and the definition of widely accepted standards would be a very important achievement.

1093
1094 Finally, while the issue of a general standard addressed above (first level) is a basic need for
1095 collaborations, a mention to the information accompanying publications is deserved. This does not
1096 involve program outputs, the collection (in tables) of spectroscopic parameters being usually
1097 exhaustive. However, cartesian coordinates for the molecular systems investigated are generally
1098 provided, while more rarely the **force constants [G]** describing a portion of PES are reported.

1099

1100 [H1] 6. Limitations and optimisations

1101
1102 Since its very beginning, computational spectroscopy has focused on deriving spectroscopic
1103 parameters to support the analysis of experimental spectra. In fact, interpretation of experimental
1104 data is often a difficult task. This is due to the fact the observed spectroscopic behavior derives from
1105 the interplay of different effects, whose specific roles are difficult to disentangle. Furthermore, the
1106 theoretical model used for their interpretation might be oversimplified.

1107
1108 Pushing the treatment of the electronic and nuclear problems to the limit ensures rigorous analyses,
1109 quantitative results, and correct interpretations of the spectroscopic outcomes. However, such
1110 accurate approaches involve high computational costs and efforts and, therefore, they are
1111 restricted to small, isolated molecules (as briefly addressed in section 5). Increasing the size and
1112 complexity of the systems often requires a sacrifice of accuracy for interpretability, thus leading to
1113 qualitative descriptions. In such cases, the main limitation is an oversimplification that might lead
1114 to the right answer for the wrong reason, which means to obtain the correct reproduction of the
1115 spectral features based on wrong spectroscopic parameters. In turn, this might also mean the
1116 derivation of wrong physicochemical properties, or even incorrect interpretation on what molecular
1117 species are actually observed. The only way to mitigate this is to try to apply a physically sounded
1118 model and possibly take corrective actions based on similar (but smaller) systems already
1119 investigated. However, the selection of the fragments and the treatment of the boundary among
1120 them are open questions that require considerable experience, good knowledge of the system to
1121 be investigated and, above all, further algorithmic developments and implementations.

1122
1123 Modern computational spectroscopy aims to bridge the gap between sophisticated experimental
1124 techniques and oversimplified analyses, also exploiting visualization and simulation techniques. An
1125 interesting example is provided by oxirane derivatives, whose spectral features could not be
1126 described by more simplified theoretical models. State-of-the-art simulations of IR, Raman, VCD,
1127 ROA, OPA, ECD are in good agreement with their experimental counterparts allowing also to
1128 reconcile theory and experiment.^{35,112,235,236}

1129
1130 As mentioned in the previous section and along this primer, accurate methodologies have been
1131 developed for the treatment of small- to medium-sized molecular systems (see e.g. refs. ^{34,150,237}),
1132 linear-scaling and hybrid approaches (that will be addressed later in this section) allowing for their
1133 extension to larger systems. However, a current challenge for computational spectroscopy tools is
1134 provided by large flexible molecules, for which the analysis of the conformational PES is the first
1135 obstacle to be overcome. In fact, in order to correctly interpret their spectroscopic features, the
1136 knowledge of the structures contributing to them is mandatory. In this respect, in the last decade,
1137 significant progress has been made thanks to stochastic (molecular dynamics or Monte Carlo)
1138 techniques¹⁵⁰ and machine-learning algorithms,^{230,234} all of them helping in deriving an exhaustive
1139 account of the number and type of conformers relevant for the spectroscopic analysis.

1140
1141 Moving to spectral simulations, the number and types of LAMs are still a strong limitation for
1142 accuracy. In fact, while a decoupling (or a minimization of the coupling) between SAMs and LAMs
1143 together with a variational treatment of the latter modes can pose the basis for an accurate
1144 spectroscopic treatment, this approach is currently effective for dealing with only one LAM.²³⁸
1145 Nevertheless, a further issue is the level of theory employed for the description of the portion of
1146 PES (or PESs) required to the spectroscopic technique under consideration. In fact, the scaling of
1147 most of the accurate QC models is prohibitive, thus hampering their application already to medium-

1148 sized molecular systems. However, for the latter, composite schemes often provide an effective
1149 solution. For larger systems, a possible way-out is offered by fragment-based approaches such the
1150 molecules-in-molecules,²³⁸ which is a multilevel partitioning approach coupled with electronic
1151 structure studies at different levels of theory with the final aim of providing a hierarchical strategy
1152 for systematically improving the computed results. At the same time, further improvements on the
1153 reliability of methods rooted in the density functional theory (e.g. double-hybrid functionals, long
1154 range corrections, etc.)²³⁹ and the development of linear-scaling techniques, especially for the
1155 exact-exchange²⁴⁰ and MP2²⁴¹ parts, paves the route toward more reliable computations for large
1156 systems. In parallel, explicitly-correlated F12 treatments¹⁰⁵ allows the reduction of the basis-set
1157 dimensions in electronic structure computations, thus improving the reachable accuracy. A further
1158 step is provided by local-correlation treatments based on PNO,^{106,107} which - as already mentioned
1159 - allow for improving the scaling of coupled cluster treatments with the number of electrons.

1160
1161 While being aware that limitations and optimizations in the field of computational molecular
1162 spectroscopy cannot be exhaustively addressed in this section, it should be noted that the accurate
1163 spectroscopic characterization of open-shell species is more challenging than that of their closed-
1164 shell counterparts, regardless of the size of the molecular system under consideration.²⁴² The
1165 situation is even more involved for systems showing large static correlation effects (e.g. low-spin
1166 states of most transition metals, see section 4.3), with methods rooted in the DMRG¹³⁶ or quantum
1167 Monte Carlo²⁴³ being good alternatives with respect to multi-reference methods and opening
1168 promising routes toward effective treatments.

1169 [H1] 7. Outlook

1170
1171 The previous sections have shown that the ongoing developments of hardware and software are
1172 allowing the study of the spectroscopic outcomes of several systems and processes of current
1173 scientific and technological interest with an accuracy simply unthinkable even ten years ago.
1174 Furthermore, the range of applications of computational spectroscopy has considerably widened
1175 including now diverse fields as astrochemistry,²⁴⁴ atmospheric chemistry²⁴⁵ or catalysis,²²⁰ just to
1176 mention a few. However, the historical dichotomy between accuracy and interpretability (not to
1177 speak of feasibility and user-friendliness)³⁴ remains one of the hardest obstacles against the
1178 definitive transformation of computational spectroscopy from a highly specialized field to a general-
1179 purpose tool aiding both theoretically- and experimentally-oriented scientists in their research
1180 work. This aspect is even more important since state-of-the-art spectroscopic investigations usually
1181 involve the contemporary use of several experimental techniques and new, highly sophisticated
1182 computational tools are constantly proposed and implemented. In this framework, the most needed
1183 developments concern the extension of accurate evaluations of spectroscopic parameters from
1184 small semi-rigid closed-shell systems containing light atoms in the gas phase²³⁷ to a general
1185 workflow for the spectroscopic characterization of large, flexible chromophores in condensed
1186 phases.²⁴⁶ While most of the building blocks of the procedure are already available, their integration
1187 into a robust, general, and user-friendly tool calls for further developments and validations.

1188
1189 One aspect to consider is the extension and validation of composite models for electronic structure
1190 calculations to transition metals and heavy atoms, large systems, open-shell species, and excited
1191 electronic states. Possible routes to achieve this include explicitly-correlated coupled-cluster
1192 approaches,^{105,247} localized treatments of correlation (e.g. local pair natural orbitals, **LPNO**
1193 **[G]**),^{231,232} effective treatment of static correlation,^{136,248} further improvements of density
1194 functionals for comprehensive scans of PESs²⁴⁹ as well as reliable structure and force-field
1195 evaluations,²³⁹ more effective treatments of excited electronic states.^{250,251}

1196
1197 Another important aspect to take into consideration is the vis-à-vis comparisons between computed
1198 and experimental spectra, including positions and heights (i.e. intensities) of band maxima, but also
1199 spectral shapes⁶¹ and the extension of such comparisons to all possible spectroscopies. This in turn
1200 requires accurate yet effective evaluations of all the parameters needed by different spectroscopic
1201 techniques^{133,252} and their post-processing. Indeed, the vis-à-vis comparison is probably the best
1202 way to exploit the interplay of experiment and theory.

1203
1204 To improve the spectroscopic analysis of flexible molecules, in particular in the fields of rotational
1205 and vibrational spectroscopies, general-purpose treatments of their spectra in terms of curvilinear
1206 internal coordinates, possibly coupling the variational treatment of LAMs with the perturbative
1207 treatment of SAMs and couplings, need to be developed and implemented.^{249,253} A promising
1208 alternative is offered by integrated treatments of electronic and high-frequency nuclear motions by
1209 means of nuclear-electronic orbitals.²⁵⁴ In the framework of electronic spectroscopies, the
1210 extension to large chromophores of anharmonic vibronic models²⁵⁵ for absorption and emission
1211 electronic spectroscopy, also including chiroptical spectra, is important to take a step forward in the
1212 characterization of biomolecules.

1213
1214 Effective coupling between explicit dynamic treatment of soft degrees of freedom (e.g., torsions
1215 around single bonds, ring puckerings, and solvent fluctuations) involving large-mass moieties (for
1216 which classical equations of motion are fully adequate) and quantum-mechanical treatment of hard

1217 degrees of freedom.²⁵⁶ These developments will allow the accurate yet effective treatment of large
1218 flexible systems in condensed phases, which is hardly feasible with current software and hardware.

1219

1220 Integration of the variational (QM, QM/QM' or QM/MM, MM standing for molecular mechanics and
1221 the "slash" used to denote that two levels of treatments are employed, thus implying a partitioning
1222 of the system) evaluation of large-scale deformations (e.g. different conformers and/or different
1223 topologies of solute-solvent interactions in the cybotactic region) with the perturbative (e.g. **PMM**
1224 **[G]**) evaluation of fluctuations within different basins.¹⁵¹ Also in this case, clever coupling of
1225 variational (QM/QM, etc.) and perturbative (PMM) approaches will strongly reduce the computer
1226 requirements (both time and memory) without sacrificing the accuracy of the overall computation.

1227

1228 In the framework of ro-vibrational spectroscopy, effective determination of partition functions
1229 (and/or density and number of states) beyond the rigid-rotor/harmonic-oscillator model^{1257,258}
1230 would allow the computation of accurate thermodynamic functions and reaction rates for flexible
1231 systems possibly in condensed phases.

1232

1233 Implementation of artificial-intelligence tools for the sampling of PESs after their training with
1234 reference to state-of-the-art QC results paves the route toward very accurate energies, structures
1235 and force fields of both local minima and transition states at a cost comparable to that of
1236 inexpensive MM methods.²³⁰ On the other hand, implementation of immersive virtual- and
1237 augmented-reality tools for the effective setup of general spectroscopic studies and the interactive
1238 analysis of the results²⁵⁹ can revolutionize the whole field (as well as many others), thereby changing
1239 the perspective from abstraction to perception by bringing the objects under study to the same
1240 spatial-temporal scale of human beings. In a more distant perspective, effective use of quantum
1241 computing will improve the rate of state-of-the-art techniques.²⁶⁰ As a matter of fact, the exact
1242 solution of the Schrödinger equation has an intrinsic exponential scaling with the dimension of the
1243 problem and the most accurate QC techniques scale as high powers (at least 10^8) of the number of
1244 active particles. In parallel, the speed of traditional computers scales linearly with the number of
1245 cores, whereas the scaling of quantum computers is, in principle, exponential.

1246

1247 In summary, in this Primer --focusing on a selection of molecular spectroscopic techniques-- we have
1248 shown how Computational Spectroscopy works, briefly presenting its foundations as well as
1249 significant results and applications. Furthermore, along this Primer, the fundamental role of
1250 Computational Spectroscopy in supporting and complementing experimental investigations has
1251 been addressed. A critical analysis of its current limitations and possible improvements has also
1252 been performed, which has been concluded by an exhaustive presentation of future perspectives
1253 and needs.

