Accurate Calculation of Chemical Shifts in Highly Dynamic H_2@C_{60} through an Integrated Quantum Mechanics/Molecular Dynamics Scheme

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ABSTRACT
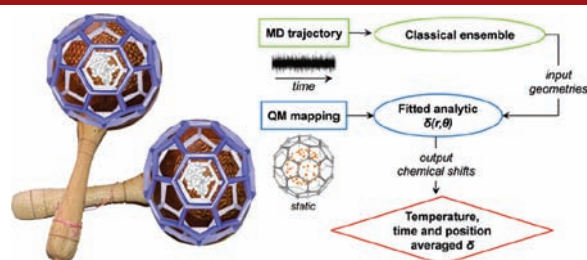
A new protocol combining classical MD simulations and DFT calculations is presented to accurately estimate the ^{1}H NMR chemical shifts of highly mobile guest−host systems and their thermal dependence. This strategy has been successfully applied for the hydrogen molecule trapped into C_{60} fullerene, an unresolved and challenging prototypical case for which experimental values have never been reproduced. The dependence of the final values on the theoretical method and their implications to avoid over interpretation of the obtained results are carefully described.

Since its very first preparation by Komatsu et al. through an exquisite molecular surgery protocol,[1] the puzzling spectroscopic properties of the guest hydrogen molecule encapsulated into C_{60} fullerene cages have intrigued both experimental and theoretical chemists beyond the potential interests of these materials for hydrogen storage applications. Despite the energy minimum of the H_2 molecule lying on the center of the C_{60} cage,[2] time-dependent simulations reveal that it actually spends most of the time around the equilibrium position (Figure S2), as discussed below. Indeed, excellent contributions have been made very recently to accurately describe the coupled translation−rotation states of H_2 molecules inside C_{60} and C_{70} cages through Quantum Dynamics simulations.[3] Simultaneously, state-of-the-art spectroscopic experiments have further confirmed these predictions.[4] With respect to NMR properties, many investigations on the outstanding

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nuclear relaxation and allotrope interconversion properties of $H_2@C_{60}$ and $HD@C_{60}$ have been done.[3] Furthermore, the particular NMR properties of encapsulated H_2 molecules have been very recently used for the challenging structural characterization of isomeric $H_2@C_{60}$ nitroxide derivatives.[5] On the contrary, only a few theoretical studies have been performed to rationalize the particular chemical shielding properties of incarcerated molecules,[1,6] with limited success. The general underestimation of calculated values with respect to experimental ones has been attributed to deficiencies in Quantum Mechanics methods. Other recent studies have proposed semiempirical relationships between calculated and experimental chemical shift values of several endohedral fullerenes through linear parametric models.[7]

However, the molecular physics of the problem remains unexplained, and no theoretical methodology has succeeded in describing it properly to date. All these attempts to reproduce theoretically the strong high-field shifts observed in the ^1H NMR spectrum of endohedral $H_2@C_{60}$ at 293 K (δ -1.44 ppm in solution of o-dichlorobenzene-d_4[1a] and -1.1 ppm in the solid state[4]) with respect to isolated H_2 (δ about $+4.5$ ppm depending on the trapping conditions[1b,8]) have been done using optimized minimum energy structures. It has been shown that, irrespective of the orientation of the guest H_2 molecule inside the host, the average anisotropic effects occurring at the center of the cage are not strong enough to account for the large chemical shielding experimentally measured for the encapsulated hydrogen nuclei. Surprisingly, the highly dynamic character of this system has been ignored in these studies. In this sense, it can be easily guessed that the continuous swinging inside the cavity would allow guest H_2 to reach those regions of maximum anisotropic shielding influence, which will depend on the aromatic or antiaromatic character of each carbon ring, an aspect which has been studied in more detail[1b,5a] (see Figure S3 in the Supporting Information). This reasoning is qualitatively different from the classical consideration of the total ring currents affecting the geometric center of the fullerene; the guest

molecules are not influenced by the overall anisotropy occurring at the minimum energy positions because they do not reside at these positions in practice, even at temperatures close to 0 K, due to the significant quantum translational effects experimentally determined for closely related species.[4b] Thus, *any attempt to calculate any property at fixed energy-minimized geometries will be inherently wrong*, irrespective of the "goodness" or quality of the theoretical method employed. We confirmed this at a very early stage of our study by calculating the ^1H NMR chemical shift of $H_2@C_{60}$ with different ab initio and DFT methods and basis sets, for which we obtained a continuous distribution of values of δ ranging from $+6.20$ to -7.55 ppm (see Figure S4 in the Supporting Information for further discussion).

Thus, one simplistic (but unrealistic) solution in these situations could be to choose the most convenient theoretical method by the simple trial and error technique; after a more or less arbitrary survey of the plethora of functionals available nowadays, some "magic" methods able to reproduce the experimental values will surely arise (i.e., functionals with a high contribution of Hartree−Fock exchange—thus eliminating self-exchange interactions at long-range—such as the modern M06-HF[9] and the quite old BH&HLYP[10] showed the closest values to experiment in our preliminary calculations).

