# Quantum Mechanical Computations and Spectroscopy: From Small Rigid Molecules in the Gas Phase to Large Flexible Molecules in Solution

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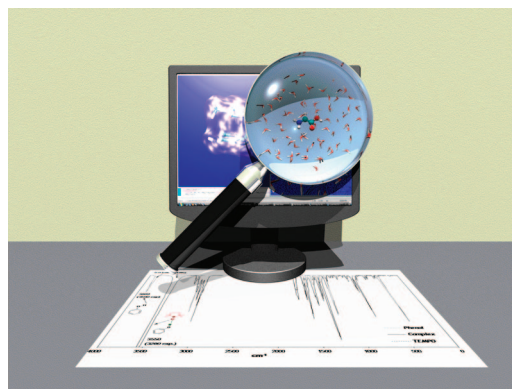RECEIVED ON SEPTEMBER 22, 2007

## CONSPECTUS

Interpretation of structural properties and dynamic behavior of molecules in solution is of fundamental importance to understand their stability, chemical reactivity, and catalytic action. While information can be gained, in principle, by a variety of spectroscopic techniques, the interpretation of the rich indirect information that can be inferred from the analysis of experimental spectra is seldom straightforward because of the subtle interplay of several different effects, whose specific role is not easy to separate and evaluate. In such a complex scenario, theoretical studies can be very helpful at two different levels: (i) supporting and complementing experimental results to determine the structure of the target molecule starting from its spectral properties; (ii) dissecting and evaluating the role of different effects in determining the observed spectroscopic properties. This is the reason why computational spectroscopy is rapidly evolving from a highly specialized research field into a versatile and widespread tool for the assignment of experimental spectra and their interpretation in terms of chemical physical effects. In such a situation, it becomes important that both computationally and experimentally oriented chemists are aware that new methodological advances and integrated computational strategies are available, providing reliable estimates of fundamental spectral parameters not only for relatively small molecules in the gas phase but also for large and flexible molecules in condensed phases.

In this Account, we review the most significant methodological contributions from our research group in this field, and by exploiting some recent results of their application to the computation of IR, UV–vis, NMR, and EPR spectral parameters, we discuss the microscopic mechanisms underlying solvent and vibrational effects on the spectral parameters.

After reporting some recent achievements for the study of excited states by first principle quantum mechanical approaches, we focus on the treatment of environmental effects by means of mixed discrete-continuum solvent models and on effective methods for computing vibronic contributions to the spectra. We then discuss some new developments, mainly based on time-dependent approaches, allowing us to go beyond the determination of spectroscopic parameters toward the simulation of line widths and shapes.

Although further developments are surely needed to improve the accuracy and effectiveness of several items in the proposed approach, we try to show that the first important steps toward a direct comparison between the results obtained in vitro and those obtained in silico have been made, making easier fruitful crossovers among experiments, computations and theoretical models, which would be decisive for a deeper understanding of the spectral behavior associated with complex systems and processes.

# 1. Introduction

The prediction and interpretation of structural properties and dynamic behavior of molecules in solution is at the heart of a deeper understanding of their stability, chemical reactivity, and catalytic action. Information can be gained, in principle, by a number of spectroscopic techniques, magnetic as well as optical. However, the interpretation of the rich indirect information that can be inferred from the analysis of experimental spectra is seldom straightforward without reference to some theoretical model. This is the reason why computational spectroscopy is rapidly evolving from a highly specialized research field into a versatile and widespread tool for the assignment and interpretation of experimental spectra.[1−4]

However, the large majority of accurate quantum mechanical studies refer to equilibrium structures in the gas phase, whereas experiments are usually performed in condensed phases and include dynamical averaging effects by both intramolecular (e.g., solute vibrations) and intermolecular (e.g., solvent librations) degrees of freedom. Furthermore, experiments do not provide just a "number" (the spectroscopic parameter) but a whole spectrum with its own (more or less structured) shape, where fundamental pieces of information about the system or process under investigation are often hidden. Unraveling the role of the different effects whose interplay determines the overall spectral pattern is a nontrivial task requiring an effective integration of experimental and computational approaches toward the elaboration of more and more accurate and reliable interpretative and predictive tools. To this aim, bridging the gap between the systems examined in vitro or in vivo and those modeled in silico is of paramount importance and requires theoretical methods able to go beyond the computation of a single spectral parameter in the gas phase toward the simulation of entire spectra in solution.

In this Account, we will report some significant steps in this direction and review some basic aspects of computational spectroscopy, highlighting how intramolecular and intermolecular degrees of freedom influence several spectroscopic parameters. The focus we have chosen, namely, organic molecular systems, has implications both on the kind of experimental spectroscopic techniques and on the level of computational description. Thus, we will pay particular attention to IR, UV−vis, NMR, and EPR spectroscopic parameters of medium to large size molecules involving atoms of the first two rows of the periodic table in solution. Of course, several groups have provided significant contributions related to different aspects covered here (e.g., see ref 5), but we will mainly refer to our own experience in the field.[6−21]

In the first part of our presentation, we will focus mainly on the microscopic mechanisms underlying environmental and vibrational effects on the spectroscopic parameters. Concerning solvent effects, we shall discuss in some detail available methods for including both bulk effects and specific solute−solvent interactions on the spectral parameters. We will also discuss the main problems and the most effective strategies for studying the spectroscopic behavior of medium/large size molecules, those most interesting for biological and technological applications.

The second part of our contribution concerns, instead, more recent developments enabling calculations of whole spectra that can be directly compared with experimental ones, that is going beyond the determination of the spectroscopic parameters toward the simulation of line widths and shapes. This step involves a number of problems, ranging from the selection of reliable yet computationally feasible quantum mechanical (QM) approaches for large molecules to the proper account of vibrational averaging and environmental (e.g., solvent) effects. Furthermore, in a real system, all the effects (e.g., intra- and intermolecular interactions) are mutually related, so that feedback contributions must be included coupling, for instance, solute vibrational modes and solvent librations by suitable time-independent or time-dependent approaches. These considerations point out the need for integrated computational strategies in which different parts of the system or time scales are treated at different levels of approximation but allowing in an effective way interactions and transfers between the different regions. Only in this way does it become possible, for instance, to switch specific interactions on and off in order to analyze their role on the overall observable. The development of such a tool, its validation, and its application to systems and processes of current interest will be sketched. Of course, this is an ongoing research project, so some of its building blocks are still under development, and others are not yet fully validated. Also taking these considerations into account, we will try to show that a number of interesting spectroscopic processes can already be analyzed in their full complexity.