1254

1255

Glossary (terms in text annotated with [G])

AC	Absolute Configuration: indicates the spatial arrangement of atoms in a chiral system and its stereochemical description.
AILFT	Ab-initio ligand field theory: is a method connecting the results of ab initio calculations with the parameters entering ligand field theory.
Anharmonicity	Deviation from the harmonic-oscillator behavior.
BO (approximation)	The Born-Oppenheimer Approximation: is the assumption that the motion of atomic nuclei and electrons can be treated separately, based on the much larger mass of nuclei.
CASPT2	Complete active space perturbation theory to second order: is one specific generalization of MP2 (see below) to multiconfigurational reference wave-functions.
CC (theory)	Coupled-cluster (theory): is a hierarchy of electron correlation methods that, by means of an exponential Ansatz, systematically converge to the exact solution of the molecular Schrödinger equation starting from the independent particle Hartree-Fock model.
CD	Circular Dichroism: is dichroism (splitting of a beam of light into two beams with different wavelengths) involving circularly polarized light, i.e., the differential absorption of left- and right-handed light.
CCSD(T)	CC method that considers full account of single and double excitations and a perturbative treatment of triple excitations.
CFT	Crystal field theory: describes the splitting of the (relativistic) many particle multiplet states of an ion in a d^n or f^n configuration incurred by the electrostatic interaction with its coordinating ligands that are treated as point charges.
CIS	Configuration interaction (i.e. mixing of ground and excited electronic states) including only single excitations from a reference Slater determinant.
Combination band	A combination band is observed when two or more vibrations are excited simultaneously
Conformer	Isomer that can be converted into another one by rotation about a formally single bond.
Contact transformation	Unitary transformation with an exponential operator $U = \exp(iS)$, where S is Hermitean and antisymmetric with respect to time reversal, thus ensuring that U is unitary and invariant to time reversal.
Cybotactic (region)	The region around a solute molecule including solvent molecules belonging to the first solvation shell, i.e. showing close solute-solvent contacts
DFT	Density functional theory: is a quantum-mechanical method in which the properties of a many-electron system are determined using functionals (i.e. functions of another function) of the spatially dependent electron density and, possibly, its derivatives.
DMC	Diffusion Monte Carlo: provides a Monte Carlo based approach for obtaining the exact ground state solution to Equation 2.
DMRG	Density matrix renormalization group: is a very efficient numerical variational technique devised to obtain the lowest-energy wavefunction of a given Hamiltonian expressed in terms of a matrix product state.
(DL)PNO	(Domain-based local) pair natural orbitals: are electron pair specific localized natural orbitals expanded in a set of local atomic orbitals belonging to pair specific domains.
Double-perturbative approach	Simultaneous perturbative treatment of the energy and one property (e.g. the electric dipole moment in infrared spectroscopy) around a stationary point.
ECD	Electronic version of the circular dichroism (see above)
Electron correlation	Electron Correlation: describes the effects of electron-electron interactions beyond the mean field Hartree-Fock model.
Electron Correlation: Dynamic	Electron correlation effects describing the “instantaneous” electron-electron interaction if groups of electrons approach each other in close proximity.
Electron Correlation: Static	Electron correlation effects describing the correlated motion of electrons not captured correctly by the single Slater determinant treatment offered by the Hartree-Fock model.
Energy level	According to quantum mechanics (see below), the allowed energy for a system is not continuous, but discretized in energy levels.

Ensemble of walkers	A large number of virtual copies of a single particle moving randomly over a given potential energy surface.
EOM	Equation-of-Motion: in a quantum chemistry context it refers to the coupled cluster treatment of electronically excited or ionized states
ESR	Electron spin resonance: is a spectroscopic techniques equivalent to NMR (see below) but dealing with excitation of the electronic spins in open-shell systems.
EPR	Electron paramagnetic resonance: is a synonym of electron spin resonance.
Force constant	Derivative of the potential energy with respect to nuclear coordinates evaluated at the minimum structure (e.g. the quadratic force constant is the second derivative).
Fundamental band	Vibrational transition from the vibrational ground state to the first excited state of a given vibrational mode.
FWHM/HWHM	Full/Half width at half maximum: is the width (or half the width) between the two points where the value of the function is its half maximum.
Hamiltonian	In quantum mechanics, it is the operator corresponding to the energy of a system.
Harmonic	Model in which the vibrational motion is described in terms of masses attached to a spring, whose energy is governed by a quadratic potential.
Hybrid/Double-hybrid density functional	Families of density functionals including a percentage of Hartree-Fock exchange (hybrid) and MP2-type correlation (only double-hybrid).
Imaginary time	Since the time evolution of a quantum system starting from time t_0 is governed by $\exp[-iH(t-t_0)]$ where H is the Hamiltonian operator, $\tau = i(t-t_0)$ is usually referred to as imaginary time.
Infrared spectroscopy	Spectroscopy using the infrared region of the electromagnetic field to study the excitation of the vibrational states of molecules.
LFT	Ligand Field Theory: a semi-empirical "perturbed ion" model, based on CFT, that describes the electronic structure and properties of transition metal complexes.
Line-shape function	A mathematical function (usually Gaussian, Lorentzian or a combination of both) describing phenomenologically the shape of a spectral band.
MCD	The Circular Dichroism induced by a static, longitudinal external magnetic field.
LAM	Large amplitude motion: refers to a molecular vibration whose amplitude is so large that the harmonic oscillator model is no more a reliable zero-order approximation.
Mössbauer isomer shift	The shift in resonance frequency of the nuclear gamma-ray transition in a Mössbauer active isotope (e.g. ^{57}Fe) caused by its interaction with the molecular environment.
MM	Molecular mechanics (or force-field methods) uses classical type models to predict the energy of a molecule as a function of its conformation.
MP2	Møller-Plesset theory including many-body effects on top of the mean field Hartree-Fock reference wavefunction up to the second order of perturbation theory.
MRCI	Multi reference configuration interaction: extends the configuration interaction approach to multireference wavefunctions.
Multiplet	The ensemble of many particle states that arise from the distribution of a given number of electrons among sets of degenerate atomic or molecular orbitals under the action of the electron-electron (and perhaps the spin-orbit coupling) interaction.
NEVPT2	N-electron valence state perturbation theory to the second order: is a variant of second order multireference perturbation theory similar to CASPT2.
NMR	Nuclear magnetic resonance: is a spectroscopic technique based on the perturbation of nuclei in a strong constant magnetic field by a weak oscillating magnetic field (in their close environment), which produces an electromagnetic signal with a frequency related to the magnetic field at the nucleus.
Normal mode / Normal coordinate	Vibrational motion of the molecules where all atoms vibrate in phase with the same frequency but with different amplitudes, and the center of mass remains fixed. A normal coordinate is a linear combination of Cartesian displacement coordinates. The motion described by a normal coordinate is called a normal mode.
OPA	Spectroscopic technique in which one-photon absorption leads from the electronic ground state to an excited electronic state.
OPE	Spectroscopic technique in which one-photon emission leads from an excited electronic state to a less-excited (lower energy, usually the ground) state.

OR	Optical rotation: is the rotation angle of the polarization plane of polarized light issuing from its passage through a layer or a liquid and is determined by the concentration of chiral molecules and their structure in a substance.
Orbital splitting	Splitting of a specific orbital due to external factors (e.g. electric or magnetic field).
ORD	Optical rotatory dispersion: is the variation of the optical rotation of a substance with a change in the wavelength of light.
Overtone	Vibrational transition involving the excitation of two or more quanta of a given vibration mode (i.e. the quantum number describing the vibrational energy levels change varies by two or more)
PCM	Polarizable continuum model: description of bulk solvent effects in terms of a polarizable continuum in which the solute is fully embedded.
PES	Potential energy surface (multi-dimensional, hyper-surface): describes the variations of the electron energy of a system in terms of suitable nuclear coordinates.
PMM	Perturbed matrix method: describes solvent effects on a quantum center in terms of CIS, whose elements are the energies of the isolated solute perturbed by the electric field produced by the different configurations of the solvent issuing from a molecular dynamics simulation.
Position array	Array containing the coordinates of the position of a specific point in a multi-dimensional space.
PS	Property surface (multi-dimensional): describes the variations of a property as a function of suitable nuclear coordinates.
QC	Quantum chemistry (quantum chemical being the corresponding adjective): refers to the application of quantum mechanics to chemistry.
QM	Quantum mechanics (quantum mechanical being the corresponding adjective): is a fundamental theory of contemporary physics that provides a description of the properties of the matter at the atomic and subatomic level.
Raman spectroscopy	Rotational or vibrational spectroscopy that exploits the Raman effect (inelastic scattering).
Rigid-rotor harmonic-oscillator model	A reference model in which a molecular system as a whole is described in terms of a rigid rotating object and in terms of decoupled harmonic oscillators for its vibrational motion.
ROA	Raman optical activity: is a vibrational spectroscopy based on the differential Raman scattering of left and right circularly polarized light due to molecular chirality.
Rotational Spectroscopy	Spectroscopy using the microwave region of the electromagnetic field to study the excitation of the rotational states of molecules.
Rovibrational Spectroscopy	Spectroscopy dealing with rotational and vibrational states of molecules.
SAM	Small amplitude motion/mode: refers to a molecular vibration whose amplitude is small enough so that the harmonic oscillator is a reliable zero-order approximation.
Schrödinger equation	Equation associated to the Hamiltonian operator: its resolution provides the allowed energy levels (eigenvalues) and the corresponding wave functions (eigenfunctions).
Slater determinant	Representation of a many particle 'mean-field' wavefunction in terms of the antisymmetrized products of single-electron wavefunctions (molecular orbitals).
SOC	Spin orbit coupling: refers to the coupling between the spin and the orbital angular momenta.
Spectroscopic transition	The passage between two energy levels, i.e. from an initial to a final state, detected by a spectroscopic technique.
SQUID	Magnetometer based on superconducting loops used to measure very low magnetic fields.
STEOM	Similarity transformed equations of motion (see above).
TDA	Tamm Dancoff approximation: is, from a practical point of view, a synonym of CIS.
Template approach	A model in which the structure of a molecular system is refined with reference to suitable fragments, whose structures are accurately known.
VCD	Vibrational version of the circular dichroism.
VCI	Vibrational configuration interaction: exploits the configuration interaction model to treat vibrational motions.

Vibronic spectroscopy	Spectroscopy involving the simultaneous excitations of vibrational and electronic states of molecules.
VPT2	Vibrational perturbation theory to second order: exploits perturbation theory to the second order to treat the vibrational motions.
VSCF	Vibrational self-consistent field: exploits the self-consistent model to treat the vibrational motion.
Wave function	Mathematical description of the quantum state of an isolated quantum system resulting from the corresponding Schrödinger equation.
ZFS	Zero field splitting: describes the lifting of the degeneracy of the $2S+1$ magnetic sublevels of a spin multiplet with total spin S in the absence of a magnetic field, caused by the effects of SOC and electron-electron spin-spin interactions.
ZPE	Zero-point energy: is the lowest energy that a quantum system may have, which, contrary to the classical case, is nonzero due to the Heisenberg uncertainty principle.

1258

1259

1260

1261

1262
1263
1264
1265
1266
1267
1268
1269

1270

1271

1272
1273
1274

Author contributions

Introduction (V.B., M.B., F.N., C.P.); Experimentation (V.B., M.B., J.R.C., A. B. M., F.N., C.P.); Results (M.M., C.P., V.B., M.B., A.B.M., R.D., J.R.C.); Applications (M.M., C.P., D.C.C., F.N.); Reproducibility and data deposition (S.A., V.B., M.B., A.M.B., C.P.); Limitations and optimizations (S.A., V.B., M.B., J.R.C., C.P.); Outlook (V.B.); Overview of the Primer (C.P.).

Competing interests

All authors declare no competing interests.

Selected key references

[1] Nafie, L. A. in *Vibrational Optical Activity: Principles and Applications* (John Wiley & Sons, Chichester, United Kingdom, 2011).

Book that provides a comprehensive description of the underlying theory of the chiroptical spectroscopic methods VCD and ROA, and includes computational and experimental aspects as well as applications.

