

The prediction of ^1H NMR chemical shifts in organic compounds

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Introduction and historical

Proton (^1H) nuclear magnetic resonance, NMR, spectroscopy began in 1951 with the historic experiment of Arnold, Dharmatti and Packard,¹ when they resolved the three types of hydrogen atoms in ethanol, and this illustrated the immense potential of ^1H NMR in structural organic chemistry. Since this discovery ^1H NMR has become one of the commonest and most powerful analytical tools of the research scientist and it is now even part of the high school syllabus. It is therefore, both from the educational and practical point of view, remarkable that there is still no theoretical calculation nor even a semi-empirical scheme capable of predicting ^1H chemical shifts of organic compounds to sufficient accuracy to be of use to the structural chemist. For several years our research group at Liverpool has been developing such a scheme, the CHARGE programme, which is now of sufficient accuracy and generality to be of predictive use to the research scientist.

^1H chemical shifts are usually measured on the δ scale, i.e. in ppm from internal TMS (SiMe_4) and the common range of ^1H chemical shifts in organic compounds is *ca* 0–10 δ . Modern NMR spectrometers routinely measure these shifts to *ca* 0.01 ppm, thus any calculation of ^1H chemical shifts to be practically useful would need to approach this accuracy. We have been attempting in the CHARGE scheme to predict ^1H chemical shifts to *ca* 0.1 ppm.

The influence of any substituent (X) on the chemical shift of any proton is termed the substituent chemical shift (SCS) and defined as

$$\text{SCS} = \delta(\text{RX}) - \delta(\text{RH})$$

It is convenient to divide the SCSs into a one-bond or α effect (i.e. $\text{H}-\text{X}$), a two-bond or β effect (i.e. $\text{H}-\text{C}-\text{X}$), a three-bond or γ effect (i.e. $\text{H}-\text{C}-\text{C}-\text{X}$) and long range effects (i.e. > three bonds removed). The one-bond or α effect is clearly of considerable theoretical value, but little practical importance, as the great majority of ^1H chemical shifts are of protons attached to carbon atoms. Protons attached to almost all other atoms (OH, NH, SH, F, Cl, Br, I etc.) often show chemical shift changes with solvent and/or concentration of several ppm due to hydrogen bonding interactions. In consequence these ^1H chemical shifts are seldom used for structural identification.

The two-bond or β SCS in methyl derivatives (MeX) was shown in early investigations² to be linearly related to the electronegativity of X. However, for multivalent atoms (e.g. carbon) the chemical shift of the methyl protons is also a function of the γ substituent, i.e. H.C.C.X. Originally, group electronegativity scales were proposed to take account of this γ effect. In the CHARGE scheme presented here the β and γ effects of substituents are considered separately and additive (see later).

The γ effects of substituents (H.C.C.X) are very different from the β effects. Early investigators^{2,3} found that ^1H chemical shifts are not simply due to the transmission of inductive effects along the carbon-carbon σ bonds. Both electric field and magnetic anisotropy effects were suggested to account for γ SCSs but no generally accepted quantitative explanation was given.

The effects of substituent groups on more distant protons in saturated compounds were investigated and explained as due to two separate contributions.⁴ These were:

- 1) The electric field produced by the substituent polarises the C–H bond of the proton considered, which affects the proton chemical shift ($\Delta\delta_{\text{El}}$).
- 2) Magnetically anisotropic substituents will give rise to magnetic fields at the proton considered, which do not average to zero over the molecular tumbling ($\Delta\delta_{\text{AN}}$).

The substituent SCS is given by the sum of these effects. The major limitation of this early work was that due to the NMR instrumentation available at that time, the only protons which could be measured in the spectra were the methyl groups of the compounds investigated (steroids and bornanes). These were not sufficient to precisely quantify the various terms above. Also this approach failed for the vicinal protons of a CH_2CHX fragment.

It was subsequently realised that the steric effect due to the proximity of the proton and the substituent was an important factor in ^1H chemical shifts. For aromatic molecules π effects and ring current contributions also need to be included. The chemical shift of any H atom in a molecule is then given by the sum of these SCS from all the substituents in the molecule.