This approach could be one more example of the *"right answer by the wrong reasons"* paradigm. Nevertheless, the problem of choosing an adequate theoretical method and basis set is unavoidable, and thus, some kind of benchmarking must be done to follow the right direction (vide infra). More importantly, in such highly dynamic systems like $H_2@C_{60}$, not only the influence of the theoretical method but also the effects of translational, rotational, and vibrational motions must be taken into account. Ideally, the time- and temperature-dependent evaluation of the NMR properties at each step of an unrestricted Quantum Dynamics trajectory should be the most exact approach, but it is obviously unfeasible in practice due to current computing limitations.

A reasonable compromise solution to this issue is to obtain a classical trajectory of the motion of the guest molecule inside the host through simple Molecular Dynamics (MD) simulations. Despite quantum coupling of translational and rotational motions, which is more relevant at cryogenic temperatures, classical molecular dynamics should recover most of the dynamic behavior of the guest at higher temperatures. Otherwise, at cryogenic temperatures,[4] the classical MD description should be taken with more caution. Although experimental evidence of nearly isotropic rotational motion of H_2 within the C_{60} cage has been reported,[4] a reviewer noted that quantum effects are probably significant even at room temperature. In spite of this, it is expected that this *nuclear* effect does not play a primary role in the chemical shield of H_2, which is mainly influenced by the anisotropy generated by the delocalized π-electron density of the C_{60} cage at different positions of the guest.

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Therefore, the main goal of the work presented herein is to integrate MD simulations and QM calculations in a stepwise protocol in order to obtain more realistic temperature-, time-, and position-averaged values of δ. The proposed workflow diagram is presented in Figure 1.
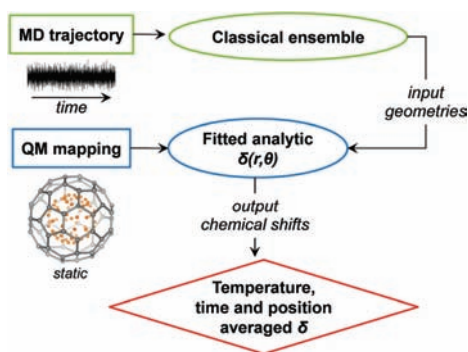

Figure 1. Workflow diagram of the integrated QM/MD scheme used to calculate the NMR properties of dynamic systems.

Within this approach, temperature-dependent distributions of structures along the distance between the host and guest centers of mass (henceforth, C_{60}* and H_2*) can be easily obtained from a MD trajectory. In parallel, ^{1}H NMR chemical shifts inside the C_{60} cage are systematically mapped through GIAO (gauge independent atomic orbital)[11] calculations by placing the H_2 molecule in a number of symmetrically nonequivalent positions and then fitted to a multidimensional analytic function in which δ depends on the radial and angular components of the guest motion. In the final step, geometric data obtained along the trajectory are used as input in this expression to obtain a distribution of δ along the simulation time. The final temperature-, time-, and position-averaged value of δ is obtained from the statistical analysis of this distribution.[12]

It must be noted that the allotropic rotational states of H_2 (*ortho* and *para*) cannot be distinguished in the MD simulations nor in the GIAO calculation of the isotropic shieldings, for which only the NMR active species with parallel nuclear spin orientation (↑↑) (the rotational triplet excited state *ortho*-H_2, $J = 1$ Hz) is considered. It has been reported[13] that at low temperature (where the equilibrium is completely displaced to the *para*-hydrogen state) there is no decrease in the observed NMR signal, indicating that the endohedral H_2 species are not in equilibrium at low temperature. These considerations do not apply to the classical approach used in MD simulations, given that rotational states of the H_2 molecule are not considered in the force field.

The population distributions describing the translational motion of H_2 inside C_{60} at several temperatures (see the computational details in the Supporting Information) are depicted in Figure S6. Previous studies have established that the translational ground-state wave function of *ortho*-H_2 hydrogen is delocalized around the potential minimum.[3,14] In qualitative agreement with these prior results, the H_2 molecule lies out of the equilibrium position (the center of the fullerene) even at very low temperatures. At room temperature (293 K), most of the H_2 molecules swirl between 0.3–0.8 Å from C_{60}*, the distribution maximum being located at around 0.6 Å.

Average values of host−guest distances and energies of the coupled translation-rotation (T-R) states of $H_2@C_{60}$ have been previously derived from quantum five-dimesional calculations.[3b,c] As a reviewer indicated, these values can be used to calculate average distances as a function of temperature. The calculated average distance in the lowest T−R state for three different potentials ranges from 0.3 to 0.4 Å. This suggests that the force field employed in the simlations described herein (see the Supporting Information) is somewhat more restrictive of the H_2 motion than the potential used in refs 3b and 3c, although the direct comparison of both results is not straightforward.