[18] Neese, F., Petrenko, T., Ganyushin, D. & Olbrich, G. Advanced aspects of ab initio theoretical optical spectroscopy of transition metal complexes: Multiplets, spin-orbit coupling and resonance Raman intensities. *Coord. Chem. Rev.* **251**, 288-327 (2007).

Review reporting a careful analysis of quantum-chemical approaches for the study of transition metal complexes.

[33] Neese, F. Quantum Chemistry and EPR Parameters. *eMagRes* **6**, 1-22 (2017).

The most recent and exhaustive review on the quantum-chemical computation of the parameters involved in the EPR spectroscopy.

[34] Puzzarini, C., Bloino, J., Tasinato, N. & Barone, V. Accuracy and Interpretability: The Devil and the Holy Grail. New Routes across Old Boundaries in Computational Spectroscopy. *Chem. Rev.* **119**, 8131-8191 (2019).

The most recent review on computational (rotational and vibrational) spectroscopy, also addressing the challenges of accuracy and interpretability.

[43] Franke, P. R., Stanton, J. F. & Douberly, G. E. How to VPT2: Accurate and Intuitive Simulations of CH Stretching Infrared Spectra Using VPT2+K with Large Effective Hamiltonian Resonance Treatments. *J. Phys. Chem. A* **125**, 1301-1324 (2021).

Recent instructive review on vibrational perturbation theory, also discussing in detail the treatment of resonances.

[61] Barone, V. The Virtual Multifrequency Spectrometer: a new paradigm for spectroscopy. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **6**, 86-110 (2016).

Recent review that introduces a new (also more intuitive) approach of computational spectroscopy based on the vis-à-vis comparison of calculated and experimental spectra instead of the mere computation of spectroscopic parameters.

[62] Bloino, J., Baiardi, A. & Biczysko, M. Aiming at an accurate prediction of vibrational and electronic spectra for medium-to-large molecules: An overview. *Int. J. Quantum Chem.* **116**, 1543-1574 (2016).

Tutorial review presenting detailed computational protocol and guidelines for the simulation of vibrational and vibrationally resolved electronic spectra for medium-to-large molecular systems of increasing flexibility.

[65] Srebro-Hooper, M. & Autschbach, J. Calculating Natural Optical Activity of Molecules from First Principles. *Annu. Rev. Phys. Chem.* **68**, 399-420 (2017).

Recent review that outlines computational models and methodological developments for chiroptical spectroscopic methods which include OR, ECD, VCD and ROA.

1322
1323
1324
1325
1326
1327
1328
1329
1330
1331
1332
1333
1334
1335
1336
1337
1338
1339
1340
1341
1342
1343
1344
1345
1346
1347
1348
1349
1350
1351
1352
1353
1354
1355
1356
1357
1358
1359
1360
1361
1362
1363
1364
1365
1366
1367

[84] Suhm, M. A. & Watts, R. O. Quantum Monte Carlo studies of vibrational states in molecules and clusters. *Phys. Rep.* **204**, 293-329 (1991).

Extensive review of the Diffusion Monte Carlo approach and its application to studies of nuclear quantum effects in molecules and clusters.

[85] Anderson, J. B. A random-walk simulation of the Schrödinger equation: H^+ . *J. Chem. Phys.* **63**, 1499-1503 (1975).

Key publication that introduced the diffusion Monte Carlo approaches described in this primer to the chemistry community.

[110] Grimme, S. Semiempirical hybrid density functional with perturbative second-order correlation. *J. Chem. Phys.* **124**, 034108 (2006).

Key publication reporting the introduction of double-hybrid functionals, which in turn allow quantitative spectroscopic studies by DFT.

[107] Neese, F., Wennmohs, F. & Hansen, A. Efficient and accurate local approximations to coupled-electron pair approaches: An attempt to revive the pair natural orbital method. *J. Chem. Phys.* **130**, 114108 (2009).

Key publication reporting the development and validation of an approach to extend the application of accurate quantum-chemical methods to large molecular systems.

[136] Baiardi, A. & Reiher, M. The density matrix renormalization group in chemistry and molecular physics: Recent developments and new challenges. *J. Chem. Phys.* **152**, 040903 (2020).

The most recent review on the use of methods rooted in the density matrix renormalization group for vibrational and electronic spectroscopy.

[140] Puzzarini, C., Stanton, J. F. & Gauss, J. Quantum-chemical calculation of spectroscopic parameters for rotational spectroscopy. *Int. Rev. Phys. Chem.* **29**, 273-367 (2010).

The most authoritative review on computational rotational spectroscopy.

[174]. Bogaerts, J. et al. A combined Raman optical activity and vibrational circular dichroism study on artemisinin-type products. *Phys. Chem. Chem. Phys.* **22**, 18014-18024 (2020).

A very recent study that demonstrates the combined use of two chiroptical spectroscopic methods, VCD and ROA, in determining the AC of a molecule with seven chiral centers.

[188] Puzzarini, C., Barone, V. A never-ending story in the sky: the secrets of chemical evolution, *Phys. Life Rev.* **32**, 59-94 (2020).

Recent review addressing the role of spectroscopic investigation for the characterization of molecules of astrochemical interest and their detection in space.

[200] Keutsch, F. N. & Saykally, R. J. Water clusters: Untangling the mysteries of the liquid, one molecule at a time. *Proc. Natl. Acad. Sci. U.S.A.* **98**, 10533-10540 (2001).

Comprehensive review on how theory is used to predict and interpret experimental measurements of spectra for water clusters.

1368 [213] Beć, K. B. & Huck, C. W. Breakthrough Potential in Near-Infrared Spectroscopy: Spectra
1369 Simulation. A Review of Recent Developments. *Front. Chem.* **7**, 48 (2019).
1370 Detailed review on the computational methods used for calculating the near-infrared spectra of
1371 larger polyatomic molecules.
1372
1373 [230] Dral, P. O. Quantum Chemistry in the Age of Machine Learning. *J. Phys. Chem. Lett.* **11**, 2336-
1374 2347 (2020).
1375 A general introduction on the use of machine learning in quantum chemistry.
1376
1377 [250] Loos, P.-F., Scemama, A. & Jacquemin, D. The Quest for Highly Accurate Excitation Energies: A
1378 Computational Perspective. *J. Phys. Chem. Lett.* **11**, 2374-2383 (2020).
1379 Recent perspective article on accurate computations of excitation energies.
1380
1381
1382

1383
1384
1385
1386
1387
1388
1389
1390
1391
1392
1393
1394
1395
1396
1397
1398
1399
1400
1401
1402
1403
1404
1405
1406
1407
1408
1409
1410
1411
1412
1413
1414
1415
1416
1417
1418
1419
1420
1421
1422
1423
1424
1425
1426
1427
1428
1429
1430
1431
1432

References

- 1 Nafie, L. A. in *Vibrational Optical Activity: Principles and Applications* (John Wiley & Sons, Chichester, United Kingdom, 2011).
- 2 Merkt, F. & Quack, M. *Handbook of High-resolution Spectroscopy*. (John Wiley & Sons, New York, NY, USA, 2011).
- 3 Laane, J. *Frontiers of Molecular Spectroscopy*. (Elsevier, Amsterdam, The Netherlands, 2008).
- 4 Berova, N., Nakanishi, K. & Woody, R. W. *Circular Dichroism: Principles and Applications*. 2 edn, (Wiley-VCH, New York, NY, USA, 2000).
- 5 Rijs, A. M. & Oomens, J. *Gas-phase IR Spectroscopy and Structure of Biological Molecules. Topics in Current Chemistry*. . Vol. 364 (Springer International Publishing, Switzerland, 2015).
- 6 Pulay, P., Meyer, W. & Boggs, J. E. Cubic force constants and equilibrium geometry of methane from Hartree–Fock and correlated wavefunctions. *J. Chem. Phys.* **68**, 5077-5085 (1978).
- 7 Obenchain, D. A. *et al.* Unveiling the Sulfur-Sulfur Bridge: Accurate Structural and Energetic Characterization of a Homochalcogen Intermolecular Bond. *Angew. Chem. Int. Ed.* **57**, 15822-15826 (2018).
- 8 Caminati, W. in *Handbook of High-resolution Spectroscopy* (eds F. Merkt & M. Quack) (John Wiley & Sons, New York, NY, USA, 2011).
- 9 Park, G. B. & Field, R. W. Perspective: The first ten years of broadband chirped pulse Fourier transform microwave spectroscopy. *J. Chem. Phys.* **144**, 200901 (2016).
- 10 Xie, F. *et al.* Discovering the Elusive Global Minimum in a Ternary Chiral Cluster: Rotational Spectra of Propylene Oxide Trimer. *Angew. Chem. Int. Ed.* **59**, 22427-22430 (2020).
- 11 Wang, J. *et al.* The Unexplored World of Cycloalkene–Water Complexes: Primary and Assisting Interactions Unraveled by Experimental and Computational Spectroscopy. *Angew. Chem. Int. Ed.* **58**, 13935–13941 (2019).
- 12 Alonso, J. L. & López, J. C. in *Gas-Phase IR Spectroscopy and Structure of Biological Molecules* (eds Anouk M. Rijs & Jos Oomens) 335-401 (Springer International Publishing, 2015).
- 13 Atanasov, M. *et al.* First principles approach to the electronic structure, magnetic anisotropy and spin relaxation in mononuclear 3d-transition metal single molecule magnets. *Coord. Chem. Rev.* **289-290**, 177-214 (2015).
- 14 Barone, V. in *Computational strategies for spectroscopy: from small molecules to nano systems* (John Wiley & Sons, Hoboken, New Jersey, 2011).
- 15 Grunenberg, J. in *Computational spectroscopy: methods, experiments and applications* (John Wiley & Sons, Weinheim, Germany, 2011).
- 16 Jensen, P., Bunker P. R. . in *Computational Molecular Spectroscopy* (Wiley & Sons, Chichester, United Kingdom, 2000).
- 17 Neese, F. Prediction of molecular properties and molecular spectroscopy with density functional theory: From fundamental theory to exchange-coupling. *Coord. Chem. Rev.* **253**, 526-563 (2009).
- 18 Neese, F., Petrenko, T., Ganyushin, D. & Olbrich, G. Advanced aspects of ab initio theoretical optical spectroscopy of transition metal complexes: Multiplets, spin-orbit coupling and resonance Raman intensities. *Coord. Chem. Rev.* **251**, 288-327 (2007).
- 19 Mata, R. A. & Suhm, M. A. Benchmarking Quantum Chemical Methods: Are We Heading in the Right Direction? *Angew. Chem. Int. Ed.* **56**, 11011-11018 (2017).
- 20 Born, M. & Oppenheimer, R. Zur quantentheorie der molekeln. *Ann. Phys. (Berlin)* **389**, 457-484 (1927).