Overview of the semi-empirical method

The central problem of any semi-empirical calculation of ^1H chemical shifts is how to combine the above theories of

substituent effects (which are only valid for distant substituents) with the effect of near substituents. This is achieved in CHARGE by calculating the one-bond, two-bond and three-bond effects of substituents on the partial atomic charges of the bonded atoms. The ^1H chemical shift is directly proportional to the partial atomic charge on the hydrogen atom. These calculations are monitored by the experimental values of the ^1H chemical shifts. Thus the CHARGE routine is a composite program made up of a neural network data based approach for the one-, two- and three-bond substituent effects plus a theoretical calculation of the long range effects of substituents in terms of the above interactions responsible for ^1H SCS. A brief summary of the latest version (CHARGE7)^{5,6} is as follows.

Short range effects

The CHARGE scheme calculates the effects of atoms on the partial atomic charge of the atom under consideration, based upon classical concepts of inductive and resonance contributions. If we consider an atom I in a four-atom fragment I–J–K–L the partial atomic charge on I is due to three effects. There is an α effect from atom J proportional to the difference in the electronegativity of atoms I and J. A β effect from atom K proportional to both the electronegativity of atom K and the polarisability of atom I. There is also a γ effect from atom L given by the product of the atomic polarisabilities of atoms I and L for I = H and L = halogen. However, for chain atoms (C, N, O, S etc.) the γ effect (i.e. C.C.C.H) is parameterised separately and is given by $A + B \cos\theta$ where θ is the C.C.C.H dihedral angle and A and B empirical parameters.

The total charge is given by summing these effects and the partial atomic charges (q) converted to shift values using Equation (1).

$$\delta_{\text{charge}} = 160.84 q - 6.68 \quad (1)$$

Long range effects

The effects of more distant atoms on the proton chemical shifts are due to steric (δ_{steric}), anisotropic (δ_{anis}) and electric field (δ_{el}) contributions. H..H steric interactions

were found to be shielding in alkanes and deshielding in aromatics, and X–H interactions deshielding according to a simple r^{-6} dependence⁷ (where r is the H–H or H–X distance).

The effects of the electric field of the substituents are calculated as proportional to the component of the electric field along the C–H bond.

The magnetic anisotropy contribution of a bond is obtained from the appropriate McConnell equation. This differs for bonds with cylindrical symmetry (e.g. $\text{C}\equiv\text{C}$) with one anisotropy contribution and non-symmetric groups such as the carbonyl group in which the parallel and perpendicular anisotropy for the bond must be considered.⁶ For aromatic compounds it is necessary to include the shifts due to the aromatic ring current (δ_{ringcur}) and the π electron densities (δ_{π}) in the aromatic ring.^{8–10} The equivalent dipole approximation is used to calculate the ring current shifts and the π electron densities are calculated from Huckel theory.^{9,10} The coulomb and resonance integrals for a carbon $2p_z$ atomic orbital and the factors modifying these integrals for orbitals other than sp^2 carbon are obtained so that the π densities calculated from the Huckel routine reproduce the π densities from *ab initio* calculations.

The effect on the proton chemical shifts of the excess π electron density at a neighbouring carbon atom is given by considering the π densities on both the α and β carbon atoms with respect to the proton.

The above contributions are added to Equation (1) to give the calculated shift of Equation (2).

$$\delta_{\text{total}} = \delta_{\text{charge}} + \delta_{\text{steric}} + \delta_{\text{anis}} + \delta_{\text{el}} + \delta_{\pi} + \delta_{\text{ringcur}} \quad (2)$$

Functional Groups parameterised in the CHARGE program can be put into the following four categories containing:

- 1) Groups which have been well parameterised with a number of compounds used.
- 2) Groups which have been parameterised by the use of only one or two compounds.
- 3) Unparameterised groups which can be run but have so far not been considered.

4) Atoms for which the programme would not run at the moment.

1) Alkanes, alkenes, alkynes, aromatics, heteroaromatics (including five- and six-membered rings), halocompounds*, ethers, aldehydes*, ketones*, amides*, esters*, nitriles*, nitro* compounds and sulphides. (*Compounds where parameterisation has been performed in aliphatic and aromatic systems.)