# 2. General Background

As mentioned in the Introduction, very reliable results can be obtained for small to medium-size semirigid molecules in vacuum using the most refined post-Hartree−Fock (HF) approaches coupled to large basis sets. Coupled-cluster (e.g., CCSD(T))[3,4] and multireference perturbation theory (e.g., CASPT2)[2] represent the de facto standards for ground and
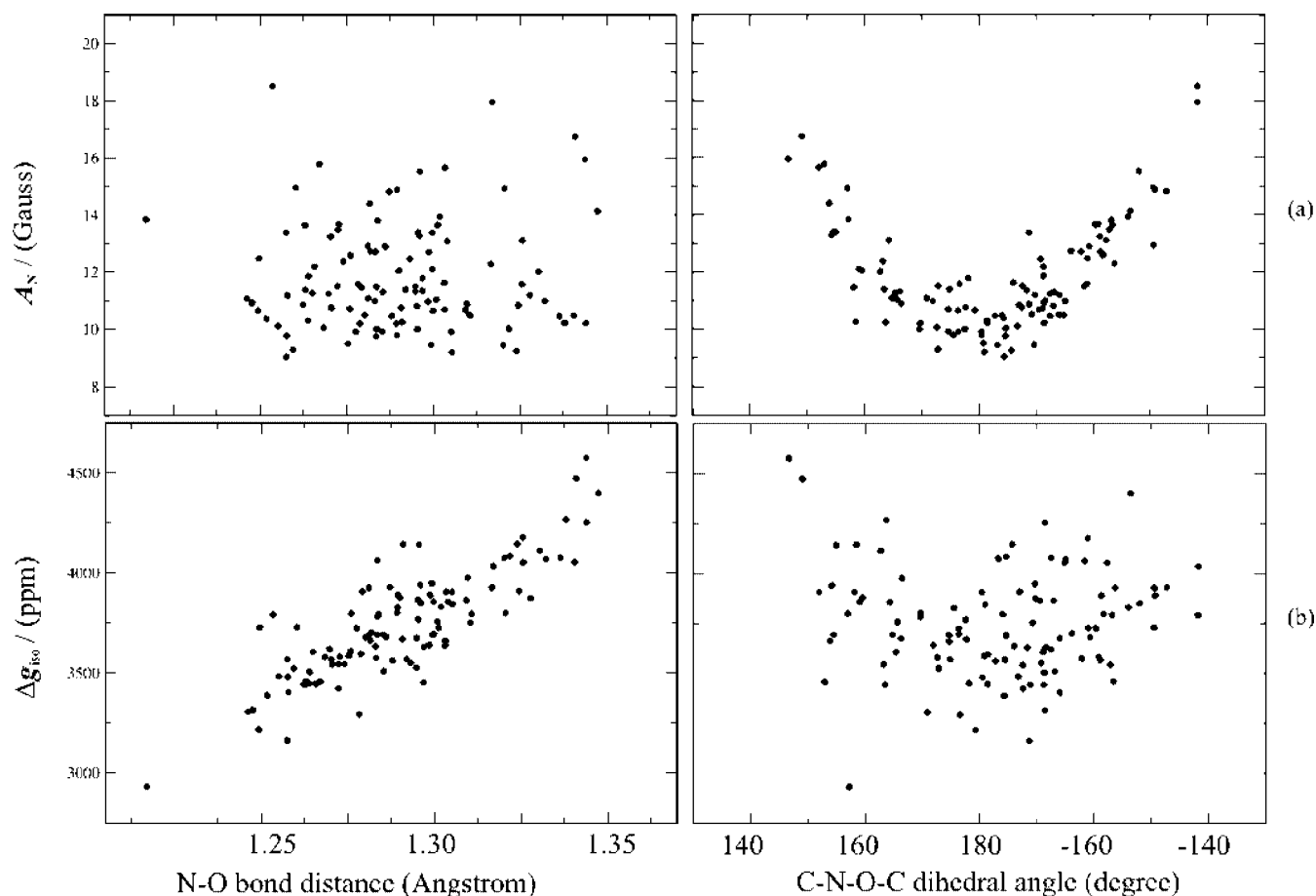
**FIGURE 1.** Computed hcc and isotropic *g*-tensor shifts from a MD simulation of PROXYL in the gas phase.

excited electronic states, respectively. The situation is more involved for large flexible molecules in condensed phases where some degree of approximation is probably unavoidable. Here, methods rooted in density functional theory (DFT) have revolutionized the situation, paving the route toward a general purpose approach with semiquantitative accuracy along the whole periodic table without the need for prohibitively large basis sets. As a rule of thumb, polarized split-valence basis sets augmented by diffuse functions (e.g., 6-31+G(d,p) to which most of the results presented in the following refer) provide semiquantitative results, and doubly polarized triple-$\zeta$ basis sets again augmented by diffuse functions (e.g., 6-311+G(2df,2p) or aug-cc-pVTZ) approach the basis set limit. The subsequent development of linear scaling implementations[22] and of reliable discrete-continuum solvent models,[23] together with the time-dependent (TD-DFT) route to excited electronic states,[24,25] have further enlarged the field of application of QM approaches. Of course, a number of problems remain to be solved (e.g., true multireference states, charge transfer, van der Waals interactions, etc.), and the development of improved functionals represents a very active research field. However, when coupled with a suitable func-

tional (e.g., the parameter-free PBE0 model,[26] systematically used in the examples given in the following) DFT and TD-DFT approaches already provide reliable results.[10,12,13,17]

The recent availability of TD-DFT analytical gradients both in the gas phase[27] and in solution[28] provides direct access to the structure and the properties of excited electronic states at a reasonable computational cost. Thus, while taking into account the caveats mentioned above, DFT and TD-DFT will be our reference levels in the present Account.

Direct comparison with experimental results then calls for the contemporary computation of reliable structural and spectroscopic parameters. In this connection it is not yet fully appreciated that different spectroscopic properties are sensitive to different structural parameters: this is nicely illustrated in Figure 1, which sketches the dependence of isotropic *g*-tensor shifts ($\Delta g_{iso}$) and nitrogen hyperfine coupling constants ($a_N$) on the NO bond length and the out of plane displacement of the oxygen atom in a typical nitroxide radical (2,2,5,5-tetramethyl-pyrroline-*N*-oxyl, hereafter PROXYL). The results obtained from a simulation in the gas phase (see below for details) point out that $\Delta g_{iso}$ is almost linearly dependent on the NO bond length, whereas it does not display any regular varia-

tion with respect to out-of-plane motion; $a_N$ shows just the opposite trend.[18] This means that QM methods (e.g., GGA functionals) or basis sets (e.g., lack of diffuse functions) that provide poor NO bond lengths cannot deliver reliable magnetic parameters, irrespective of the sophistication of the solvent and dynamical models employed. As a matter of fact, all the building blocks of an integrated computational strategy must be checked independently for their accuracy.

