

CALCULATING NMR SPECTRA

There are several reasons why NMR spectroscopy, in particular proton and ^{13}C NMR, is the most important analytical technique for characterizing organic molecules. The experiment is straightforward and can be carried out rapidly. It requires relatively small samples and is non destructive. The so-called proton-decoupled ^{13}C NMR is particularly simple, comprising a single line (resonance) for each and every unique carbon. Despite its simplicity (or perhaps because of it), associating an ^{13}C spectra to a particular molecular structure can be problematic and prone to error, in particular, where alternative structures might be very similar. 2D spectra, in particular, COSY and HMBC spectra that combine chemical shifts and HH and CH coupling constants are more and more commonly employed to assist in assignment.

A routine and reliable method to predict ^{13}C chemical shifts as a function of three-dimensional structure would clearly be of value in helping to assign experimental NMR spectra of complex molecules, at the very least, either providing supporting evidence or casting doubt on a proposed assignment. One might argue that such a method already exists in the form of extensive NMR spectral databases. An exact match to an existing spectrum provides a definitive structure, while one or more close matches to entries in a database suggest what types of structures are reasonable. Of course, entirely new compounds will never give exact matches, simply because the spectrum is not in the database. Closely related are empirical relationships based primarily on connectivity and obtained from fitting previously assigned (and presumed correctly assigned) spectra. While these can achieve some degree of success, the fact that NMR chemical shifts (and of course three-bond HH and CH coupling constants) are sensitive to conformation means that molecules that appear to be very similar may give rise to entirely different spectra. Closely related to this is the fact that most organic molecules are not rigid and described by a single 3D structure. Rather, they comprise a connection of different 3D structures (conformers) and the resulting spectrum is a weighted average of energy weighted spectra of the individual conformer.

One alternative to databases and purely empirical schemes would be to calculate chemical shifts *a priori* using quantum mechanics.* In so doing, differences in structure and conformation are directly taken into account. The underlying methodology has been available for several decades for both Hartree-Fock and density functional models. However, calculations have only rarely been used to actually assist in the interpretation of spectra, and few practicing chemists seem to be aware that quantum chemical calculations are now possible (and practical) for real molecules, and how well calculations perform in accounting for chemical shifts. Those who are aware, are confronted and all too often stymied, with what must seem to be an endless list of calculation methods. We believe that the full potential of quantum chemical calculations as assists to assigning NMR spectra will only be realized after a small number of alternatives or standard models are elaborated and their limits and reliability clearly defined. Stated differently, chemists need to approach quantum chemical calculations much in the same way that they now approach a spectrometer.

Underlying Theory

Application of an external magnetic field causes the nuclear spins to align either parallel or antiparallel to the field. The difference in energy (ΔE) between nuclear spin states is given by.

$$\Delta E = \gamma \hbar B_0$$

γ is the gyromagnetic ratio, a constant that depends on the magnetic moment of the nucleus, \hbar is Planck's constant/ 2π and B_0 is the strength of the magnetic field *at the nucleus*. What makes nuclear magnetic resonance (NMR) spectroscopy useful to chemists is that the magnetic field felt at the nucleus is different for each chemically distinct nucleus in a molecule. This is because the applied magnetic field is slightly weakened by electrons around the nucleus and the extent of this weakening depends on the detailed chemical environment. Nuclei that are well shielded by the electron cloud experience a lesser field than those that are poorly shielded and, as

* Neural nets offer another alternative, the downside being that their construction requires very large datasets. We are in the process of exploring this replacing experimental chemical shifts as reference data by values calculated from quantum chemical models.

a result, show a smaller energy splitting. The splitting, relative to a standard, is termed a *chemical shift*.

Two additional comments need to be made. First, not all nuclei possess non-zero magnetic moments and, therefore, give rise to an NMR signal. The magnetic moment for the proton is non-zero, although that of the dominant isotope of carbon (^{12}C) is not. Fortunately, the minor (1%) isotope ^{13}C possesses a finite magnetic moment. The fact that the dominant isotope of carbon has a zero magnetic moment is both a "curse" and a "blessing". A curse because it certainly slowed the application of carbon NMR to organic chemistry by several decades (waiting for magnet and spectrometer technology to catch up). A blessing because it results in a ^{13}C spectrum being much simpler (and easier to interpret) than a proton NMR spectrum.