2) Alcohols, amines, three-membered rings, α,β -unsaturated ketones, haloolefines, sulphoxides and sulphones.

3) Three- and four-membered heterocyclic rings, azo compounds, silicon and phosphorus compounds and charged compounds (salts, amino acids).

4) Atoms which will fail in CHARGE include Li, Be, B, Na, Mg, Al, K, Ca etc.

Alternative approaches

An alternative method of calculating NMR chemical shifts is by the *ab initio* gauge-invariant atomic orbital (GIAO) method in which the nuclear shielding tensor is calculated. This method has been used successfully in the calculation of heavy atom chemical shifts.¹¹ Pualy *et al.*¹¹ in a discussion of the GIAO method note that since the chemical shift range of ^1H is the smallest of all atoms it will be very sensitive to variation in the methodology such as the geometry, basis set etc. Also, since the protons are located on the periphery of the molecule their chemical shifts will be more sensitive to intermolecular interactions (solvent effects etc.), which have so far not been included in these calculations. However, recently this method has been used to calculate ^1H chemical shifts in organic compounds. Lampert *et al.*¹² calculated the ^1H shifts of a range of aromatic aldehydes and phenols and Colombo *et al.*¹³ used these calculations to determine the configuration of the 3-hydroxy metabolites of a synthetic steroid tibolone. The major problem with these calculations is the basis set dependence. Colombo *et al.*¹³ used a variety of basis sets and methodology (6-31G* and 6-31G** with HF, B3LYP, B3PW91) in their calculations. These six different calculations give variations in the calculated ^1H shifts of 0.5–1.5 ppm, depending on the particular proton considered. Thus this method

cannot be used to calculate the ^1H shifts of an unknown compound as an uncertainty of 1.5 ppm is too large to be of much use. We use here a different approach in that only one density functional theory and basis set will be used for the geometry optimisation and GIAO calculations. The GIAO derived ^1H chemical shifts will then be compared with those from CHARGE.

Another method of predicting ^1H chemical shifts is the database approach, probably the most widely used approach in industry. Here we use the Advanced Chemistry Development (ACD) predictor¹⁴ as an example. There are few publications¹⁵ on ^1H NMR predictions by ACD. Brühl *et al.*¹⁶ found that for ^{13}C predictions of pyridines ACD gave good answers. Masunov¹⁷ in a review of ACD/I-Lab 4.5 (an internet service) noted that the average error of the data-based methods is usually smaller when applied to common compounds.

For less common compounds the predictions can be very poor. This is because if the atom site being analysed is in the database good comparisons will be obtained, but if the atom site being predicted is not found in the database poorer results would be expected. Other points of uncertainty present when analysing ^1H chemical shifts are solvent and concentration effects. If the data in the database is not obtained in the same solvent or concentration fewer accurate predictions may be produced. Masunov also noted that better results are obtained if the user interacts with the database and expands the data with their own range of compounds.

It is of general interest to compare the existing models for proton predictions. Here we will compare (see Comparing Predictors) the experimental chemical shifts of a set of phenols and halo compounds with predictions from CHARGE, the GIAO technique and from the ^1H NMR predictor of ACD.

Predicting molecular conformation

Both the semi-empirical and the *ab initio* approach rely on accurate molecular geometries to perform their calculations. For the *ab initio* calculations it is recom-

mended to use the B3LYP density functional theory (DFT) with at least the 6-31G(d) basis set for geometry optimisation prior to the GIAO NMR calculations. For CHARGE, however, we will show (see Optimised geometries) that although using the more sophisticated, and computationally more expensive, quantum chemical calculations yield better results, molecular mechanics (MM) force fields can be used with great success in determining input geometries for CHARGE.

