From Covalent Systems to Bulk Phases: Addressing Structural Complexity with Computational NMR

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In a typical NMR experiment, the chemical shifts, δ, and the spin-spin coupling constants, *J*, contain a plethora of information concerning the system investigated. Both parameters, and especially the chemical shifts, are extremely sensitive to intramolecular and intermolecular perturbations. For this reason, they can be used as probes for the covalent structure of the molecule and for the average bulk structure of the solvent. A very well-known application is the determination of the structure of organic molecules from the analysis of their ^{1}H and ^{13}C spectra.

The same protocols are applied in natural products studies to deduce the molecular structure of newly isolated compounds. However, natural substances often have very complex carbon skeletons with a variety of unusual structural motifs, like fused rings, strained bonds, high number of stereocenters, which make the interpretation of the NMR data far from trivial: the structural information is too deeply buried within the overlapping high-order multiplets and close resonances. A very nice review paper on the topic, highlighting the many cases of structural misassignment due to erroneous interpretation of the NMR spectra, is the essay by Nicolaou and Snyder about "chasing molecules that never were there" [1]. In these cases, computational NMR has emerged as a very useful complementary tool to help the experimental chemist in structural elucidation. The basic idea, pioneered more than 25 years ago by Bagno [2] and Bifulco [3], is to compare the experimental NMR data of the unknown substance with the ones predicted by quantum chemical methods, mostly rooted in Density Functional Theory (DFT), for hypothetical molecules. Ideally, one will discard all putative structures which result in disagreement with the experiments and will keep the only one in agreement, within the benchmarked accuracy of the level of theory used. This field is now well established and sophisticated tools for the comparison of calculated and experimental data, which go beyond the simple linear correlation, have been developed by the group of Sarotti [4].

In addition to the topological complexity of natural substances, there are two other sources of complexity that can strongly affect the interpretation of the NMR spectra. One is related to the presence of heavy atoms in a covalent molecule, which brings in relativistic effects in the electronic structure and in turn in the NMR. Even for a simple molecule, they turn the interpretation of the NMR spectrum into a very difficult task since empirical rules often do not allow a full elucidation of the structure. In these cases, relativistic versions of DFT need to be used. The other source of complication is the existence of strong non-covalent interactions of the NMR probe molecule with its environment. Here, the full dynamics of the solute and solvent system need to be considered and the structure which is responsible for the observed NMR is in fact the average bulk structure of the solute-solvent system. Molecular Dynamics (MD) simulations can be coupled with the DFT-NMR calculations in order to predict the NMR properties. In turn, the comparison between the calculated and experimental data can shed light on the Force Field (FF) parameters used in the MD simulation.

Therefore, computational NMR can be used to shed light on both covalent (topological and electronic complexity) as well as non-covalent (time-dependence complexity) structural problems, see Figure 1: in the first two cases the exploration of a discrete structural space will allow to select the correct structure of an unknown compound among several hypothesis; in the last one, it will enable the fine tuning of classical FF parameters over a continuum range of possibilities. Of course, it is also possible to encounter systems where such effects are mixed either in pairs - natural products with heavy elements, natural products in strongly interacting environments, simple molecules with heavy atoms in strongly interacting environments – or all three at once, multiplying then the efforts needed for a full rationalization.

In this presentation I will highlight the computational NMR protocols used to address the problems discussed above, using few examples and following a recently published Account [5]. The first example is concerned with

the determination of the structure - at the time unknown - of the natural product vannusal B, whose total synthesis defied several attempts by different groups [6]. Then I will show the application of relativistic DFT-NMR protocols to systems containing heavy metals, such as ^{1}H of iridium hydrides [7] and ^{205}Tl in thallium organometallic derivatives [8]. Finally, I will move to ionic liquids as an example of complex fluids where strong non-covalent interactions have a high impact on the NMR properties and a fine tuning of the FF is necessary in order to achieve a good agreement [9].

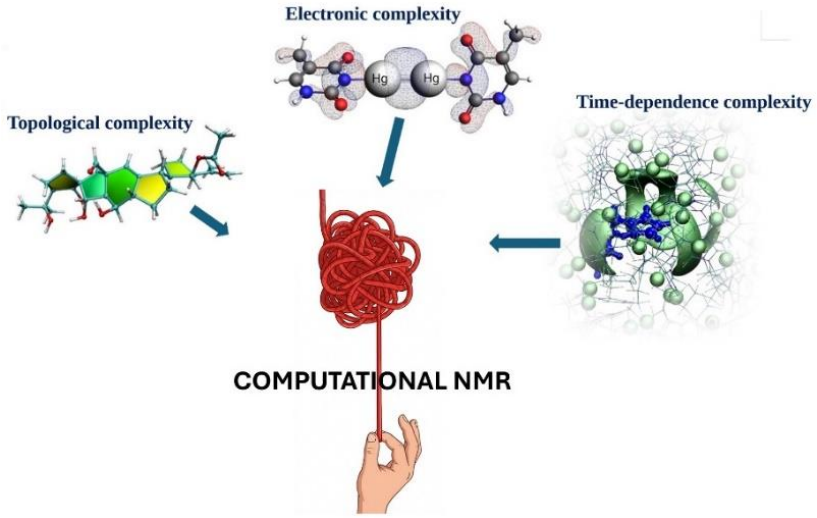

Figure 1 – Three sources of complexity may result in NMR spectra that cannot be easily interpreted: *i*) topological complexity of natural products; *ii*) relativistic effects with heavy elements; *iii*) time-dependence complexity in structured fluids. In such cases, computational NMR can help in the structural assignment.

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