Furthermore, dynamic effects need to be taken into the proper account. Although this is, in general, a quite ambitious long-term target, which will be discussed in further detail in the next sections, we point out that, under some favorable circumstances, reliable results can be already obtained. In the particular case of electron paramagnetic resonance (EPR) spectroscopy, a new general computational approach combining QM calculations of structures and magnetic tensors with the treatment of rotational diffusion in solution by the stochastic Liouville equation (SLE) approach is leading to remarkable agreement between experimental and computed spectra for a number of test cases.[20,21] Although time scale separation cannot be used to the same extent for optical spectroscopies, reasonable simulations of line broadenings can be performed also in this case by a wise integration of time-dependent and time-independent approaches.

At the heart of all these approaches is the proper treatment of molecular vibrations, which play the double role of direct spectroscopic signatures (IR and Raman spectra)[6,7] and of backstage for, at least, line shapes in all the other spectroscopies.[10] A basic but often overlooked effect is the difference of zero-point energy (ZPE) between ground and excited electronic states. The occupation of antibonding molecular orbitals in excited states leads to a different (usually reduced) ZPE: for example, for uracil in aqueous solution, the zero-point correction of the ground state is 0.16 eV larger than that of the bright excited state[9] (for other pyrimidine bases, similar values are obtained). For coumarin C153 in DMSO, the difference between the zero-point corrections, though smaller, still amounts to 0.1 eV.[10] Since the most sophisticated post-HF methods are claimed to provide an agreement with experiments within 0.2−0.3 eV, it is clear that the effect of zero-point corrections should be considered not only for a better comparison with experiments, but also for putting on a firmer ground any consideration about the accuracy of different QM calculations.

## 3. Solvent Effects

Almost all the spectroscopic parameters of a molecule exhibit a more or less marked dependence on the nature of the embedding medium (hereafter broadly referred to as solvent).[29]

The treatment of "static" solvent effects can be considered well assessed for several spectroscopic techniques. Bulk contributions can be accounted for by at least two different approaches. The most direct procedure consists in including in the calculations a number of explicit solvent molecules large enough to reproduce the properties of the bulk (e.g., the macroscopic dielectric constant). However, when this kind of approach is used, a correct placement of the first solvent shell molecules is required, since it can strongly influence the quality of the computed solvent shifts of the spectroscopic observables. Furthermore, a correct reproduction of bulk effects by explicit solvent molecules requires a proper averaging of different configurations, thus leading to unreasonable computer costs unless simplified models or a low number of solvent molecules are used. As a consequence, continuum models (in particular, the so-called polarizable continuum model, PCM) emerged in the last two decades as the most effective tools to treat bulk solvent effects for both ground and excited states.[23] It is also noteworthy that the extension of continuum models to the study of large systems can now be considered an assessed problem thanks to the implementation of effective and fast procedures.[31]

On the grounds of our experience, we can say that PCM alone is sufficient to reproduce the effect of non-hydrogen-bonding (even significantly polar) solvents on the spectroscopic parameters. See, for example, the study of the absorption spectra of coumarin C153 in DMSO and in cyclohexane[10] and of nucleobases in acetonitrile,[9] as well as the computation of the EPR/NMR parameters of several molecules in different solvents.[13,17] On the other hand, in hydrogen-bonding solvents, the inclusion of the cybotactic region is mandatory:[9,17,19] mixed discrete/continuum models appear very effective in such cases, allowing inclusion of a small number of molecules belonging to the first solvation shell, while bulk effects are taken into account at the PCM level.

As illustrative example, we can consider the energy of the two lowest energy excited states in pyrimidine nucleobases (uracil, thymine, etc.): one (dark) state corresponds to a transition from a carbonyl lone pair toward the $\pi^*$ LUMO; the other (bright) state originates from a $\pi \rightarrow \pi^*$ HOMO−LUMO transition. Only when an integrated discrete−continuum approach is employed does it become possible to reproduce
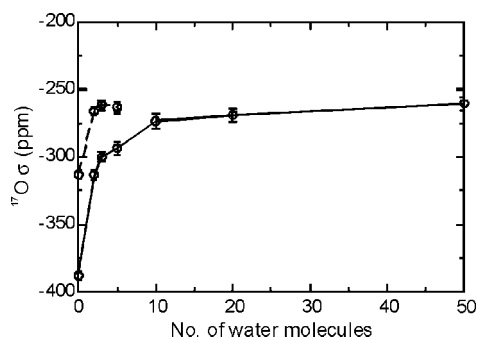
**FIGURE 2.** Average $^{17}O$ NMR shielding constants of acetone either in the absence (full line) or in the presence (dashed line) of the PCM on acetone–water clusters of different size.

the effect of aqueous solution on the excitation energy of the bright state and on the relative energy of both excited states.[9]

A key problem to be solved in this context is the number of solvent molecules to be explicitly included in the calculations. Although a general answer can hardly be given, some experience is being gathered on a number of aspects. The first point is that, concerning property evaluation, use of continuum solvent methods leads to a quite rapid convergence with the number of explicit solvent molecules. This is nicely illustrated by Figure 2, which shows the convergence of the $^{17}O$ NMR shielding of acetone with the number of explicit solvent molecules.[13] It is quite evident that bulk effects cannot be neglected, but at the same time, the difference between explicit and continuum models nearly vanishes beyond the first solvent shell.

A more subtle issue concerns the nature of solute–solvent interactions, since solvent molecules can be safely described by simple molecular mechanics (MM) force fields, instead of being treated at the QM level, only when electrostatic interactions rule the studied process. This can be sufficient in a number of situations concerning structures and interaction energies, but the situation is more involved when it comes to computation of properties, since the response of the solute wave function to solvent effects often depends on non-classical terms (e.g., Pauli repulsion), which are outside the field of MM, irrespective of the sophistication of the parametrization (polarizable force fields, flexible geometry, etc.). Furthermore, whenever one or more solvent molecules are involved in electron (or spin) transfer from the solute, their treatment at the QM level becomes mandatory. Here a two-step procedure can be profitably employed in which (i) a sufficient number of reference structures is generated by geometry optimizations or dynamic simulations at a suitable computational level and (ii) the property evaluation is performed a posteriori possibly adopting a higher computational level or a number of explicit solvent molecules smaller than that used in the former stage.