For the determination of the parameters in a semi-empirical method, using experimental data, rigid molecules are needed where a single conformation can be assigned and modelled accurately. For this purpose using geometries optimised by quantum chemical calculations is ideal. Once the parameters have been determined an accurate molecular mechanics force field will be sufficient for prediction purposes. The greater difficulty, however, lies in predicting chemical shifts of a compound of unknown geometry or multiple inter converting geometries. This issue is not considered at all when using a database since the geometries are two-dimensional and based on chemical shifts stored in a database where the absolute three-dimensional geometry is not determined. Using the quantum chemical approach the already time consuming geometry and GIAO calculations become an even greater hurdle, since any conformation search would need to optimise a large number of geometries to find the relevant minimum energy conformations. It is here where we see the great potential in using a semi-empirical approach. Since geometries optimised using MM force fields can be used to accurately predict chemical shifts we can use one of the many methods developed for conformer generation using MM.¹⁸ These methods can be divided in two main groups, the deterministic searches where conformational space is systematically covered and the stochastic methods where a random element is used for the search. These methods are generally applied to large systems such as proteins,¹⁹ but provide us with an ideal tool for conformation generation and NMR prediction.

Predicting ^1H NMR spectra

We have now discussed all the tools needed to predict ^1H NMR spectra accurately. Here we will see how they are implemented into the NMRPredict software.²⁰ First, we will discuss how different approaches for optimising molecular geometry affect the chemical shift calculations of CHARGE. We will then compare the different methods mentioned above for ^1H NMR chemical shift prediction. An account of the calculations used for HH coupling constants, needed to predict spectra, will then be given. Finally, we will discuss the implementation of conformational searching as a step towards complete proton NMR prediction of organic molecules.

Optimised geometries

When parameterising the CHARGE program the initial geometries used are often calculated by *ab initio* methods. However, in order to use CHARGE as a practical predictor we need to use molecular mechanics force fields for geometry optimisations. It is then of interest to know how these force fields compare with the *ab initio* calculations. In a study⁶ of aromatic carbonyl compounds, benzosuberone was investigated for this purpose using CHARGE. Geometries optimised by various methods were used to examine their influence on the chemical shift calculations; these were then compared with experimental shift data.

Assuming that the dominant structure of this compound is that which is shown in Figure 1, we can see how different methods of obtaining geometries compare.

From the results, Table 1, we see that the largest discrepancy is for H-9. This is dependent on the dihedral angle formed between the carbonyl group and H-9 and also the distance to the carbonyl group. We see from this study that it indeed is preferable to use more sophisticated calculations to obtain high accuracy but also that an acceptable overall rms error of 0.1 ppm is achieved when MM force fields are used. This would suggest that when time permits one should use *ab initio* determined geometries, but also

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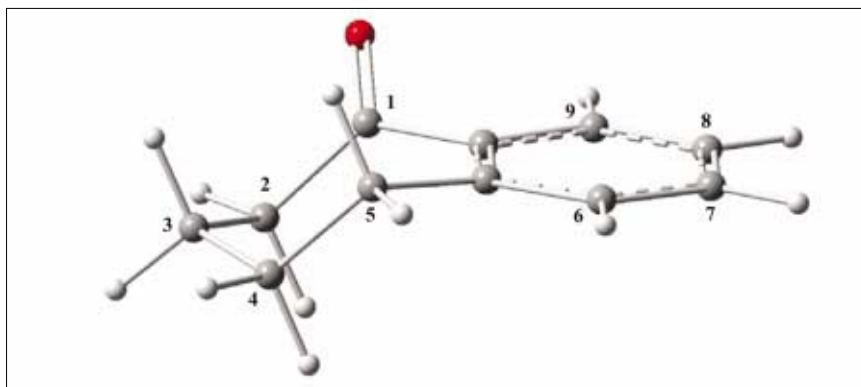


Figure 1. Minimised structure, and relevant numbering, of benzosuberone.

that MM is sufficient for routine predictions.