- 1433 21 Eckart, C. Some Studies Concerning Rotating Axes and Polyatomic Molecules. *Phys. Rev.* **47**, 552-558 (1935).
1434
- 1435 22 Sayvetz, A. The Kinetic Energy of Polyatomic Molecules. *J. Chem. Phys.* **7**, 383-389 (1939).
1436 23 Watson, J. K. G. Simplification of the molecular vibration-rotation hamiltonian. *Mol. Phys.* **15**, 479-490 (1968).
1437
- 1438 24 Watson, J. K. G. The vibration-rotation hamiltonian of linear molecules. *Mol. Phys.* **19**, 465-
1439 487 (1970).
- 1440 25 Furtenbacher, T., Császár, A. G. & Tennyson, J. MARVEL: measured active rotational-
1441 vibrational energy levels. *J. Mol. Spectrosc.* **245**, 115-125 (2007).
- 1442 26 Furtenbacher, T. & Császár, A. G. On employing H₂¹⁶O, H₂¹⁷O, H₂¹⁸O, and D₂¹⁶O lines as
1443 frequency standards in the 15–170 cm⁻¹ window. *J. Quant. Spectrosc. Radiat. Transfer* **109**,
1444 1234-1251 (2008).
- 1445 27 Aliev, M. R. & Watson, J. K. G. in *Molecular Spectroscopy: Modern Research* (ed Narahari
1446 Rao K.) Ch. Higher-order effects in the vibration-rotation spectra of semirigid molecules 1-
1447 67 (Academic Press, London, 1985).
- 1448 28 Gordy, W. & Cook, R. L. in *Microwave Molecular Spectra* (ed Weissberger A) (Wiley,
1449 New York, 1984).
- 1450 29 Watson, J. K. G. in *Vibrational Spectra and Structure: a series of advances* (ed Durig J. R.)
1451 (Elsevier, Amsterdam, 1977).
- 1452 30 Kaupp, M., Buhl, M. & Malkin, V. G. in *Calculation of NMR and EPR Parameters. Theory*
1453 *and Applications* (eds Kaupp M., Buhl M., & Malkin V. G.) (Wiley, Weinheim, 2004).
- 1454 31 Barone, V. & Polimeno, A. in *Electron Paramagnetic Resonance: A Practitioner's Toolkit*
1455 (eds Brustolon M. & Giamello E.) Ch. The Virtual Electron Paramagnetic Resonance
1456 Laboratory: A User Guide to ab initio Modeling, 251-284 (John Wiley & Sons, Hoboken,
1457 New Jersey, 2008).
- 1458 32 Jose, K. V. & Raghavachari, K. Fragment-Based Approach for the Evaluation of NMR
1459 Chemical Shifts for Large Biomolecules Incorporating the Effects of the Solvent
1460 Environment. *J. Chem. Theory Comput.* **13**, 1147-1158 (2017).
- 1461 33 Neese, F. Quantum Chemistry and EPR Parameters. *eMagRes* **6**, 1-22 (2017).
- 1462 34 Puzzarini, C., Bloino, J., Tasinato, N. & Barone, V. Accuracy and Interpretability: The Devil
1463 and the Holy Grail. New Routes across Old Boundaries in Computational Spectroscopy.
1464 *Chem. Rev.* **119**, 8131-8191 (2019).
- 1465 35 Bloino, J., Biczysko, M. & Barone, V. Anharmonic Effects on Vibrational Spectra Intensities:
1466 Infrared, Raman, Vibrational Circular Dichroism, and Raman Optical Activity. *J. Phys.*
1467 *Chem. A* **119**, 11862-11874 (2015).
- 1468 36 Nielsen, H. H. The Vibration-Rotation Energies of Molecules. *Rev. Mod. Phys.* **23**, 90-136
1469 (1951).
- 1470 37 Mills, I. A. in *Molecular Spectroscopy: Modern Research* (eds K. Narahari Rao & C. Weldon
1471 Mathews) (Academic Press, New York, NY, USA, 1972).
- 1472 38 Barone, V. Anharmonic vibrational properties by a fully automated second-order perturbative
1473 approach. *J. Chem. Phys.* **122**, 14108 (2005).
- 1474 39 Bloino, J. & Barone, V. A second-order perturbation theory route to vibrational averages and
1475 transition properties of molecules: General formulation and application to infrared and
1476 vibrational circular dichroism spectroscopies. *J. Chem. Phys.* **136**, 124108 (2012).
- 1477 40 Vázquez, J. & Stanton, J. F. Simple(r) algebraic equation for transition moments of
1478 fundamental transitions in vibrational second-order perturbation theory. *Mol. Phys.* **104**, 377-
1479 388 (2006).
- 1480 41 Willetts, A., Handy, N. C., Green, W. H. & Jayatilaka, D. Anharmonic corrections to
1481 vibrational transition intensities. *J. Phys. Chem.* **94**, 5608-5616 (1990).
- 1482 42 Császár, A. G. Anharmonic molecular force fields. *WIREs Comput. Mol. Sci.* **2**, 273-289
1483 (2012).

- 1484 43 Franke, P. R., Stanton, J. F. & Douberly, G. E. How to VPT2: Accurate and Intuitive
1485 Simulations of CH Stretching Infrared Spectra Using VPT2+K with Large Effective
1486 Hamiltonian Resonance Treatments. *J. Phys. Chem. A* **125**, 1301-1324 (2021).
- 1487 44 Cornaton, Y., Ringholm, M., Louant, O. & Ruud, K. Analytic calculations of anharmonic
1488 infrared and Raman vibrational spectra. *Phys. Chem. Chem. Phys.* **18**, 4201-4215 (2016).
- 1489 45 Maslen, P. E., Jayatilaka, D., Colwell, S. M., Amos, R. D. & Handy, N. C. Higher analytic
1490 derivatives. II. The fourth derivative of self-consistent-field energy. *J. Chem. Phys.* **95**, 7409-
1491 7417 (1991).
- 1492 46 Piccardo, M., Bloino, J. & Barone, V. Generalized vibrational perturbation theory for
1493 roto-vibrational energies of linear, symmetric and asymmetric tops: Theory, approximations,
1494 and automated approaches to deal with medium-to-large molecular systems. *Int. J. Quantum
1495 Chem.* **115**, 948-982 (2015).
- 1496 47 Roy, T. K. & Gerber, R. B. Vibrational self-consistent field calculations for spectroscopy of
1497 biological molecules: new algorithmic developments and applications. *Phys. Chem. Chem.
1498 Phys.* **15**, 9468-9492 (2013).
- 1499 48 Neff, M. & Rauhut, G. Toward large scale vibrational configuration interaction calculations.
1500 *J. Chem. Phys.* **131**, 124129 (2009).
- 1501 49 Christiansen, O. Vibrational coupled cluster theory. *J. Chem. Phys.* **120**, 2149-2159 (2004).
- 1502 50 Erfort, S., Tschöpe, M. & Rauhut, G. Toward a fully automated calculation of rovibrational
1503 infrared intensities for semi-rigid polyatomic molecules. *J. Chem. Phys.* **152**, 244104 (2020).
- 1504 51 Biczysko, M., Bloino, J., Santoro, F. and Barone, V. in *Computational Strategies for
1505 Spectroscopy: From Small Molecules to Nano Systems* (ed Barone V) Ch. Time-Independent
1506 Approaches to Simulate Electronic Spectra Lineshapes: From Small Molecules to
1507 Macrosystems, 361-443 (John Wiley & Sons, Hoboken, New Jersey, 2011).
- 1508 52 Bloino, J., Biczysko, M., Santoro, F. & Barone, V. General Approach to Compute
1509 Vibrationally Resolved One-Photon Electronic Spectra. *J. Chem. Theoy Comput.* **6**, 1256-
1510 1274 (2010).
- 1511 53 Baiardi, A., Bloino, J. & Barone, V. General Time Dependent Approach to Vibronic
1512 Spectroscopy Including Franck–Condon, Herzberg–Teller, and Duschinsky Effects. *J. Chem.
1513 Theoy Comput.* **9**, 4097-4115 (2013).
- 1514 54 Franck, J. & Dymond, E. G. Elementary processes of photochemical reactions. *Trans.
1515 Faraday Society* **21**, 536-542 (1926).
- 1516 55 Condon, E. U. Nuclear Motions Associated with Electron Transitions in Diatomic Molecules.
1517 *Phys. Rev.* **32**, 858-872 (1928).
- 1518 56 Herzberg, G. & Teller, E. Schwingungsstruktur der Elektronenübergänge bei mehratomigen
1519 Molekülen. *Z. Phys. Chem.* **21B**, 410 - 446 (1933).
- 1520 57 Duschinsky, F. *Acta Physicochim. URSS.* 551 (1937).
- 1521 58 Baiardi, A., Bloino, J. & Barone, V. General formulation of vibronic spectroscopy in internal
1522 coordinates. *J. Chem. Phys.* **144**, 084114 (2016).
- 1523 59 Reimers, J. R. A practical method for the use of curvilinear coordinates in calculations of
1524 normal-mode-projected displacements and Duschinsky rotation matrices for large molecules.
1525 *J. Chem. Phys.* **115**, 9103-9109 (2001).
- 1526 60 Baiardi, A., Bloino, J. & Barone, V. Simulation of Vibronic Spectra of Flexible Systems:
1527 Hybrid DVR-Harmonic Approaches. *J. Chem. Theoy Comput.* **13**, 2804-2822 (2017).
- 1528 61 Barone, V. The Virtual Multifrequency Spectrometer: a new paradigm for spectroscopy.
1529 *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **6**, 86-110 (2016).
- 1530 62 Bloino, J., Baiardi, A. & Biczysko, M. Aiming at an accurate prediction of vibrational and
1531 electronic spectra for medium-to-large molecules: An overview. *Int. J. Quantum Chem.* **116**,
1532 1543-1574 (2016).
- 1533 63 Autschbach, J. in *Comprehensive Chiroptical Spectroscopy: Instrumentation, Methodologies,
1534 and Theoretical Simulations, Volume 1* (eds Berova N, Polavarapu P L, Nakanishi K, &

- 1535 Woody R W) Ch. AB Initio Electronic Circular Dichroism and Optical Rotatory Dispersion:
1536 From Organic Molecules to Transition Metal Complexes, 593-642 (John Wiley & Sons,
1537 Hoboken, New Jersey, 2011).
- 1538 64 Crawford, T. D. in *Comprehensive Chiroptical Spectroscopy: Instrumentation,
1539 Methodologies, and Theoretical Simulations, Volume 1* (eds Berova N, Polavarapu P L,
1540 Nakanishi K, & Woody R W) Ch. High-Accuracy Quantum Chemistry and Chiroptical
1541 Properties, 675-697 (John Wiley & Sons, Hoboken, New Jersey, 2011).
- 1542 65 Srebro-Hooper, M. & Autschbach, J. Calculating Natural Optical Activity of Molecules from
1543 First Principles. *Annu. Rev. Phys. Chem.* **68**, 399-420 (2017).
- 1544 66 Stephens, P. J., Devlin, F. J. & Cheeseman, J. R. in *VCD Spectroscopy for Organic Chemists*
1545 (CRC Press, Taylor & Francis Group, Boca Raton, Florida, 2012).
- 1546 67 Ruud, K. in *Comprehensive Chiroptical Spectroscopy: Instrumentation, Methodologies, and
1547 Theoretical Simulations, Volume 1* (eds Berova N, Polavarapu P L, Nakanishi K, & Woody
1548 R W) Ch. AB Initio Methods for Vibrational Circular Dichroism and Raman Optical Activity,
1549 699-727 (John Wiley & Sons, Hoboken, New Jersey, 2011).
- 1550 68 Beer. Bestimmung der Absorption des rothen Lichts in farbigen Flüssigkeiten. *Ann. Phys.*
1551 (*Berlin*) **162**, 78-88 (1852).
- 1552 69 Polavarapu, P. L. in *Chiroptical spectroscopy: fundamentals and applications* (CRC Press,
1553 Taylor & Francis Group, Boca Raton, Florida, 2016).
- 1554 70 Stephens, P. J. & Harada, N. ECD cotton effect approximated by the Gaussian curve and other
1555 methods. *Chirality* **22**, 229-233 (2010).
- 1556 71 Cheeseman, J. R. & Frisch, M. J. Basis Set Dependence of Vibrational Raman and Raman
1557 Optical Activity Intensities. *J. Chem. Theory Comput.* **7**, 3323-3334 (2011).
- 1558 72 Liégeois, V., Ruud, K. & Champagne, B. An analytical derivative procedure for the
1559 calculation of vibrational Raman optical activity spectra. *J. Chem. Phys.* **127**, 204105 (2007).
- 1560 73 Nafie, L. A. Theory of Raman scattering and Raman optical activity: near resonance theory
1561 and levels of approximation. *Theor. Chem. Acc.* **119**, 39-55 (2008).
- 1562 74 Barron, L. D. in *Molecular Light Scattering and Optical Activity* (Cambridge University
1563 Press, Cambridge, 2004).
- 1564 75 Long, D. A. in *The Raman effect: a unified treatment of the theory of Raman scattering by
1565 molecules* (John Wiley & Sons, Chichester, United Kingdom, 2002).
- 1566 76 Neugebauer, J., Reiher, M., Kind, C. & Hess, B. A. Quantum chemical calculation of
1567 vibrational spectra of large molecules--Raman and IR spectra for Buckminsterfullerene. *J.*
1568 *Comput. Chem.* **23**, 895-910 (2002).
- 1569 77 Dzugan, L. C., DiRisio, R. J., Madison, L. R. & McCoy, A. B. Spectral signatures of proton
1570 delocalization in $H^+(H_2O)_{n=1-4}$ ions. *Faraday Discuss.* **212**, 443-466 (2018).
- 1571 78 Tanaka, S., Roy, P.-N. & Mitas, L. in *Recent progress in Quantum Monte Carlo* Vol. 1234
1572 (ACS Publications, Washington DC, 2016).
- 1573 79 Tanaka, S., Rothstein, S. M. & Lester Jr, W. A. in *Advances in Quantum Monte Carlo* Vol.
1574 1094 (ACS Publications, Washington DC, 2012).
- 1575 80 Anderson, J. B. & Rothstein, S. M. in *Advances in Quantum Monte Carlo* Vol. 953 (ACS
1576 Publications, Washington DC, 2007).
- 1577 81 Lester, W. A., Rothstein, S. M. & Tanaka, S. in *Recent Advances in Quantum Monte Carlo*
1578 *Methods: Part II Recent Advances in Computational Chemistry: Volume 2* (World
1579 Scientific, Singapore, 2002).
- 1580 82 Lester, W. A., Rothstein, S. M. & Tanaka, S. in *Recent Advances in Quantum Monte Carlo*
1581 *Methods Recent Advances in Computational Chemistry* (World Scientific, Singapore, 1997).
- 1582 83 McCoy, A. B. Diffusion Monte Carlo approaches for investigating the structure and
1583 vibrational spectra of fluxional systems. *Int. Rev. Phys. Chem.* **25**, 77-107 (2006).
- 1584 84 Suhm, M. A. & Watts, R. O. Quantum Monte Carlo studies of vibrational states in molecules
1585 and clusters. *Phys. Rep.* **204**, 293-329 (1991).