Several studies suggest that NMR and EPR parameters are often tuned by nonelectrostatic (essentially Pauli repulsion) first-shell contributions, whereas solvent shifts of UV transitions are dominated by electrostatic contributions, even if non-bonded interaction can also play some role.[7] At the same time, NMR shieldings and EPR hyperfine coupling constants (hcc's) are local parameters, so the solvent molecules to be treated at the QM level can be selectively chosen depending on the solute atoms whose NMR or EPR parameters are sought. Figure 3 sketches the role of different contributions in determining the overall hcc's for different atoms of the dipeptide analogue of tirosyl radical.[16]

## 4. Time-Independent and Time-Dependent Models

For isolated systems, time-independent approaches are often very effective. Here, the harmonic level of approximation can be taken for realized both in vacuum and in condensed phases. For semirigid molecules, second-order perturbation theory (PT2) is leading to very effective computational implementations including anharmonic contributions and providing remarkable agreement with experiment when the underlying electronic QM model is sufficiently reliable.[6]

Let us consider, as an example, the interaction between a typical nitroxide radical (2,2,6,6-tetramethyl-piperidine-*N*-oxyl, hereafter TEMPO) and phenol. Since the NO stretching has a very low intensity, the best experimental probe is the OH stretching, which is, however, highly anharmonic. In the gas phase, the computed (harmonic) IR spectra of the free phenol and of the TEMPO–phenol complex show peaks at 3889 and 3550 cm$^{-1}$, respectively (Figure 4); when the CHCl$_3$ solution used in experiments is accounted for by the PCM, these wavenumbers are shifted to 3854 and 3491 cm$^{-1}$, respectively. Thus, formation of the adduct between TEMPO and phenol leads to a computed red shift of the O–H stretching (339 cm$^{-1}$ in the gas phase, 363 cm$^{-1}$ in CHCl$_3$ solution) in remarkable agreement with its experimental counterpart (310 cm$^{-1}$). While the computed frequencies are overestimated (by about 300 cm$^{-1}$) with respect to the experimental ones, inclusion of anharmonicity for XH stretchings and their couplings with other modes at the PT2 level leads to an OH stretching in quantitative agreement with experiment (harmonic = 3889 cm$^{-1}$; anharmonic = 3688 cm$^{-1}$; experimental = 3656 cm$^{-1}$).

However, band shifts induced by hydrogen bond (harmonic 339 cm$^{-1}$, anharmonic 345 cm$^{-1}$) and solvent effects (harmonic 363 cm$^{-1}$, anharmonic 358 cm$^{-1}$) are reproduced with
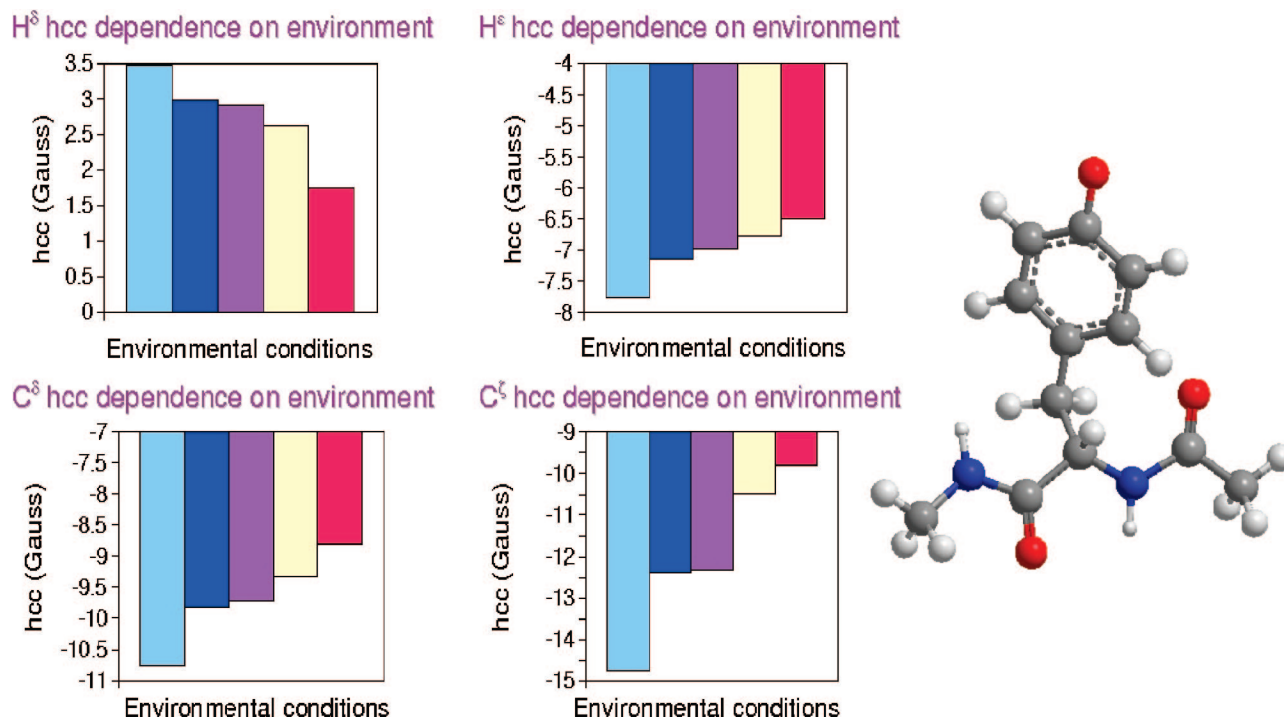
**FIGURE 3.** Different contributions to the hcc's of the dipeptide analogue of tyrosine radical: blue, in vacuum; dark blue, rigid geometry PCM effect; purple, geometry reoptimization with PCM; yellow, two water molecules + PCM; red, experiment.
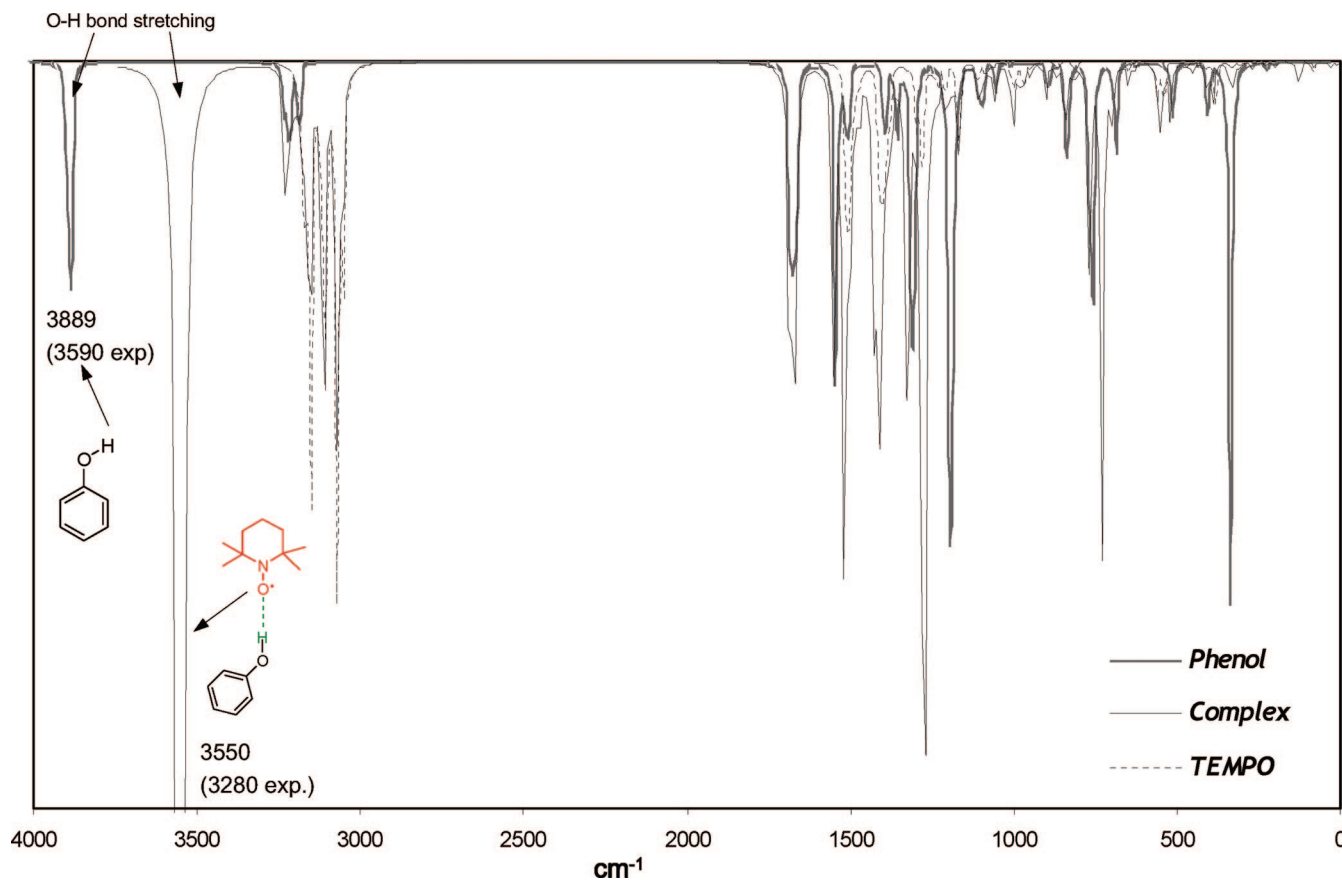