Comparing predictors

In a study²¹ of hydrogen bonding in phenols it was noted that for compounds with strong intra-molecular hydrogen bonds poor agreement was found when comparing the experimental ¹H chemical shifts of the hydroxyl hydrogen with those calculated by CHARGE. In order to determine the nature of this interaction a wide variety of phenolic compounds was investigated. It was found that the interactions causing the error were noticeable only for compounds forming a six-membered “ring” where the hydroxy group was hydrogen bonded with a strongly electronegative atom (typically oxygens in a nitro or carbonyl group). However, it was shown that for all other

weak hydrogen bonds, e.g. 2-chlorophenol, the existing models in CHARGE produced excellent agreement with the experimental data. The sensitivity of the OH chemical shift is a good probe to measure the accuracy of a chemical shift predictor, therefore the calculations by CHARGE were compared with calculations from other approaches to ¹H NMR shift calculations, these were the ACD predictor¹⁴ and the GIAO quantum chemical shielding calculations performed by the Gaussian software.²²

The dataset consisted of 94 ¹H chemical shifts measured in CDCl₃, and should provide a good overview of the accuracy of the different methods. The chemical shift of the hydroxyl protons of phenols in chloroform is typically around 4–6 ppm, and we see from the plot, Figure 2, that it is here that the other predictors are

having most difficulties. The scatter produced by the ACD predictor in this region may be due to the database data including measurements in dimethyl sulfoxide, DMSO, (where there is intermolecular hydrogen bonding present) and CDCl₃ and then averaged. Even though this is an extreme example it illustrates that solvent effects have a major impact on the chemical shift and generally need to be considered in some way. The GIAO calculations generally gave good predictions but were, however, less accurate when larger atoms were involved, such as bromine and iodine. Also here we could see poor results in the OH region, probably due to solvent effects and the sensitivity of the short range OH–X interactions. In the CHARGE calculations any solvent effect in CDCl₃ is intrinsic to the calculations and is therefore not a limiting factor. It is also worth mentioning that CHARGE produces the best correlation even when no OH chemical shifts are included.

In a separate study of the through space effects of the halogens in aliphatic and aromatic systems a similar comparison was undertaken. Here the chemical shifts of a set of 1-X-naphthalenes (X = F, Cl, Br, I) were measured and used to compare CHARGE with ACD and GIAO, Figure 3.

Even though the dataset is small, 28 protons, some observations can be made. We see a number of outliers in the ACD prediction, due to either solvent effects or insufficient database information. From the GIAO calculations we see again that there seems to be some difficulties when heavier atoms are involved. Specifically we note that for the peri proton, typically at around 8 ppm, the alternative approaches are very unreliable.

The prediction of ¹H NMR spectra

In order to predict the ¹H NMR spectrum of a molecule we need to know the HH couplings in the molecule as well as the ¹H chemical shifts. In order for this to be achieved routinely from the molecular geometry the CHARGE programme now includes a routine for calculating the HH couplings in a molecule. This includes the two-bond, three-bond and four-bond

Table 1. Observed chemical shifts (CDCl₃) of benzosuberone compared with those calculated by CHARGE using different input geometries.

Proton	Exp.	MMX	MMFF94	B3LYP (3-21G*)	B3LYP (6-31++G(d,p))
2	2.733	2.850	2.796	2.677	2.755
3	1.813	1.808	1.832	1.862	1.859
4	1.882	1.835	1.875	1.903	1.906
5	2.931	2.684	2.715	2.740	2.741
6	7.196	7.249	7.317	7.377	7.354
7	7.415	7.389	7.473	7.533	7.495
8	7.297	7.262	7.317	7.348	7.323
9	7.717	7.175	7.349	7.836	7.557
rms		0.134	0.109	0.098	0.088

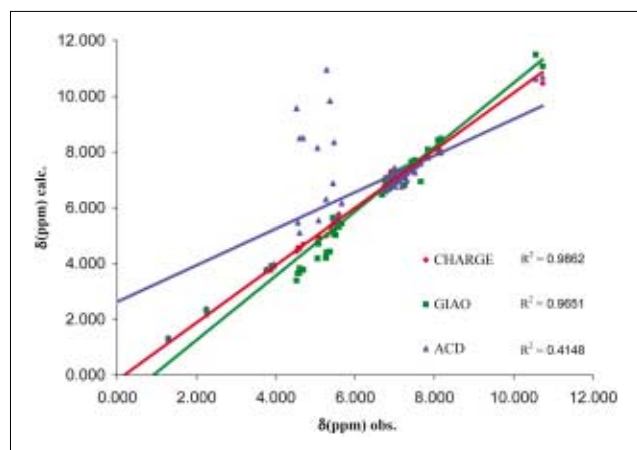


Figure 2. Correlation of observed and calculated chemical shifts of phenols using different methods.

couplings in all the common molecular fragments. The important vicinal (H.C.C.H) couplings in saturated fragments are given by a modified Karplus equation which was shown²³ to give better results for simple C-CH₂-CH₂-C fragments in five- and six-membered rings than the well known Haasnoot, de Leeuw and Altona equation. The orientation effect of electronegative substituents is also included in these calculations which have been tested in a variety of inositols and sugar molecules.²⁴ The comparable couplings in aromatics and olefinic groups are well known and simple to model.

