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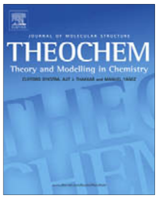

Quantitative evaluation of the aqueous dihydronitroxide nitrogen hyperfine coupling constant from QM/MM//MD computations

Céline Houriez [a], Nicolas Ferré [a,*], Michel Masella [b], Didier Siri [a]

[a] *UMR 6264 Laboratoire Chimie Provence, Equipe Chimie Théorique, Faculté des Sciences de Saint-Jérôme Case 521, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France*

[b] *Laboratoire de Chimie du Vivant, Service d'ingénierie moléculaire des protéines, Institut de biologie et de technologies de Saclay, Commissariat à l'énergie atomique, Centre de Saclay, 91191 Gif-sur-Yvette Cedex, France*

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ABSTRACT

A sequential molecular dynamics + hybrid quantum mechanical/molecular mechanical (QM/MM//MD) approach is presented and applied to the determination of the nitrogen hyperfine coupling constant in the dihydronitroxide radical solvated in water. The model relies on a sophisticated polarizable force-field featuring a many-body hydrogen bond potential, whose parameters have been carefully fitted to QM calculations with special attention paid to the nitrogen out-of-plane angle. It involves also an electronic embedding of the QM subsystem thanks to the ElectroStatic Potential Fitted (ESPF) operator method which is shown to be superior to continuum methods like the polarizable continuum method when anisotropic electrostatic interactions take place between the QM subsystem and its classical surroundings.

1. Introduction

The computation of accurate nitrogen isotropic (Fermi contact) hyperfine coupling constants (a_N), i.e. comparable with available experimental values, of nitrogen-centered radical usually requires a very high *ab initio* level of theory (e.g. QCISD or CCSD(T)) [1] or suitable density functionals [2], used in conjunction with very large and decontracted Gaussian basis sets. Hence, it is generally restricted to small model molecular systems, such as the dihydronitroxide H_2NO molecule or the dimethylnitroxide $(CH_3)_2NO$ molecule in the case of nitroxides (i.e. radicals containing a three-electrons $(\pi)^2(\pi^*)^1$ bond between a nitrogen atom and an oxygen one). However, as the value of a_N reflects the local conformation of both the NO moiety and of its chemical environment, nitroxides are widely used as molecular probes of local structures in large systems such as proteins [3–5]. In that case, many degrees of freedom can potentially affect the value of a_N and, therefore, have to be accounted for in the computation. However, the available computational resources still prevent to consider them at the above levels of theory, and this explains why elaborating theoretical approaches able to give quantitative predictions of nitroxide a_N in a complex environment is still challenging.

The quantum mechanical/molecular mechanical (QM/MM) hybrid methods developed these last 20 years [6–9] represent a promising approach to compute a_N values in complex chemical environment. Those methods are based on a hierarchical decomposition of the levels of theory. The "reactive" center of an extended molecular system, i.e. the place where the electronic distribution has to be described explicitly, is treated quantum mechanically, while the remaining spectator environment is treated with a fully empirical model potential, involving only classical degrees of freedom. Hence, the energy of the whole system can be decomposed into three terms:

$$E = E_{QM} + E_{MM} + E_{QM/MM} \qquad (1)$$

where E_{QM} stands for the energy of the QM subsystem, E_{MM} for the energy of the environment and $E_{QM/MM}$ for the interaction energy between the two subsystems. Because the QM/MM term is often defined using the same decomposition rules as the total MM interaction energy (e.g. the bonded and non-bonded terms), the integration of the QM and MM models focus mainly on the interaction between the quantum distribution of charges (nuclei and electrons) and the electrostatic potential ϕ arising from the MM subsystem. Note that the calculation of this latter quantity can be based either on a continuous approach or on a discrete description, as well as on a static or on a dynamic electrostatic scheme, thus giving rise to several ways for achieving the QM/MM electrostatic coupling. In the following, the discussion will be restricted to the

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* Corresponding author.
E-mail address: nicolas.ferre@univ-provence.fr (N. Ferré).

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category of QM/MM models in which the MM electrostatic potential polarizes the QM wave function. In that case, often referred as an electronic or electrostatic embedding, the electronic Hamiltonian $\mathscr{H}^0$ must be modified accordingly:

$$\mathscr{H} = \mathscr{H}^0 + \mathscr{V}^e(\phi) \tag{2}$$

with $\mathscr{V}^e(\phi)$ the operator coupling the QM wave function with the MM electrostatic potential ϕ. Hence the quality of the "perturbing" operator will strongly affect the quality of the QM wave function.

Moreover, the comparison with experiment requires also to take into account the statistical nature of a macroscopic measurement, i.e. the averaging of the instantaneous microscopic property over the accessible molecular states during a finite time period. The molecular dynamics (MD) simulation is a common tool for sampling efficiently the configurational space [10]. In the limit of an infinite-time simulation, the ergodic hypothesis is fulfilled and the macroscopic property of interest $\overline{X}$ can be evaluated as its mean value:

$$\overline{X} = \frac{1}{\mathrm{N}}\sum_{i=1}^{\mathrm{N}\to\infty} X(t_0 + i\Delta t) \tag{3}$$

where t_0 stands for the initial time of the data acquisition and Δt for the time interval between two samples. Δt must be chosen carefully, in such a way two successive instantaneous values of the property X are not correlated. From a practical point of view, only finite-length MD simulations are carried on (routinely with time scales from the ps to hundreds of ns) and the averaging of a property is performed on a finite number of extracted samples. To insure the quality of the resulting $\overline{X}$, several MD simulations with different initial conditions must be compared.