**FIGURE 4.** IR spectra for the free phenol, TEMPO, and the hydrogen-bonded complex computed in the gas phase at the harmonic level.

satisfactory accuracy by a simple harmonic treatment, a general trend that is confirmed also in the present case.

It is well-known that large amplitude, low frequency vibrational motions, in particular hindered rotations and inversions,
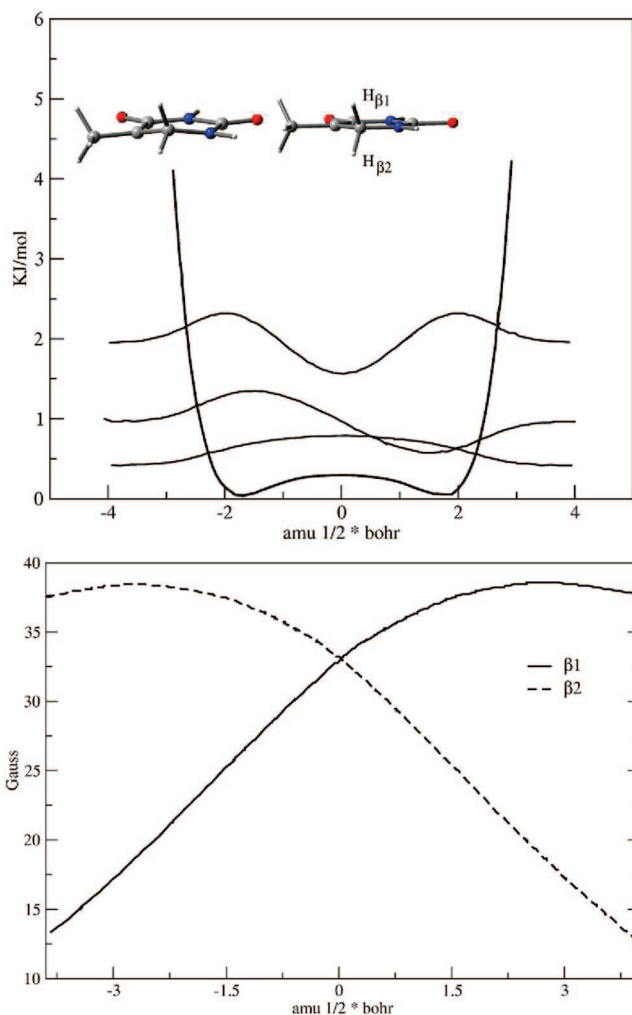
**FIGURE 5.** Potential energy, lower vibrational wave functions (upper panel) and hcc's of $\beta$-hydrogen atoms (lower panel) as a function of the out of plane motion of C6 for 5-yl radical.

**TABLE 1.** Isotropic hcc's (gauss) of the $\beta$-Hydrogen Atoms in the 5-yl Radical Calculated at the B3LYP/EPRII Level

|         | minimum | $a_{0K}$ | $\langle a \rangle_{77K}$ | $\langle a \rangle_{298K}$ | expt |
|---------|---------|----------|---------------------------|----------------------------|------|
| H$\beta$1 | 25.4    | 33.0     | 32.7                      | 32.3                       | 34.5 |
| H$\beta$2 | 40      | 33.0     | 32.7                      | 32.3                       | 34.5 |

represented by the inversion of the C6 methylene group. This internal mode is well separated from the other ones, and its vibrational states can be obtained with good accuracy by an effective vibrational Hamiltonian depending explicitly only on the large amplitude coordinate and its conjugate momentum. Averaging of the hcc's over the corresponding vibrational states leads to identical coupling constants for both $\beta$-hydrogens at 0, 77, and 298 K (Figure 5b and Table 1), which are, furthermore, in remarkable agreement with their experimental counterparts.[15]