The second comment is that proximate nuclei with finite magnetic moments will contribute to the magnetic field felt by the nuclei under investigation. Whereas nearby protons interact (couple) leading to splitting of the individual lines in the proton NMR spectrum, the very low probability (1% x 1%) that two ^{13}C nuclei will be adjacent all but eliminates carbon-carbon coupling. Proton- ^{13}C coupling does occur but can be (and nearly almost always is) removed. The result is that the ^{13}C NMR spectrum contains only one line per unique carbon.

From the perspective of the experiment, the fact that the difference in energy between nuclear spin states (and ultimately the ability of an NMR spectrometer to distinguish chemically-different nuclei) is directly proportional to the magnetic field strength is disheartening. Magnets used in NMR spectrometers are now approaching practical and perhaps theoretical limits, and a mere 10-20% increase in field strength (translating to an equivalent increase in resolution) can mean more than doubling the cost of the spectrometer. Without a major breakthrough in magnet technology, the prognosis for greatly improved resolution over what is now possible (practical) is bleak. On the other hand, computer performance continues to double every few years (anticipated by Moore's law), and NMR spectra calculations on larger and ever more complex molecules continue to become more routine.

Correcting ¹³C Chemical Shifts from B3LYP/6-31G*, ωB97X-D/6-31G* and ωB97X-V/6-31G* Density Functional Models

Spartan can calculate NMR chemical shifts using Hartree-Fock models as well as a range of density functional models. We have focused on and carefully examined three density functional models, specifically B3LYP, ωB97X-D and ωB97X-V models with the 6-31G* basis set. Used directly, all three models lead to rms errors in ¹³C chemical shifts on the order of 5-6 ppm (over a range from 0-250 ppm), and are not reduced by replacing 6-31G* by a larger more complete basis set. Errors of this magnitude are likely to be too large for reliably assigning the lines in an experimental ¹³C spectrum, for supporting a proposed structure assignment or perhaps most important for casting doubt on one.

Empirically Corrected ¹³C Chemical Shifts

Empirical schemes have been developed to dramatically reduce errors in ¹³C chemical shifts, specifically for B3LYP/6-31G*, ωB97X-D/6-31G* and ωB97X-V/6-31G* models. These utilize the same dataset for the linear regression comprising ~8000 sp³ carbons, ~6200 sp² carbons (including aromatic carbons) and ~450 sp carbons.* The functional form is as follows:

$$^{13}\text{C}_i = ^{13}\text{C}_i \cdot \text{Scale} + \sum_k [X^{(0)}_k + X^{(1)}_k(R_{i,k} - 1) + X^{(2)}_k(R_{i,k} - 1)^2]$$

¹³C_i is the corrected chemical shift and ¹³C is the uncorrected chemical shift and *Scale* is a scaling factor. Summation is carried out over all bonds (1 or 2 for sp carbons, 3 for sp² carbons and 4 for sp³ carbons). $X^{(0)}_k$, $X^{(1)}_k$ and $X^{(2)}_k$ are parameters that depend on the atom bonded to carbon (H, C, N, O, F, Si, P, S, Cl or Br) and $R_{i,k}$ are bond lengths to carbon. Different expressions apply to sp, sp² and sp³ carbons. The equation for sp carbon involves four $X^{(0)}$ parameters, four $X^{(1)}$ parameters and one $X^{(2)}$ parameter (11 parameters in total), that for sp² carbon involves all ten $X^{(0)}$ parameters, six $X^{(1)}$ parameters and four $X^{(2)}$ parameters (21 parameters in total), and that for sp³ carbon involves all ten $X^{(0)}$ parameters but no $X^{(1)}$ or $X^{(2)}$ parameters (11

* Care has been taken to select either rigid molecules or molecules where a single conformer dominates the equilibrium (Boltzmann) distribution.

parameters in total).*

Resulting rms errors are 2.4, 2.1 and 2.1 ppm for B3LYP, ω B97X-D, and ω B97X-V models, all significantly (factor of 2-3) smaller than the uncorrected shifts. In our view, these are close to experimental deviations in ^{13}C shifts commonly noted due to changes in solvent.

* Parameter files are available for review from: http://downloads.wavefun.com/NMR_Correction_Parameters.zip.