- 1586 85 Anderson, J. B. A random-walk simulation of the Schrödinger equation: H^{+3} . *J. Chem. Phys.* **63**, 1499-1503 (1975).
- 1587
- 1588 86 Anderson, J. B. Quantum chemistry by random walk. H^2P , $H^{+3} D_{3h}^1 A'_1$, $H_2^3 \Sigma^{+u}$, $H_4^1 \Sigma^{+g}$, $Be^1 S$. *J. Chem. Phys.* **65**, 4121-4127 (1976).
- 1589
- 1590 87 Barnett, R. N., Reynolds, P. J. & Lester, W. A. Monte Carlo algorithms for expectation values of coordinate operators. *J. Comput. Phys.* **96**, 258-276 (1991).
- 1591
- 1592 88 Petit, A. S., Wellen, B. A. & McCoy, A. B. Using fixed-node diffusion Monte Carlo to investigate the effects of rotation-vibration coupling in highly fluxional asymmetric top molecules: Application to H_2D^+ . *J. Chem. Phys.* **138** (2013).
- 1593
- 1594
- 1595 89 Lee, H.-S., Herbert, J. M. & McCoy, A. B. Adiabatic diffusion Monte Carlo approaches for studies of ground and excited state properties of van der Waals complexes. *J. Chem. Phys.* **110**, 5481-5484 (1999).
- 1596
- 1597
- 1598 90 Csaszar, A. G., Allen, W. D. & Schaefer III, H. F. In pursuit of the ab initio limit for conformational energy prototypes. *J. Chem. Phys.* **108**, 9751-9764 (1998).
- 1599
- 1600 91 Montgomery, J. A., Frisch, M. J., Ochterski, J. W. & Petersson, G. A. A complete basis set model chemistry. VI. Use of density functional geometries and frequencies. *J. Chem. Phys.* **110**, 2822-2827 (1999).
- 1601
- 1602
- 1603 92 Demaison, J., Margules, L. & Boggs, J. E. The equilibrium C-Cl, C-Br, and C-I bond lengths from ab initio calculations, microwave and infrared spectroscopies, and empirical correlations. *Struct. Chem.* **14**, 159-174 (2003).
- 1604
- 1605
- 1606 93 Puzzarini, C. Extrapolation to the Complete Basis Set Limit of Structural Parameters: Comparison of Different Approaches. *J. Phys. Chem. A* **113**, 14530-14535 (2009).
- 1607
- 1608 94 Puzzarini, C. & Barone, V. Extending the molecular size in accurate quantum-chemical calculations: the equilibrium structure and spectroscopic properties of uracil. *Phys. Chem. Chem. Phys.* **13**, 7189-7197 (2011).
- 1609
- 1610
- 1611 95 Alessandrini, S., Barone, V. & Puzzarini, C. Extension of the "Cheap" Composite Approach to Noncovalent Interactions: The jun-ChS Scheme. *J. Chem. Theory Comput.* **16**, 988-1006 (2020).
- 1612
- 1613
- 1614 96 Tajti, A. *et al.* HEAT: High accuracy extrapolated ab initio thermochemistry. *J. Chem. Phys.* **121**, 11599-11613 (2004).
- 1615
- 1616 97 Heckert, M., Kállay, M., Tew, D. P., Klopper, W. & Gauss, J. Basis-set extrapolation techniques for the accurate calculation of molecular equilibrium geometries using coupled-cluster theory. *J. Chem. Phys.* **125**, 044108 (2006).
- 1617
- 1618
- 1619 98 Puzzarini, C., Heckert, M. & Gauss, J. The accuracy of rotational constants predicted by high-level quantum-chemical calculations. I. Molecules containing first-row atoms. *J. Chem. Phys.* **128**, 194108 (2008).
- 1620
- 1621
- 1622 99 Yu, Q. *et al.* Structure, Anharmonic Vibrational Frequencies, and Intensities of $NNHNN^+$. *J. Phys. Chem. A* **119**, 11623-11631 (2015).
- 1623
- 1624 100 Boese, A. D. *et al.* W3 theory: Robust computational thermochemistry in the kJ/mol accuracy range. *J. Chem. Phys.* **120**, 4129-4141 (2004).
- 1625
- 1626 101 Karton, A., Rabinovich, E., Martin, J. M. L. & Ruscic, B. W4 theory for computational thermochemistry: In pursuit of confident sub-kJ/mol predictions. *J. Chem. Phys.* **125**, 144108 (2006).
- 1627
- 1628
- 1629 102 Peterson, K. A., Feller, D. & Dixon, D. A. Chemical accuracy in ab initio thermochemistry and spectroscopy: current strategies and future challenges. *Theor. Chem. Acc.* **131**, 1079 (2012).
- 1630
- 1631
- 1632 103 Shavitt, I. & Bartlett, R. J. in *Many-Body Methods in Chemistry and Physics: MBPT and Coupled-Cluster Theory Cambridge Molecular Science* (Cambridge University Press, Cambridge, 2009).
- 1633
- 1634
- 1635 104 Raghavachari, K., Trucks, G. W., Pople, J. A. & Head-Gordon, M. A fifth-order perturbation comparison of electron correlation theories *Chem. Phys. Lett.* **589**, 37-40 (2013).
- 1636

- 1637 105 Kong, L., Bischoff, F. A. & Valeev, E. F. Explicitly Correlated R12/F12 Methods for
1638 Electronic Structure. *Chem. Rev.* **112**, 75-107 (2012).
- 1639 106 Neese, F., Hansen, A. & Liakos, D. G. Efficient and accurate approximations to the local
1640 coupled cluster singles doubles method using a truncated pair natural orbital basis. *J. Chem.*
1641 *Phys.* **131**, 064103 (2009).
- 1642 107 Neese, F., Wennmohs, F. & Hansen, A. Efficient and accurate local approximations to
1643 coupled-electron pair approaches: An attempt to revive the pair natural orbital method. *J.*
1644 *Chem. Phys.* **130**, 114108 (2009).
- 1645 108 Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. *J. Chem.*
1646 *Phys.* **98**, 5648-5652 (1993).
- 1647 109 Lee, C., Yang, W. & Parr, R. G. Development of the Colle-Salvetti correlation-energy formula
1648 into a functional of the electron density. *Phys. Rev. B* **37**, 785-789 (1988).
- 1649 110 Grimme, S. Semiempirical hybrid density functional with perturbative second-order
1650 correlation. *J. Chem. Phys.* **124**, 034108 (2006).
- 1651 111 Møller, C. & Plesset, M. S. Note on an Approximation Treatment for Many-Electron Systems.
1652 *Phys. Rev.* **46**, 618-622 (1934).
- 1653 112 Barone, V., Biczysko, M., Bloino, J. & Puzzarini, C. Accurate molecular structures and
1654 infrared spectra of trans-2,3-dideuteriooxirane, methyloxirane, and trans-2,3-dimethyloxirane.
1655 *J. Chem. Phys.* **141**, 034107 (2014).
- 1656 113 Barone, V., Biczysko, M., Bloino, J. & Puzzarini, C. Accurate structure, thermodynamic and
1657 spectroscopic parameters from CC and CC/DFT schemes: the challenge of the conformational
1658 equilibrium in glycine. *Phys. Chem. Chem. Phys.* **15**, 10094-10111 (2013).
- 1659 114 Jurečka, P., Šponer, J., Černý, J. & Hobza, P. Benchmark database of accurate (MP2 and
1660 CCSD(T) complete basis set limit) interaction energies of small model complexes, DNA base
1661 pairs, and amino acid pairs. *Phys. Chem. Chem. Phys.* **8**, 1985-1993 (2006).
- 1662 115 Řezáč, J., Riley, K. E. & Hobza, P. S66: A Well-balanced Database of Benchmark Interaction
1663 Energies Relevant to Biomolecular Structures. *J. Chem. Theory Comput.* **7**, 2427-2438 (2011).
- 1664 116 Řezáč, J., Bím, D., Gutten, O. & Rulíšek, L. Toward Accurate Conformational Energies of
1665 Smaller Peptides and Medium-Sized Macrocycles: MPCONF196 Benchmark Energy Data
1666 Set. *J. Chem. Theory Comput.* **14**, 1254-1266 (2018).
- 1667 117 Goerigk, L. *et al.* A look at the density functional theory zoo with the advanced GMTKN55
1668 database for general main group thermochemistry, kinetics and noncovalent interactions.
1669 *Phys. Chem. Chem. Phys.* **19**, 32184-32215 (2017).
- 1670 118 Biczysko, M., Panek, P., Scalmani, G., Bloino, J. & Barone, V. Harmonic and Anharmonic
1671 Vibrational Frequency Calculations with the Double-Hybrid B2PLYP Method: Analytic
1672 Second Derivatives and Benchmark Studies. *J. Chem. Theory Comput.* **6**, 2115-2125 (2010).
- 1673 119 Barone, V., Biczysko, M. & Bloino, J. Fully anharmonic IR and Raman spectra of medium-
1674 size molecular systems: accuracy and interpretation. *Phys. Chem. Chem. Phys.* **16**, 1759-1787
1675 (2014).
- 1676 120 Shu, C., Jiang, Z. & Biczysko, M. Toward accurate prediction of amino acid derivatives
1677 structure and energetics from DFT: glycine conformers and their interconversions. *J. Mol.*
1678 *Model.* **26**, 129 (2020).
- 1679 121 Brémond, É. *et al.* Benchmarking Density Functionals on Structural Parameters of Small-
1680 /Medium-Sized Organic Molecules. *J. Chem. Theory Comput.* **12**, 459-465 (2016).
- 1681 122 Risthaus, T., Steinmetz, M. & Grimme, S. Implementation of nuclear gradients of range-
1682 separated hybrid density functionals and benchmarking on rotational constants for organic
1683 molecules. *J. Comput. Chem.* **35**, 1509-1516 (2014).
- 1684 123 Su, N. Q. & Xu, X. Beyond energies: geometry predictions with the XYG3 type of doubly
1685 hybrid density functionals. *Chem. Commun.* **52**, 13840-13860 (2016).