An alternative and complementary approach relies on statistical analysis of ab initio molecular dynamics simulations. Extended Lagrangian approaches introduced by Car and Parrinello[32] are particularly effective to compute on the fly potential energies and forces at quantum mechanical level. While periodic boundary conditions (PBC) represent the natural choice in standard plane wave implementations, use of localized basis functions (like in the so-called atom-centered density matrix propagation (ADMP) approach)[33,34] calls for the development of alternative nonperiodic boundary conditions. According to this new model, hereafter referred to as general liquid optimized boundary (GLOB),[7,8,19] (Figure 6), the solute−solvent system is described by an effective Hamiltonian,
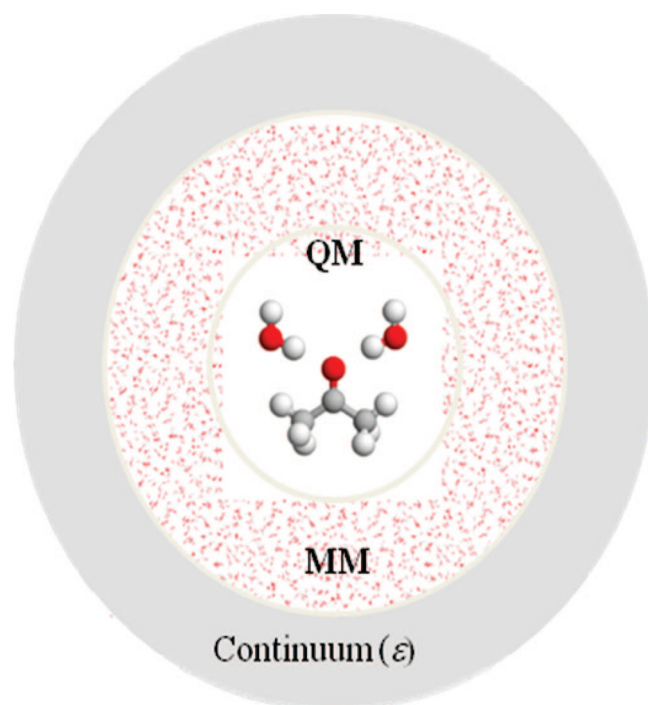
may affect the spectroscopic parameters significantly.[17] As a consequence, effective computational procedures able to take vibrational averaging effects into proper account have been developed, which, in several cases (concerning mainly magnetic spectroscopies), have allowed significant improvement in the agreement between computed and experimentally derived parameters.

Let us consider, as an example, the EPR spectrum of the 5,6-dihydro-5-thymyl radical (referred to as 5-yl, see Figure 5) issuing from the addition of hydrogen atoms to thymine. When the spectrum is recorded at finite temperature, a single hcc (34.5 G) is observed for both $\beta$-hydrogen atoms. The theoretical determination of such parameters on the basis of a static model is inadequate (see the parameters calculated for the minimum structure in the ground state in Table 1).[15] Magnetic equivalence can be restored only after proper averaging with respect to large amplitude motions mainly



**FIGURE 6.** GLOB model for an aqueous solution of acetone.

## UV ($\Delta E$ n -> $\pi^*$ acetone)

## NMR ($\Delta\sigma_{iso}$ $^{17}$O acetone)

## EPR ($\Delta hcc_N$ DTBN)
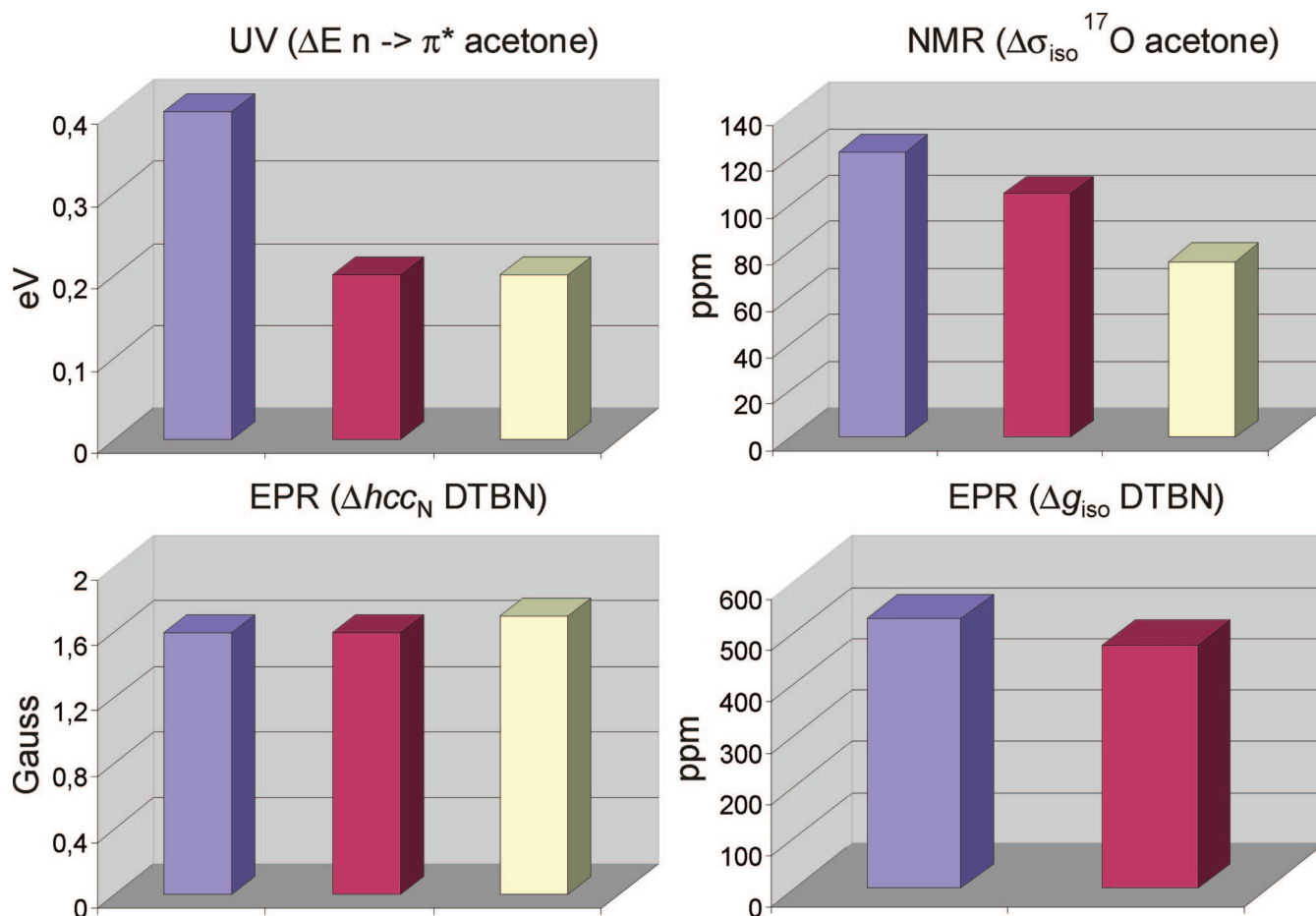
## EPR ($\Delta g_{iso}$ DTBN)

**FIGURE 7.** Solvent shifts of spectroscopic properties: blue, values computed on minimum-energy structures; magenta, values averaged over the MD trajectories; yellow, experimental values (when available).

composed of a "high-level" region treated at full QM level representing the solute and, possibly, a few solvent molecules and a "low level" region treated by a MM force field, which includes all the surrounding solvent molecules providing an electrostatic embedding (generated by their charge distribution) of the quantum core. Moreover, both QM and MM interactions with bulk solvent are taken into account by a mean field approach including an exact treatment of the electrostatic reaction field and an effective representation of short-range (repulsion and dispersion) interactions derived so as to minimize edge effects on the solvent orientation, density, and average energy.