To save computational time and space, the spectra in NMRPredict are calculated on a first order basis. In order to achieve the correct spectral pattern for magnetically equivalent groups on this basis the routine sets all couplings between magnetically equivalent groups equal to zero. Thus this gives, for example, the ¹H spectrum of benzene as one line, the correct result without recourse to complex second order spectral calculations. The success of this simple model is illustrated in the calculated spectra shown here.

Conformational averaging and the benzaldehyde problem

When searching conformational space it is often not of interest to generate chemically equivalent isomers. However, for chemical shift prediction purposes it is crucial to do so in order to average chemically equivalent protons. An obvious

example is a compound such as benzaldehyde. Even though most chemists would consider it to have one conformation, it actually is interconverting between two rotational isomers.

In Figure 4 we see how the calculated spectrum of benzaldehyde shows two doublets, one for each of the *ortho* protons. This spectrum is very misleading since the actual spectrum is an average of the two conformers, Figure 5. This is achieved by averaging the spectrum of the two conformers based on their energies, using their relative Boltzman populations.

Application

The CHARGE model is now parameterised to run a range of functionalities and by using modern modelling techniques it can be used as a powerful tool for the chemist in proton NMR prediction. In Figure 6 we see how extensive NMR

data can be accessed swiftly (in seconds) for a complex molecule such as benzochromenone combining all the tools described here.

The NMRPredict²⁰ software uses conformer generators based on molecular mechanics force fields and displays 3D structures of all low energy conformers generated and the corresponding calculated NMR spectrum, as calculated by CHARGE, together with the averaged spectrum, based on the relative energies.

Used in this way, shown in Figure 6, the program is ideal for chemical shift assignment, however, the information available can also be used for structural elucidation of both flexible and rigid structures.

Conclusions

The proton chemical shift calculations produced by the CHARGE program has now reached a point where it can be a

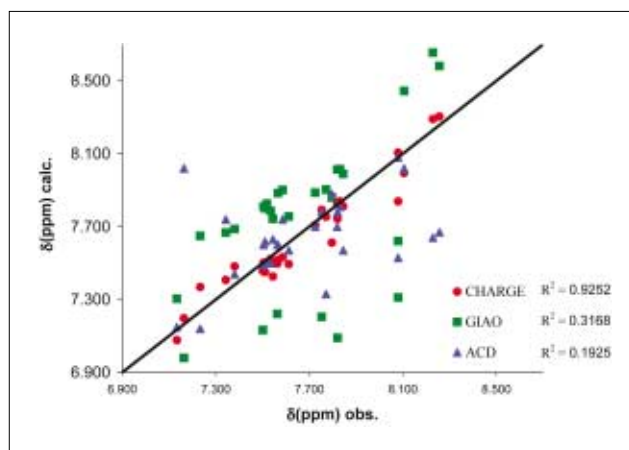


Figure 3. Correlation of observed and calculated chemical shifts of 1-halonaphthalenes using different methods.

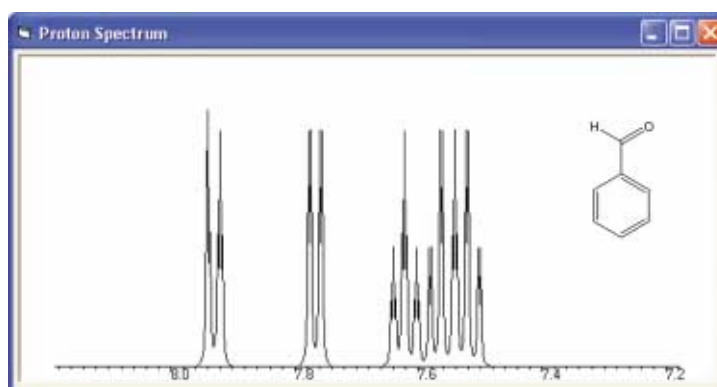


Figure 4. The calculated spectrum of benzaldehyde without conformational averaging.