When the property under investigation requires an explicit consideration of the electronic degrees of freedom, the combination of the QM/MM approach able to describe qualitatively the interactions in a large molecular system and of MD simulations may represent quite a satisfactory effective model towards a realistic comparison with the experiment. However, despite the fact that all the needed tools are available, this QM/MM//MD approach faces a great challenge: a single QM energy and gradient calculation becomes a real computational bottleneck since its cost can be several orders of magnitude higher than the same calculation at the MM level. At least two strategies have been proposed in order to circumvent the problem:

(1) Reduce the cost of the QM calculation. This implies using semi-empirical QM Hamiltonians, like the AM1, PM3 or DFTB ones [11]. As a consequence, the accuracy of the QM description decreases. Another possibility lies in the linear-scaling or Car-Parrinello methods [12,13], however, their cost remain prohibitive for long-time MD simulations and can hardly be used in nanosecond-scale molecular dynamics simulations.

(2) Parametrize the MM model in order to reproduce the QM potential energy surface. This way implies the determination of many method-specific parameters fitted to various QM calculations (e.g. relative energies of stationary points, frequencies etc.), hence the parametrization process is relatively time-consuming. However, in contrast with the first approach, the accuracy of the QM method is kept. Note this approach is twofold: first, MD simulations are run in order to generate a statistical ensemble of uncorrelated structures; second, QM/MM property calculations are performed on this set of structures.

Since many years, Barone and coworkers have been interested in the computation of nitroxide spectromagnetic properties [14–18]. Quite recently, they have chosen the first approach outlined above, based on Car-Parrinello simulations (~10 ps) using the PBE functional, followed by PBE0 + PCM a_N computations on extracted structures [19–22]. Slightly longer Car-Parrinello simulations were performed recently by Neugebauer et al. [23], where the influence of the solvent bulk is taken into account by means of a frozen-density embedding. However their evaluation of a_N in H_2NO is only two thirds of the experimental value. Finally, note that very recently Barone and coworkers have set another integrated scheme in which QM/MM or MM dynamics employ effective non periodic boundary conditions and apply this, e.g. to the determination of magnetic properties of aqueous glycine [24].

Our present work aims to evaluate the accuracy of the above second approach in computing the nitrogen isotropic hyperfine coupling constant (a_N) in aqueous phase of the simplest prototypal nitroxile radical: the dihydronitroxide H_2NO molecule. A quantitative evaluation of a_N requires the computation of the spin density ρ^S at the nitrogen nucleus position r_N:

$$a_\mathrm{N} = \frac{8}{3} g_\mathrm{e} g_\mathrm{N} \beta_\mathrm{e} \beta_\mathrm{N} \rho^S(r_\mathrm{N}) \tag{4}$$

for a mono-radical ($\langle S_z \rangle = \frac{1}{2}$), β_e is the Bohr magneton, β_N is the nuclear magneton, g_e and g_N are the g-values for the free electron and the nuclei, respectively. Several key methodological aspects are involved:

- an efficient QM level of theory able to mimic high level results;
- a correct description of the interactions between the nitroxide and the surrounding water molecules. Actually, Barone and coworkers shown it is important to include into the QM subsystem some of the closest water molecules, i.e. the ones involved in some hydrogen bonds with the nitroxide molecule [18];
- a long enough MD simulation to generate a large set of uncorrelated structures.

In a recent study, we have addressed the three above points by investigating the properties of the solvated dimethylnitroxide $(CH_3)_2NO$ radical [25]. In particular, we demonstrated that it is possible to accurately reproduce the $(CH_3)_2NO$ a_N value (within about 2%) with the following strategy:

- The MD trajectories are generated by use of the polarizable force field TCPEp [26–28], which includes a specific many-body hydrogen bond potential function. This force field is able to accurately reproduce the quantum potential energy surfaces of small $H_2NO/(H_2O)_n$ aggregates and it is also computationally efficient: it allows one to generate easily MD simulations at the nanosecond scale of the $(CH_3)_2NO$ molecule embedded in a cubic box containing about 500 water molecules;
- The nitroxide structures extracted along the trajectories are computed at the DFT PBE0 [29] level with the small 6-31+$G(d)$ basis set. This level is able to reproduce the QCISD/EPR-II a_N values (within 0.5 Gauss) when the most important degree of freedom, i.e. the nitrogen out-of-plane motion, is varied from 0° to 60°;
- The solvent effect was taken into account by considering explicitly the nitroxide first solvation shell, whereas the electrostatic coupling with the water bulk was modelled thanks to the ESPF method [30]. With this method, it is possible to take into account during the quantum computations the instantaneous MM electrostatic potential generated by the bulk water molecules for each extracted MD frame.

In the present work, the same strategy is applied to the determination of the H_2NO a_N value. The current model for the solvated H_2NO is reviewed in the first part. We will also pay attention on the