A very important point is the extent to which a dynamic (expensive) simulation is needed and when it can be replaced by a much cheaper optimization of a single representative structure. Figure 7 shows a comparison of different spectroscopic properties obtained from geometry optimizations of embedded clusters and from extended Lagrangian simulations. It is quite apparent that with the possible exception of isotropic hcc's of rigid radicals, proper account of the effects of solute vibrations and solvent librations is mandatory when

computing spectroscopic properties for systems in solution; of course, the quality of the dynamics and the extent of the sampling (time scale of the MD simulations) are also crucial for the accuracy of the final results.

This time-dependent approach is particularly suited to the computation of IR spectra in solution and to their interpretation beyond the harmonic approximation. The infrared absorption coefficient, $\alpha(\omega)$, can be obtained from the analysis of the dipole moment autocorrelation in the frequency domain. Furthermore, a vibrational analysis can be performed evaluating generalized normal modes $Q_i$, with associated frequencies $\nu_i$ from eigenvectors and eigenvalues of the covariance matrix of the nuclear linear momenta.[6] Use of the same QM level for both the quantum time-independent (gas phase) and classic time-dependent (solution) pictures allows for a synergic application of the methods in the evaluation of solvent shifts on vibrational frequencies.

In Table 2, we report the frequency analysis of the characteristic amide modes (AI, CO stretching; AII and AIII, combinations of NC stretching and CNH bending) for the *trans-N*-methylacetamide (NMA) molecule. Solvent shifts are evaluated

**TABLE 2.** Vibrational Frequencies (cm$^{-1}$) of *trans-N*-Methylacetamide[a]

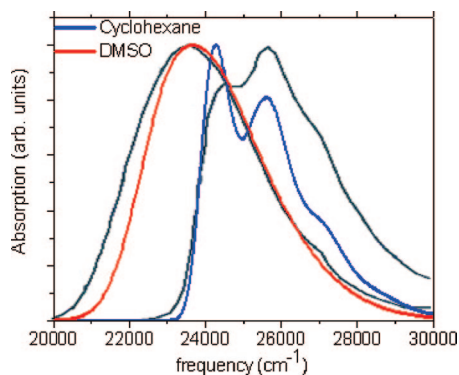|       | PT2 gas phase | GLOB/ADMP solution | expt solution (ref 36) |
|-------|---------------|--------------------|------------------------|
| AI    | 1723          | 1625 ($\Delta = -98$) | 1625 ($\Delta = -98$) |
| AII   | 1533          | 1613 ($\Delta = +80$) | 1582 ($\Delta = +82$) |
| AIII  | 1244          | 1272 ($\Delta = +28$) | 1316 ($\Delta = +51$) |

[a] Solvent shifts are given in parentheses.



**FIGURE 8.** Computed spectra for coumarin C153 in cyclohexane and in DMSO. Both spectra are red-shifted by 400 cm$^{-1}$. The experimental spectra (in black) are shown for comparison.

from the analysis of a GLOB/ADMP trajectory collected for NMA in aqueous solution at normal conditions and a perturbative anharmonic treatment performed for the NMA in gas phase.[35] The nice agreement with the experimental values[36] points out the reliability of the proposed computational approach.

## 5. From Spectral Parameters to Line Shapes

We have already sketched the key methodological steps for the calculation of absorption and emission spectra. Thanks to the availability of PCM/TD-DFT analytical gradients in solution, reliable energy minima and (numerical) vibrational modes can be obtained. Dynamical solvent effects (of paramount importance in the study of time-dependent phenomena) can be easily included by the PCM[37] and effective procedures for the calculation of the Franck–Condon factors have been implemented.[11] Combination of the above methodological advances allows computation of absorption and emission spectra of several systems, getting a very good agreement with the experiments. For example, without using any adjustable parameter (apart from inhomogeneous broadening), it is possible to reproduce the changes of the absorption spectra of coumarin C153 (a benchmark molecule for the study of solvatochromism) when going from cyclohexane to dimethylsulfoxide solvents (see Figure 8).[10]

The solution of the vibrational problem, at least at the harmonic level, is not significantly limited by the dimension of the molecule under study. Once the geometry and vibrational frequencies of the relevant electronic states are available, the bottleneck for the computation of vibrationally resolved optical spectra is represented by the huge number of overlaps among the vibrational states that should be in principle computed. However, a novel effective strategy for selecting the relevant overlaps to be calculated, especially devised for large molecules,[17,18] is able to avoid unaffordable computational costs.

Let us now turn to EPR spectroscopy, where line shapes are ruled by rotational dynamics of the probe in the medium. We shall consider, for purposes of illustration, the *p*-(methylthio)-phenyl-nitronyl-nitroxide (MTPNN) radical (Figure 9) in toluene solution. Although at least two relevant internal degrees of freedom, that is, dihedral angles, can be identified between the SCH$_3$ group and the phenyl group and between the phenyl group and the nitroxide group, QM computations indicate that the motional regime for the first angle is fast enough to be practically negligible, while the second angle is affected by localized librations around the planar conformation. To keep our example simple, we shall not consider explicitly the coupling with this relatively soft degree of freedom; thus we end up with an effective spin Hamiltonian ruled by computed **g** and **A** tensors. Since the system is dissolved in an isotropic fluid and no glassy phases will be considered, the motional regime assumed for the molecules is purely freely diffusive.

In Figure 9, we show a selection of results[20] in which experimental and calculated spectra are compared at 292 and 155 K. The results are quite satisfactory, especially when considering that no fitted parameters but only calculated quantities (via QM and hydrodynamic models) have been employed. The overall agreement of the spectral line shapes, particularly at low temperatures, is a convincing proof that the simplified dynamic modeling implemented in the stochastic Liouville equation through a purely rotational stochastic diffusive operator and the hydrodynamic calculation of the rotational diffusion tensor is sufficient to describe the main slow relaxation processes. In our opinion, the above results show the potentialities of an integrated computational approach and the validity of the assumptions made in the specific application.