- 1686 124 Witte, J., Goldey, M., Neaton, J. B. & Head-Gordon, M. Beyond Energies: Geometries of
1687 Nonbonded Molecular Complexes as Metrics for Assessing Electronic Structure Approaches.
1688 *J. Chem. Theory Comput.* **11**, 1481-1492 (2015).
- 1689 125 Yu, H. S., He, X., Li, S. L. & Truhlar, D. G. MN15: A Kohn–Sham global-hybrid exchange–
1690 correlation density functional with broad accuracy for multi-reference and single-reference
1691 systems and noncovalent interactions. *Chem. Sci.* **7**, 5032-5051 (2016).
- 1692 126 Boussessi, R., Ceselin, G., Tasinato, N. & Barone, V. DFT meets the segmented polarization
1693 consistent basis sets: Performances in the computation of molecular structures, rotational and
1694 vibrational spectroscopic properties. *J. Mol. Struct.* **1208**, 127886 (2020).
- 1695 127 Hanson-Heine, M. W. D. Benchmarking DFT-D Dispersion Corrections for Anharmonic
1696 Vibrational Frequencies and Harmonic Scaling Factors. *J. Phys. Chem. A* **123**, 9800-9808
1697 (2019).
- 1698 128 Loos, P.-F., Lipparini, F., Boggio-Pasqua, M., Scemama, A. & Jacquemin, D. A
1699 Mountaineering Strategy to Excited States: Highly Accurate Energies and Benchmarks for
1700 Medium Sized Molecules. *J. Chem. Theory Comput.* **16**, 1711-1741 (2020).
- 1701 129 Brémond, E., Savarese, M., Adamo, C. & Jacquemin, D. Accuracy of TD-DFT Geometries:
1702 A Fresh Look. *J. Chem. Theory Comput.* **14**, 3715-3727 (2018).
- 1703 130 Egidi, F. *et al.* Effective Inclusion of Mechanical and Electrical Anharmonicity in Excited
1704 Electronic States: VPT2-TDDFT Route. *J. Chem. Theory Comput.* **13**, 2789-2803 (2017).
- 1705 131 Bomble, Y. J. *et al.* Equation-of-motion coupled-cluster methods for ionized states with an
1706 approximate treatment of triple excitations. *J. Chem. Phys.* **122**, 154107 (2005).
- 1707 132 Roos, B. O., Lindh, R., Malmqvist, P. Å., Veryazov, V. & Widmark, P.-O. in
1708 *Multiconfigurational Quantum Chemistry* (John Wiley & Sons, Hoboken, New Jersey,
1709 2016).
- 1710 133 Auer, A. A. *et al.* A case study of density functional theory and domain-based local pair
1711 natural orbital coupled cluster for vibrational effects on EPR hyperfine coupling constants:
1712 vibrational perturbation theory versus ab initio molecular dynamics. *Mol. Phys.*, e1797916
1713 (2020).
- 1714 134 Datta, D., Saitow, M., Sandhöfer, B. & Neese, F. ⁵⁷Fe Mössbauer parameters from domain
1715 based local pair-natural orbital coupled-cluster theory. *J. Chem. Phys.* **153**, 204101 (2020).
- 1716 135 Sirohiwal, A., Berraud-Pache, R., Neese, F., Izsák, R. & Pantazis, D. A. Accurate
1717 Computation of the Absorption Spectrum of Chlorophyll a with Pair Natural Orbital Coupled
1718 Cluster Methods. *J. Phys. Chem. B* **124**, 8761-8771 (2020).
- 1719 136 Baiardi, A. & Reiher, M. The density matrix renormalization group in chemistry and
1720 molecular physics: Recent developments and new challenges. *J. Chem. Phys.* **152**, 040903
1721 (2020).
- 1722 137 Andersson, K., Malmqvist, P. Å. & Roos, B. O. Second-order perturbation theory with a
1723 complete active space self-consistent field reference function. *J. Chem. Phys.* **96**, 1218-1226
1724 (1992).
- 1725 138 Andersson, K., Malmqvist, P. A., Roos, B. O., Sadlej, A. J. & Wolinski, K. Second-order
1726 perturbation theory with a CASSCF reference function. *J. Phys. Chem.* **94**, 5483-5488 (1990).
- 1727 139 Angeli, C., Cimiraglia, R., Evangelisti, S., Leininger, T. & Malrieu, J.-P. Introduction of n-
1728 electron valence states for multireference perturbation theory. *J. Chem. Phys.* **114**, 10252-
1729 10264 (2001).
- 1730 140 Puzzarini, C., Stanton, J. F. & Gauss, J. Quantum-chemical calculation of spectroscopic
1731 parameters for rotational spectroscopy. *Int. Rev. Phys. Chem.* **29**, 273-367 (2010).
- 1732 141 Licari, D., Tasinato, N., Spada, L., Puzzarini, C. & Barone, V. VMS-ROT: A New Module of
1733 the Virtual Multifrequency Spectrometer for Simulation, Interpretation, and Fitting of
1734 Rotational Spectra. *J. Chem. Theory Comput.* **13**, 4382-4396 (2017).

- 1735 142 Lesarri, A., Mata, S., López, J. C. & Alonso, J. L. A laser-ablation molecular-beam Fourier-
1736 transform microwave spectrometer: The rotational spectrum of organic solids. *Rev. Sci.*
1737 *Instrum.* **74**, 4799-4804 (2003).
- 1738 143 Mancini, G., Fusè, M., Lazzari, F., Chandramouli, B. & Barone, V. Unsupervised search of
1739 low-lying conformers with spectroscopic accuracy: A two-step algorithm rooted into the
1740 island model evolutionary algorithm. *J. Chem. Phys.* **153**, 124110 (2020).
- 1741 144 Császár, A. G. *et al.* The fourth age of quantum chemistry: molecules in motion. *Phys. Chem.*
1742 *Chem. Phys.* **14**, 1085-1106 (2012).
- 1743 145 Baiardi, A., Stein, C. J., Barone, V. & Reiher, M. Vibrational Density Matrix Renormalization
1744 Group. *J. Chem. Theoy Comput.* **13**, 3764-3777 (2017).
- 1745 146 Carter, S., Sharma, A. R., Bowman, J. M., Rosmus, P. & Tarroni, R. Calculations of
1746 rovibrational energies and dipole transition intensities for polyatomic molecules using
1747 MULTIMODE. *J. Chem. Phys.* **131**, 224106 (2009).
- 1748 147 Begušić, T. & Vaniček, J. On-the-fly ab initio semiclassical evaluation of vibronic spectra at
1749 finite temperature. *J. Chem. Phys.* **153**, 024105 (2020).
- 1750 148 Hirshberg, B., Sagiv, L. & Gerber, R. B. Approximate Quantum Dynamics using Ab Initio
1751 Classical Separable Potentials: Spectroscopic Applications. *J. Chem. Theoy Comput.* **13**, 982-
1752 991 (2017).
- 1753 149 Gaigeot, M.-P. Theoretical spectroscopy of floppy peptides at room temperature. A DFTMD
1754 perspective: gas and aqueous phase. *Phys. Chem. Chem. Phys.* **12**, 3336-3359 (2010).
- 1755 150 Pracht, P., Bohle, F. & Grimme, S. Automated exploration of the low-energy chemical space
1756 with fast quantum chemical methods. *Phys. Chem. Chem. Phys.* **22**, 7169-7192 (2020).
- 1757 151 Del Galdo, S., Fusè, M. & Barone, V. The ONIOM/PMM Model for Effective Yet Accurate
1758 Simulation of Optical and Chiroptical Spectra in Solution: Camphorquinone in Methanol as
1759 a Case Study. *J. Chem. Theoy Comput.* **16**, 3294-3306 (2020).
- 1760 152 Panek, P. T. & Jacob, C. R. Anharmonic Theoretical Vibrational Spectroscopy of
1761 Polypeptides. *J. Phys. Chem. Lett.* **7**, 3084-3090 (2016).
- 1762 153 Roy, T. K., Sharma, R. & Gerber, R. B. First-principles anharmonic quantum calculations for
1763 peptide spectroscopy: VSCF calculations and comparison with experiments. *Phys. Chem.*
1764 *Chem. Phys.* **18**, 1607-1614 (2016).
- 1765 154 Barone, V., Improta, R. & Rega, N. Quantum Mechanical Computations and Spectroscopy:
1766 From Small Rigid Molecules in the Gas Phase to Large Flexible Molecules in Solution. *Acc.*
1767 *Chem. Res.* **41**, 605-616 (2008).
- 1768 155 Balabin, R. M. Conformational equilibrium in glycine: Focal-point analysis and ab initio
1769 limit. *Chem. Phys. Lett.* **479**, 195-200 (2009).
- 1770 156 Bazsó, G., Magyarfalvi, G. & Tarczay, G. Tunneling Lifetime of the ttc/VIp Conformer of
1771 Glycine in Low-Temperature Matrices. *J. Phys. Chem. A* **116**, 10539-10547 (2012).
- 1772 157 Stepanian, S. G. *et al.* Matrix-Isolation Infrared and Theoretical Studies of the Glycine
1773 Conformers. *J. Phys. Chem. A* **102**, 1041-1054 (1998).
- 1774 158 Balabin, R. M. Conformational Equilibrium in Glycine: Experimental Jet-Cooled Raman
1775 Spectrum. *J. Phys. Chem. Lett.* **1**, 20-23 (2010).
- 1776 159 Lockyear, J. F. *et al.* Isomer Specific Product Detection in the Reaction of CH with Acrolein.
1777 *J. Phys. Chem. A* **117**, 11013-11026 (2013).
- 1778 160 Barone, V., Biczysko, M., Borkowska-Panek, M. & Bloino, J. A Multifrequency Virtual
1779 Spectrometer for Complex Bio-Organic Systems: Vibronic and Environmental Effects on the
1780 UV/Vis Spectrum of Chlorophyll-a. *ChemPhysChem* **15**, 3355-3364 (2014).
- 1781 161 Gouterman, M. Spectra of porphyrins. *J. Mol. Spectrosc.* **6**, 138-163 (1961).
- 1782 162 Rätsep, M. *et al.* Absorption-emission symmetry breaking and the different origins of
1783 vibrational structures of the 1Q_y and 1Q_x electronic transitions of pheophytin a. *J. Chem. Phys.*
1784 **151**, 165102 (2019).