A careful examination of the trajectory also reveals that H_2 lies about 90% of the time close to aromatic hexagons; this ratio is superior to the 20:12 proportion of hexagons and pentagons in the C_{60} host, which reveals the force field ability to reproduce the favorable aromatic hexagon−hydrogen interactions further than yielding a simple stochastic distribution. As a consequence of this motion, a lower value of time-averaged δ should always be obtained with respect to that calculated for frozen H_2 lying on the cage geometrical center, irrespective of the theoretical method employed in the QM mapping.

In fact, for the second step, we first had to choose one (but probably not "the one") appropriate theoretical method. As a first approximation, we scanned the average chemical shift of hydrogen atoms along the C_{60}*−H_2* distance (keeping the H−H bond fixed at 0.74 Å) with H_2 perpendicular to a selected hexagon ring through the GIAO scheme using HF and several DFT methods with 6-31+G(d) as standard basis set. For the reasons outlined in Figure S5 (Supporting Information), the method selected to perform the whole QM mapping was the recent and general purpose M06-2X[15] functional. Classic B3LYP[16] was also used for comparative purposes.

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Differing from the classical (and inexact) assumption of spherical symmetry, the real symmetry of the host (truncated icosahedron) was considered in order to properly describe the distinct influence of the six-membered aromatic and five-membered antiaromatic regions of the C_{60} wall. This approach increased the complexity of the mapping significantly and made it necessary to define two sets of variables depending on the polygon type to which the H_2 molecule moves, namely the closest polygon (see computational details in the Supporting Information).

The introduction of distances and angles extracted for each step of the MD trajectory simulated at several temperatures finally led to Gaussian-like distributions of δ whose average values are summarized in Table 1. These results show a perfect match between experimental and M06-2X theoretical values, although these results should not be overinterpreted. This success arises from both the inclusion of dynamics in the calculation of average δ and also on the (unexplained) accuracy exhibited for this particular system by the selected QM method. Although both functionals follow the same qualitative trend, classic B3LYP underestimates the chemical shielding effects inside fullerene systematically, both under static or dynamic conditions, as envisaged in the first part of the study. It is important to notice that other factors like nuclear quantum effects,[3] the effect of the cage dynamics, or the particular choice for the cage geometry used in the NMR calculations[5a] might be relevant in the estimated chemical shifts, so *not these final δ values but the idea lying behind them (to introduce guest dynamics) is the real goal of this new protocol*.

Table 1. Time-Averaged ^{1}H NMR Chemical Shifts of $H_2@C_{60}$ Calculated at Several Temperatures

QM mapping method	MD simulation temperature					static minimum[a]
	293 K	50 K	10 K	4 K	1 K	
B3LYP	+0.36	+0.78	+1.19	+1.37	+1.57	+1.72
M06-2X	−1.09	−0.69	−0.27	−0.08	+0.12	+0.33
expt[b]	−1.10					

[a] Calculated on the energy-minimized global minimum. [b] Magic-angle-spinning ^{1}H NMR data acquired at 293 K.[4a]

Irrespective of the DFT method used, this combined QM and MD protocol allows, for the first time, the evaluation of thermal effects on the NMR properties of a given system; in this sense, decreasing the temperature down to near-cryogenic values reduces the H_2 motion, making it reside in regions closer to the C_{60} cage center and thus downfield-shifting the δ values. The effect of temperature on the chemical shift of $H_2@C_{60}$ has not been systematically investigated yet, but some effects following the trend predicted in this work have been reported in solid-state NMR experiments.[4] However, at present, these experimental results must not be taken as conclusive,[17] so further experimental work on this topic would be of great interest to test the classical/quantum dual behavior of incarcerated H_2 molecules.

Again, it has been demonstrated that the simple calculation of chemical shifts on fixed energy-minimized geometries is inherently an erroneous approximation given the deviation of ca. 1.5 ppm obtained with both functionals under these conditions.

In summary, this work describes a new, flexible, and computationally affordable framework to accurately calculate the NMR properties of highly flexible systems such as endohedral fullerenes. In addition, temperature effects are easily evaluated by combining fast classical molecular dynamics simulations and stand-alone DFT mapping of the available structural space. Although this methodology neglects quantum effects to find the correct distribution of H_2 molecules within the C_{60} cavity, it is expected that both classical and quantum-mechanical approaches would essentially converge at high temperatures, so predictions at room temperature will be reliable enough. Therefore, this protocol could be of great interest to precisely reproduce and predict the properties of highly dynamic systems, especially in the field of supramolecular and nanoscale chemistry in which host−guest complexes play an important role. In addition, the comparison of our computational predictions with experimental data at low temperature could provide a very fine test of our understanding of the behavior of encapsulated rotors, highlighting the important role of quantum effects. Further studies to generalize this methodology to study other systems and properties are currently in progress.

Supporting Information Available. Computational details, supplementary references, Figures S1−S6, and Tables S1−S3. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) As stated by one of the authors, these thermal effects on the chemical shift of $H_2@C_{60}$ are described marginally in Figure 7 of ref 4 are still being investigated experimentally and should not be overinterpreted (Levitt, M. H. Personal communication).