## 6. Concluding Remarks and Perspectives

We have sketched integrated and general strategies for computing spectroscopic observables of large and flexible systems
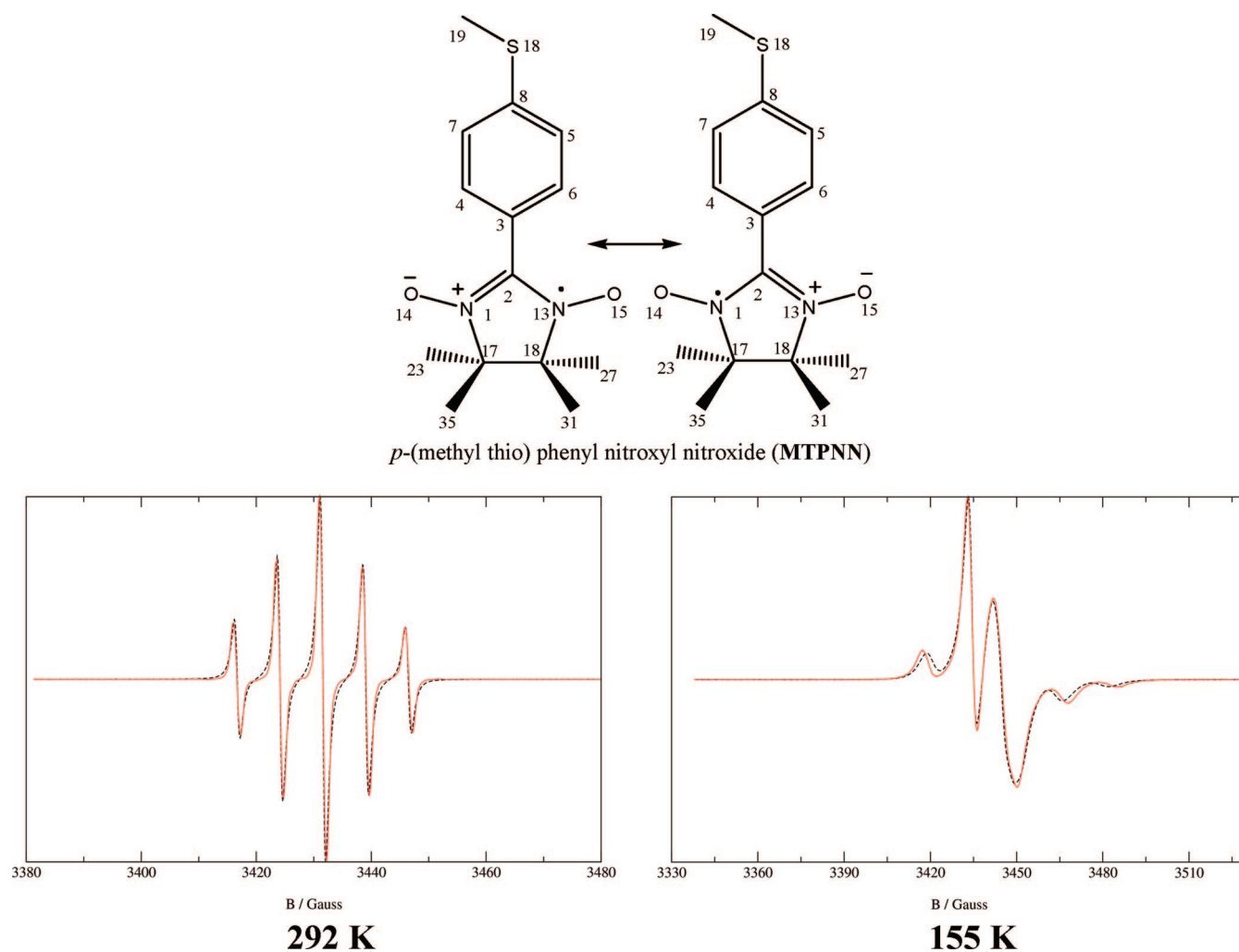
FIGURE 9. Sketch of the MTPNN structure and comparison between its experimental (continuous line) and calculated (dotted line) CW-ESR spectra in toluene at 292 and 155 K.

in condensed phases, which are the results of ongoing developments in our group. Such strategies are based on QM/MM techniques using localized basis sets and coupled to nonperiodic boundary conditions. In structural and dynamical characterizations, methods rooted in density functional theory and its time-dependent extension are used for the QM part, whereas higher-level QM methods can be used, when needed, for the a posteriori calculation of spectroscopic parameters. Short-time dynamical effects are introduced by either time-independent or time-dependent approaches. As illustrative applications, we have considered vibrational and solvent effects on NMR chemical shifts, UV–vis absorption spectra, and EPR parameters. The situation is different for long-time dynamical effects ruling line shapes. Here, only the integration of quantum mechanical and stochastic techniques could offer a viable route. The first examples of such an effort are indeed quite promising and suggest that further work will lead to exciting results for more complex situations. In general terms,

we can say that though further developments are surely needed, the accuracy of the computed spectroscopic parameters already allows for a direct comparison with measurements in a number of interesting situations and represents a valuable complement to experimental results. Furthermore, thanks to the implementation of all these items in user-friendly computer codes, this type of analyses is (or will shortly be) also feasible by nonspecialists. The possibility to rely on this kind of comparison between computed and measured spectra represents by itself an important asset and would certainly justify an interdisciplinary approach to spectroscopic and structural problems in different fields of chemistry. However, apart from this practical application, computational approaches provide, in this as well as in many other fields, a unique opportunity to dissect different contributions to a measured property, to rationalize trends, and to explore differences among various molecules or classes of compounds. Using to full advantage these interpretative potentialities requires per-

haps a larger dose of theoretical experience, but in perspective the increased understanding of the spectroscopic behavior of complex systems will probably represent the main advantage from a closer interaction between computational and experimental chemists.

## BIOGRAPHICAL INFORMATION

**Vincenzo Barone** was born in Ancona in November 1952 and has been Full Professor in Physical Chemistry since November 1994. He is president of the Physical Chemistry Division of the Italian Chemical Society (2007–2009) and national coordinator of the virtual computational laboratory VILLAGE (http://village.unina.it). His main research interests are related to the development, validation, and application of new theoretical approaches especially devised for the study of complex systems (materials, nanostructures, biomolecules) with special reference to their geometric and electronic structure and to their reactivity. He is author of more than 400 papers in international journals with more than 12000 citations.

**Roberto Improta** was born in Naples on May 12th, 1970. He graduated and received a Ph.D. in Chemistry in 1998 from the University of Naples "Federico II". He spent his postdoctoral fellowships in Pisa, in Houston, and in Naples. Since 2001, he has been a researcher at the Italian National Research Council (CNR). Beyond the theoretical study of the spectroscopic properties of organic molecules in solution, his main research interest concerns the validation and application of theoretical models and computational methods for the study of large size molecules, with special attention to the structure and reactivity of excited states in the condensed phase.

**Nadia Rega** received her degree in Chemistry on March 1997 and defended her Ph.D. thesis in February 2001. She spent her postdoctoral fellowships at the Royal School of Pharmacy (Copenhagen, Denmark), at Gaussian Inc., and at the Chemistry Department of University of Utah. Since December 2002, she has been a research associate at the Chemistry Department of University of Napoli Federico II. Her main research interests concern the dynamics and reactivity of biological systems and surfaces, the development of methods for dynamics based on hybrid QM/MM potentials, and the development of methods for computing solvent effects.

## FOOTNOTES

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