- 1785 163 Dixon, J. M., Taniguchi, M. & Lindsey, J. S. PhotochemCAD 2: a refined program with
1786 accompanying spectral databases for photochemical calculations. *Photochem. Photobiol.* **81**,
1787 212-213 (2005).
- 1788 164 Huang, X., Braams, B. J. & Bowman, J. M. Ab initio potential energy and dipole moment
1789 surfaces for H_5O_2^+ . *J. Chem. Phys.* **122**, 044308 (2005).
- 1790 165 Petit, A. S., Ford, J. E. & McCoy, A. B. Simultaneous Evaluation of Multiple Rotationally
1791 Excited States of H_3^+ , H_3O^+ , and CH_5^+ Using Diffusion Monte Carlo. *J. Phys. Chem. A* **118**,
1792 7206-7220 (2014).
- 1793 166 Petit, A. S. & McCoy, A. B. Diffusion Monte Carlo Approaches for Evaluating Rotationally
1794 Excited States of Symmetric Top Molecules: Application to H_3O^+ and D_3O^+ . *J. Phys. Chem.*
1795 *A* **113**, 12706-12714 (2009).
- 1796 167 Sandler, P., Buch, V. & Clary, D. C. Calculation of expectation values of molecular systems
1797 using diffusion Monte Carlo in conjunction with the finite field method. *J. Chem. Phys.* **101**,
1798 6353-6355 (1994).
- 1799 168 Paesani, F. & Whaley, K. B. Rotational excitations of N_2O in small helium clusters and the
1800 role of Bose permutation symmetry. *J. Chem. Phys.* **121**, 5293-5311, doi:10.1063/1.1782175
1801 (2004).
- 1802 169 Cho, H. M. & Singer, S. J. Correlation Function Quantum Monte Carlo Study of the Excited
1803 Vibrational States of H_5O_2^+ . *J. Phys. Chem. A* **108**, 8691-8702 (2004).
- 1804 170 McCoy, A. B., Diken, E. G. & Johnson, M. A. Generating Spectra from Ground-State Wave
1805 Functions: Unraveling Anharmonic Effects in the $\text{OH}^- \cdot \text{H}_2\text{O}$ Vibrational Predissociation
1806 Spectrum. *J. Phys. Chem. A* **113**, 7346-7352 (2009).
- 1807 171 Polavarapu, P. L. *et al.* A Single Chiroptical Spectroscopic Method May Not Be Able To
1808 Establish the Absolute Configurations of Diastereomers: Dimethylesters of Hibiscus and
1809 Garcinia Acids. *J. Phys. Chem. A* **115**, 5665-5673 (2011).
- 1810 172 Debie, E. *et al.* A confidence level algorithm for the determination of absolute configuration
1811 using vibrational circular dichroism or Raman optical activity. *ChemPhysChem* **12**, 1542-
1812 1549 (2011).
- 1813 173 Fusè, M. *et al.* Unbiased Determination of Absolute Configurations by vis-à-vis Comparison
1814 of Experimental and Simulated Spectra: The Challenging Case of Diplopyrone. *J. Phys.*
1815 *Chem. B* **123**, 9230-9237 (2019).
- 1816 174 Bogaerts, J. *et al.* A combined Raman optical activity and vibrational circular dichroism study
1817 on artemisinin-type products. *Phys. Chem. Chem. Phys.* **22**, 18014-18024 (2020).
- 1818 175 Johnson, J. L. *et al.* Dissymmetry Factor Spectral Analysis Can Provide Useful Diastereomer
1819 Discrimination: Chiral Molecular Structure of an Analogue of (-)-Crispine A. *ACS Omega* **4**,
1820 6154-6164 (2019).
- 1821 176 Hopmann, K. H. *et al.* Determining the Absolute Configuration of Two Marine Compounds
1822 Using Vibrational Chiroptical Spectroscopy. *J. Org. Chem* **77**, 858-869 (2012).
- 1823 177 Covington, C. L. & Polavarapu, P. L. Similarity in Dissymmetry Factor Spectra: A
1824 Quantitative Measure of Comparison between Experimental and Predicted Vibrational
1825 Circular Dichroism. *J. Phys. Chem. A* **117**, 3377-3386 (2013).
- 1826 178 Nicu, V. P. & Baerends, E. J. Robust normal modes in vibrational circular dichroism spectra.
1827 *Phys. Chem. Chem. Phys.* **11**, 6107-6118 (2009).
- 1828 179 Tommasini, M. *et al.* Mode Robustness in Raman Optical Activity. *J. Chem. Theoy Comput.*
1829 **10**, 5520-5527 (2014).
- 1830 180 Freedman, T. B., Shih, M.-L., Lee, E. & Nafie, L. A. Electron Transition Current Density in
1831 Molecules. 3. Ab Initio Calculations for Vibrational Transitions in Ethylene and
1832 Formaldehyde. *J. Am. Chem. Soc.* **119**, 10620-10626 (1997).
- 1833 181 Fusè, M., Egidi, F. & Bloino, J. Vibrational circular dichroism under the quantum magnifying
1834 glass: from the electronic flow to the spectroscopic observable. *Phys. Chem. Chem. Phys.* **21**,
1835 4224-4239 (2019).

- 1836 182 Hug, W. Visualizing Raman and Raman optical activity generation in polyatomic molecules. *Chem. Phys.* **264**, 53-69 (2001).
- 1837
- 1838 183 Yamamoto, S. in *Introduction to Astrochemistry: Chemical Evolution from Interstellar*
- 1839 *Clouds to Star and Planet Formation* (Springer, Japan, 2017).
- 1840 184 Jørgensen, J. K., Belloche, A. & Garrod, R. T. Astrochemistry During the Formation of Stars. *Annu. Rev. Astron. Astrophys.* **58**, 727-778 (2020).
- 1841
- 1842 185 McGuire, B. A. 2018 Census of Interstellar, Circumstellar, Extragalactic, Protoplanetary
- 1843 Disk, and Exoplanetary Molecules. *Astrophys. J., Suppl. Ser.* **239**, 17 (2018).
- 1844 186 Herbst, E. & Dishoeck, E. F. v. Complex Organic Interstellar Molecules. *Annu. Rev. Astron.*
- 1845 *Astrophys.* **47**, 427-480 (2009).
- 1846 187 Lattelais, M., Pauzat, F., Ellinger, Y. & Ceccarelli, C. Interstellar complex organic molecules
- 1847 and the minimum energy principle. *Astrophys. J.* **696**, L133-L136 (2009).
- 1848 188 Puzzarini, C. & Barone, V. A never-ending story in the sky: The secrets of chemical evolution.
- 1849 *Phys. Life Rev.* **32**, 59-94 (2020).
- 1850 189 Cernicharo, J., Guélin, M., Agúndez, M., McCarthy, M. C. & Thaddeus, P. Detection of C₅N⁻
- 1851 and Vibrationally Excited C₆H in IRC+10216. *Astrophys. J.* **688**, L83-L86 (2008).
- 1852 190 Botschwina, P. & Oswald, R. Carbon chains of type C_{2n+1}N⁻ (n=2–6): A theoretical study of
- 1853 potential interstellar anions. *J. Chem. Phys.* **129**, 044305 (2008).
- 1854 191 Cazzoli, G., Cludi, L., Buffa, G. & Puzzarini, C. Precise THz measurements of HCO⁺, N₂H⁺
- 1855 and CF⁺ for astrophysical observations. *Astrophys. J., Suppl. Ser.* **203**, 11 (2012).
- 1856 192 Guzmán, V. *et al.* The hyperfine structure in the rotational spectrum of CF⁺. *Astron.*
- 1857 *Astrophys.* **548**, A94 (2012).
- 1858 193 Caselli, P., Myers, P. C. & Thaddeus, P. Radio-astronomical Spectroscopy of the Hyperfine
- 1859 Structure of N₂H⁺. *Astrophys. J.* **455** (1995).
- 1860 194 Kłos, J. & Lique, F. in *Cold Chemistry: Molecular Scattering and Reactivity Near Absolute*
- 1861 *Zero* (eds Dulieu O & Osterwalder A) Ch. Cold Molecular Collisions: Quantum Scattering
- 1862 Calculations and Their Relevance in Astrophysical Applications, 46-91 (RSC Publication,
- 1863 United Kingdom, 2018).
- 1864 195 Borrego-Varillas, R. *et al.* Two-dimensional UV spectroscopy: a new insight into the structure
- 1865 and dynamics of biomolecules. *Chem. Sci.* **10**, 9907-9921 (2019).
- 1866 196 East, K. W. *et al.* NMR and computational methods for molecular resolution of allosteric
- 1867 pathways in enzyme complexes. *Biophys. Rev.* **12**, 155-174 (2020).
- 1868 197 Huang, J., Zhou, Y. & Xie, D. Predicted infrared spectra in the HF stretching band of the H₂–
- 1869 HF complex. *J. Chem. Phys.* **149**, 094307 (2018).
- 1870 198 Clary, D. C. & Nesbitt, D. J. Calculation of vibration–rotation spectra for rare gas–HCl
- 1871 complexes. *J. Chem. Phys.* **90**, 7000-7013 (1989).
- 1872 199 Felker, P. M. & Bačić, Z. H₂O–CO and D₂O–CO complexes: Intra- and intermolecular
- 1873 rovibrational states from full-dimensional and fully coupled quantum calculations. *J. Chem.*
- 1874 *Phys.* **153**, 074107 (2020).
- 1875 200 Keutsch, F. N. & Saykally, R. J. Water clusters: Untangling the mysteries of the liquid, one
- 1876 molecule at a time. *Proc. Natl. Acad. Sci. U.S.A.* **98**, 10533-10540 (2001).
- 1877 201 Mukhopadhyay, A., Xantheas, S. S. & Saykally, R. J. The water dimer II: Theoretical
- 1878 investigations. *Chem. Phys. Lett.* **700**, 163-175 (2018).
- 1879 202 Schwan, R. *et al.* Observation of the Low-Frequency Spectrum of the Water Dimer as a
- 1880 Sensitive Test of the Water Dimer Potential and Dipole Moment Surfaces. *Angew. Chem. Int.*
- 1881 *Ed.* **58**, 13119-13126 (2019).
- 1882 203 Cisneros, G. A. *et al.* Modeling Molecular Interactions in Water: From Pairwise to Many-
- 1883 Body Potential Energy Functions. *Chem. Rev.* **116**, 7501-7528 (2016).
- 1884 204 Mallory, J. D. & Mandelshtam, V. A. Diffusion Monte Carlo studies of MB-pol (H₂O)_{2–6} and
- 1885 (D₂O)_{2–6} clusters: Structures and binding energies. *J. Chem. Phys.* **145**, 064308 (2016).

- 1886 205 Liu, K. *et al.* Characterization of a cage form of the water hexamer. *Nature* **381**, 501-503
1887 (1996).
- 1888 206 Lee, V. G. M., Vetterli, N. J., Boyer, M. A. & McCoy, A. B. Diffusion Monte Carlo Studies
1889 on the Detection of Structural Changes in the Water Hexamer upon Isotopic Substitution. *J.*
1890 *Phys. Chem. A* **124**, 6903-6912 (2020).
- 1891 207 Richardson, J. O. *et al.* Concerted hydrogen-bond breaking by quantum tunneling in the water
1892 hexamer prism. *Science* **351**, 1310-1313 (2016).
- 1893 208 Vaillant, C. L., Wales, D. J. & Althorpe, S. C. Tunneling Splittings in Water Clusters from
1894 Path Integral Molecular Dynamics. *J. Phys. Chem. Lett.* **10**, 7300-7304 (2019).
- 1895 209 Gaigeot, M. P. Unravelling the Conformational Dynamics of the Aqueous Alanine Dipeptide
1896 with First-Principle Molecular Dynamics. *J. Phys. Chem. B* **113**, 10059-10062 (2009).
- 1897 210 Clary, D. C., Benoit, D. M. & van Mourik, T. H-Densities: A New Concept for Hydrated
1898 Molecules. *Acc. Chem. Res.* **33**, 441-447 (2000).
- 1899 211 Fornaro, T., Burini, D., Biczysko, M. & Barone, V. Hydrogen-Bonding Effects on Infrared
1900 Spectra from Anharmonic Computations: Uracil–Water Complexes and Uracil Dimers. *J.*
1901 *Phys. Chem. A* **119**, 4224-4236 (2015).
- 1902 212 Beć, K. B., Grabska, J., Ozaki, Y., Czarnecki, M. A. & Huck, C. W. Simulated NIR spectra
1903 as sensitive markers of the structure and interactions in nucleobases. *Sci. Rep.* **9**, 17398
1904 (2019).
- 1905 213 Beć, K. B. & Huck, C. W. Breakthrough Potential in Near-Infrared Spectroscopy: Spectra
1906 Simulation. A Review of Recent Developments. *Front. Chem.* **7** (2019).
- 1907 214 Benoit, D. M. Rationalising the vibrational spectra of biomolecules using atomistic
1908 simulations. *Front. Biosci.* **14**, 4229-4241 (2009).
- 1909 215 Atanasov, M., Ganyushin, D., Sivalingam, K. & Neese, F. in *Molecular Electronic Structures*
1910 *of Transition Metal Complexes II* (eds Mingos D M P, Day P, & Dahl J P) Ch. A Modern
1911 First-Principles View on Ligand Field Theory Through the Eyes of Correlated Multireference
1912 Wavefunctions, 149-220 (Springer, Berlin Heidelberg, 2012).
- 1913 216 Singh, S. K., Atanasov, M. & Neese, F. Challenges in Multireference Perturbation Theory for
1914 the Calculations of the g-Tensor of First-Row Transition-Metal Complexes. *J. Chem. Theory*
1915 *Comput.* **14**, 4662-4677 (2018).
- 1916 217 Maganas, D. *et al.* First principles calculations of the structure and V L-edge X-ray absorption
1917 spectra of V₂O₅ using local pair natural orbital coupled cluster theory and spin–orbit coupled
1918 configuration interaction approaches. *Phys. Chem. Chem. Phys.* **15**, 7260-7276 (2013).
- 1919 218 Roemelt, M., Maganas, D., DeBeer, S. & Neese, F. A combined DFT and restricted open-
1920 shell configuration interaction method including spin-orbit coupling: Application to transition
1921 metal L-edge X-ray absorption spectroscopy. *J. Chem. Phys.* **138**, 204101 (2013).
- 1922 219 Neese, F. A critical evaluation of DFT, including time-dependent DFT, applied to
1923 bioinorganic chemistry. *J. Biol. Inorg. Chem.* **11**, 702-711 (2006).
- 1924 220 Neese, F. High-Level Spectroscopy, Quantum Chemistry, and Catalysis: Not just a Passing
1925 Fad. *Angew. Chem. Int. Ed.* **56**, 11003-11010 (2017).
- 1926 221 Neese, F., Atanasov, M., Bistoni, G., Maganas, D. & Ye, S. Chemistry and Quantum
1927 Mechanics in 2019: Give Us Insight and Numbers. *J. Am. Chem. Soc.* **141**, 2814-2824 (2019).
- 1928 222 Zadrozny, J. M. & Long, J. R. Slow Magnetic Relaxation at Zero Field in the Tetrahedral
1929 Complex [Co(SPh)₄]²⁻. *J. Am. Chem. Soc.* **133**, 20732-20734 (2011).
- 1930 223 Neese, F. & Pantazis, D. A. What is not required to make a single molecule magnet. *Faraday*
1931 *Discuss.* **148**, 229-238 (2011).
- 1932 224 Suturina, E. A. *et al.* Magneto-Structural Correlations in Pseudotetrahedral Forms of the
1933 [Co(SPh)₄]²⁻ Complex Probed by Magnetometry, MCD Spectroscopy, Advanced EPR
1934 Techniques, and ab Initio Electronic Structure Calculations. *Inorg. Chem.* **56**, 3102-3118
1935 (2017).