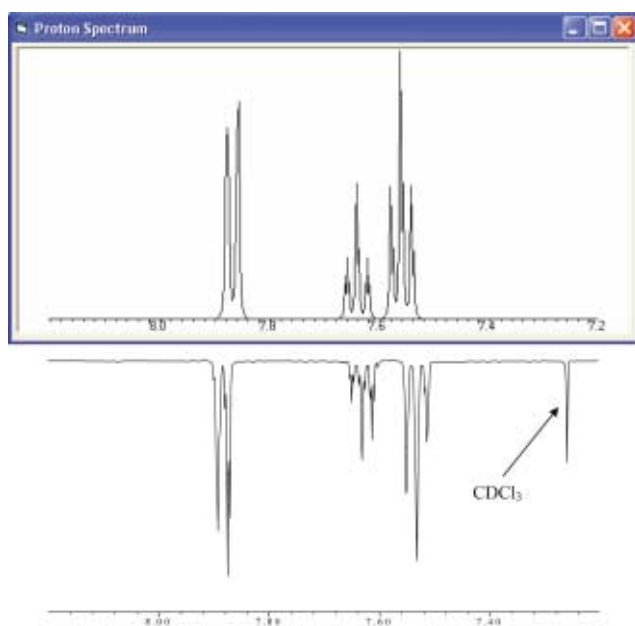


Figure 5. Calculated (top) and observed (bottom, inverted) 400 MHz spectrum of benzaldehyde with conformational averaging.

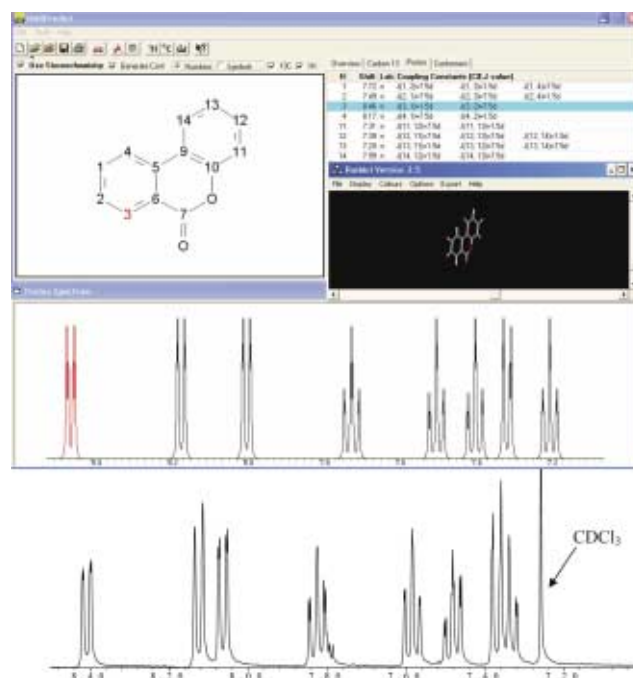


Figure 6. NMRPredict²⁰ output compared with actual spectrum (lower) of benzochromenone.

valuable aid to the chemist. At the same time we have also seen that molecular mechanical calculations of geometry as well as for conformer generation are now accurate enough to be of practical use. The combination of these semi-empirical methods provides a rapid and accurate solution for proton prediction.

The development of the NMRPredict²⁰ software (trial version available from Modgraph at www.modgraph.co.uk), which incorporates the methods mentioned, is now an invaluable tool for any chemist. The information retrieved is primarily to be used for proton prediction but the sensitivity and accuracy of the model means it can be applied to other problems. For instance, since multiple conformations are generated and one can observe the calculated spectrum for each conformer, it can be used to aid in structural elucidation. There are surely many other applications of this versatile tool, which will become apparent in the hands of the chemist.

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