- 1936 225 Suturina, E. A., Maganas, D., Bill, E., Atanasov, M. & Neese, F. Magneto-Structural
1937 Correlations in a Series of Pseudotetrahedral $[\text{Co}^{\text{II}}(\text{XR})_4]^{2-}$ Single Molecule Magnets: An ab
1938 Initio Ligand Field Study. *Inorg. Chem.* **54**, 9948-9961 (2015).
- 1939 226 Rechkemmer, Y. *et al.* A four-coordinate Cobalt(II) single-ion magnet with coercivity and a
1940 very high energy barrier. *Nat. Commun.* **7**, 10467 (2016).
- 1941 227 Penocchio, E., Piccardo, M. & Barone, V. Semiexperimental Equilibrium Structures for
1942 Building Blocks of Organic and Biological Molecules: The B2PLYP Route. *J. Chem. Theory
1943 Comput.* **11**, 4689-4707 (2015).
- 1944 228 Kodrycka, M. & Patkowski, K. Platinum, gold, and silver standards of intermolecular
1945 interaction energy calculations. *J. Chem. Phys.* **151**, 070901 (2019).
- 1946 229 Alessandrini, S., Gauss, J. & Puzzarini, C. Accuracy of Rotational Parameters Predicted by
1947 High-Level Quantum-Chemical Calculations: Case Study of Sulfur-Containing Molecules of
1948 Astrochemical Interest. *J. Chem. Theory Comput.* **14**, 5360-5371 (2018).
- 1949 230 Dral, P. O. Quantum Chemistry in the Age of Machine Learning. *J. Phys. Chem. Lett.* **11**,
1950 2336-2347 (2020).
- 1951 231 Liakos, D. G., Guo, Y. & Neese, F. Comprehensive Benchmark Results for the Domain Based
1952 Local Pair Natural Orbital Coupled Cluster Method (DLPNO-CCSD(T)) for Closed- and
1953 Open-Shell Systems. *J. Phys. Chem. A* **124**, 90-100 (2020).
- 1954 232 Nagy, P. R. & Kállay, M. Approaching the Basis Set Limit of CCSD(T) Energies for Large
1955 Molecules with Local Natural Orbital Coupled-Cluster Methods. *J. Chem. Theory Comput.* **15**,
1956 5275-5298 (2019).
- 1957 233 Sibert III, E. L. Modeling vibrational anharmonicity in infrared spectra of high frequency
1958 vibrations of polyatomic molecules. *J. Chem. Phys.* **150**, 090901 (2019).
- 1959 234 Basdogan, Y. *et al.* Machine Learning-Guided Approach for Studying Solvation
1960 Environments. *J. Chem. Theory Comput.* **16**, 633-642 (2020).
- 1961 235 Hodecker, M., Biczysko, M., Dreuw, A. & Barone, V. Simulation of Vacuum UV Absorption
1962 and Electronic Circular Dichroism Spectra of Methyl Oxirane: The Role of Vibrational
1963 Effects. *J. Chem. Theory Comput.* **12**, 2820-2833 (2016).
- 1964 236 Puzzarini, C., Biczysko, M., Bloino, J. & Barone, V. Accurate spectroscopic characterization
1965 of oxirane: a valuable route to its identification in Titan's atmosphere and the assignment of
1966 unidentified infrared bands. *Astrophys. J.* **785**, 107 (2014).
- 1967 237 Karton, A., Sylvetsky, N. & Martin, J. M. L. W4-17: A diverse and high-confidence dataset
1968 of atomization energies for benchmarking high-level electronic structure methods. *J. Comput.
1969 Chem.* **38**, 2063-2075 (2017).
- 1970 238 Mayhall, N. J. & Raghavachari, K. Molecules-in-Molecules: An Extrapolated Fragment-
1971 Based Approach for Accurate Calculations on Large Molecules and Materials. *J. Chem. Theory
1972 Comput.* **7**, 1336-1343 (2011).
- 1973 239 Santra, G., Sylvetsky, N. & Martin, J. M. L. Minimally Empirical Double-Hybrid Functionals
1974 Trained against the GMTKN55 Database: revDSD-PBEP86-D4, revDOD-PBE-D4, and
1975 DOD-SCAN-D4. *J. Phys. Chem. A* **123**, 5129-5143 (2019).
- 1976 240 Kussmann, J. & Ochsenfeld, C. Preselective Screening for Linear-Scaling Exact Exchange-
1977 Gradient Calculations for Graphics Processing Units and General Strong-Scaling Massively
1978 Parallel Calculations. *J. Chem. Theory Comput.* **11**, 918-922 (2015).
- 1979 241 Doser, B., Lambrecht, D. S. & Ochsenfeld, C. Tighter multipole-based integral estimates and
1980 parallel implementation of linear-scaling AO-MP2 theory. *Phys. Chem. Chem. Phys.* **10**,
1981 3335-3344 (2008).
- 1982 242 Ma, Q. & Werner, H.-J. Scalable Electron Correlation Methods. 7. Local Open-Shell
1983 Coupled-Cluster Methods Using Pair Natural Orbitals: PNO-RCCSD and PNO-UCCSD. *J.
1984 Chem. Theory Comput.* **16**, 3135-3151 (2020).
- 1985 243 Becca, F. & Sorella, S. in *Quantum Monte Carlo Approaches for Correlated Systems*
1986 (Cambridge University Press, Cambridge, 2017).

- 1987 244 Puzzarini, C. & Barone, V. The challenging playground of astrochemistry: an integrated
1988 rotational spectroscopy – quantum chemistry strategy. *Phys. Chem. Chem. Phys.* **22**, 6507-
1989 6523 (2020).
- 1990 245 Biczysko, M., Krupa, J. & Wierzejewska, M. Theoretical studies of atmospheric molecular
1991 complexes interacting with NIR to UV light. *Faraday Discuss.* **212**, 421-441 (2018).
- 1992 246 Raucci, U. *et al.* Ab-initio molecular dynamics and hybrid explicit-implicit solvation model
1993 for aqueous and nonaqueous solvents: GFP chromophore in water and methanol solution as
1994 case study. *J. Comput. Chem.* (2020).
- 1995 247 Zhang, W., Kong, X., Liu, S. & Zhao, Y. Multi-coefficients correlation methods. *WIREs*
1996 *Comput. Mol. Sci.* **10**, e1474 (2020).
- 1997 248 Gagliardi, L. *et al.* Multiconfiguration Pair-Density Functional Theory: A New Way To Treat
1998 Strongly Correlated Systems. *Acc. Chem. Res.* **50**, 66-73 (2017).
- 1999 249 Bannwarth, C. *et al.* Extended tight-binding quantum chemistry methods. *WIREs Comput.*
2000 *Mol. Sci.*, e01493 (2020).
- 2001 250 Loos, P.-F., Scemama, A. & Jacquemin, D. The Quest for Highly Accurate Excitation
2002 Energies: A Computational Perspective. *J. Phys. Chem. Lett.* **11**, 2374-2383 (2020).
- 2003 251 Casanova-Páez, M. & Goerigk, L. Assessing the Tamm–Dancoff approximation, singlet–
2004 singlet, and singlet–triplet excitations with the latest long-range corrected double-hybrid
2005 density functionals. *J. Chem. Phys.* **153**, 064106 (2020).
- 2006 252 Mutter, S. T. *et al.* Conformational dynamics of carbohydrates: Raman optical activity of D-
2007 glucuronic acid and N-acetyl-D-glucosamine using a combined molecular dynamics and
2008 quantum chemical approach. *Phys. Chem. Chem. Phys.* **17**, 6016-6027 (2015).
- 2009 253 Lee, V. G. M. & McCoy, A. B. An Efficient Approach for Studies of Water Clusters Using
2010 Diffusion Monte Carlo. *J. Phys. Chem. A* **123**, 8063-8070 (2019).
- 2011 254 Zhao, L. *et al.* Real-Time Time-Dependent Nuclear–Electronic Orbital Approach: Dynamics
2012 beyond the Born–Oppenheimer Approximation. *J. Phys. Chem. Lett.* **11**, 4052-4058 (2020).
- 2013 255 Petrenko, T. & Rauhut, G. A General Approach for Calculating Strongly Anharmonic
2014 Vibronic Spectra with a High Density of States: The $\tilde{X}^2B_1 \leftarrow \tilde{X}^1A_1$ Photoelectron Spectrum
2015 of Difluoromethane. *J. Chem. Theory Comput.* **13**, 5515-5527 (2017).
- 2016 256 Cerezo, J., Aranda, D., Avila Ferrer, F. J., Prampolini, G. & Santoro, F. Adiabatic-Molecular
2017 Dynamics Generalized Vertical Hessian Approach: A Mixed Quantum Classical Method To
2018 Compute Electronic Spectra of Flexible Molecules in the Condensed Phase. *J. Chem. Theory*
2019 *Comput.* **16**, 1215-1231 (2020).
- 2020 257 Jasper, A. W., Harding, L. B., Knight, C. & Georgievskii, Y. Anharmonic Rovibrational
2021 Partition Functions at High Temperatures: Tests of Reduced-Dimensional Models for
2022 Systems with up to Three Fluxional Modes. *J. Phys. Chem. A* **123**, 6210-6228 (2019).
- 2023 258 Burd, T. A. H. & Clary, D. C. Analytic Route to Tunneling Splittings Using Semiclassical
2024 Perturbation Theory. *J. Chem. Theory Comput.* **16**, 3486-3493 (2020).
- 2025 259 O’Connor, M. B. *et al.* Interactive molecular dynamics in virtual reality from quantum
2026 chemistry to drug binding: An open-source multi-person framework. *J. Chem. Phys.* **150**,
2027 220901 (2019).
- 2028 260 McArdle, S., Endo, S., Aspuru-Guzik, A., Benjamin, S. C. & Yuan, X. Quantum
2029 computational chemistry. *Rev. Mod. Phys.* **92**, 015003 (2020).
- 2030
2031
2032