CASE STUDY

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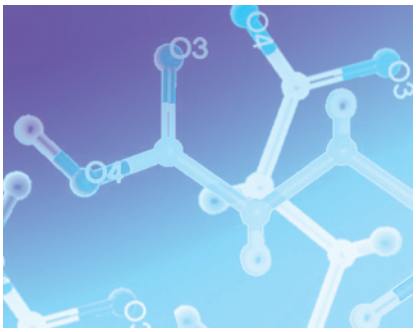
DENSITY FUNCTIONAL THEORY INVESTIGATIONS OF ^{17}O MAGNETIC RESONANCE IN GLUTAMIC ACID POLYMORPHS



Use of the advanced quantum mechanical software, NMR CASTEP, allowed predictive calculations of NMR shifts for specific oxygen atoms in a solid state structure.

Key Product

- NMR CASTEP

Industry Sectors

- Chemicals
- Drug Discovery

Organizations

- Cavendish Laboratory, Cambridge
- University of Warwick
- Université Pierre et Marie Curie

Scientists at the Cavendish Laboratory, the University of Warwick and the Université Pierre et Marie Curie have used NMR CASTEP to assign the ^{17}O NMR (Nuclear Magnetic Resonance) spectra for L-glutamic acid·HCl. By performing DFT (Density Functional Theory) calculations on periodic crystals, they were able to predict NMR shifts for several polymorphs of glutamic acid. The simulations provided an unambiguous assignment of the ^{17}O chemical shifts as well as confirming the general trend that increased hydrogen bond strengths results in increasing shielding of the carbonyl oxygens. This rule of thumb, however, is not sufficient to assign resonance peaks: a full quantum mechanical calculation with NMR CASTEP is required to make definitive assignments.

INTRODUCTION

Oxygen is an important element in determining the structure of organic and biological molecules, since it is often intimately involved in hydrogen bonding. Solid-state ^{17}O NMR provides a uniquely valuable probe as the chemical shift range of ^{17}O covers almost 1000 ppm in organic molecules.[1,2] In addition, ^{17}O has a net quadrupole moment, hence the solid state NMR spectrum is strongly affected by the electric field gradient (EFG) at the nucleus, another quantity which is known to be sensitive to molecular geometry.

Despite the low isotopic abundance of ^{17}O and the challenge of measuring chemical shifts in solid state materials, Lemaitre *et al.*[3] have recently reported ^{17}O Magic-Angle Spinning (MAS) NMR spectra for L- and D-glutamic acid·HCl.While it was possible to resolve peaks from each atomic site, it was not possible to provide an unambiguous assignment of the shifts to specific atoms. Such an assignment is necessary in order to understand the detailed molecular bonding arrangement in these crystals and to explain the changes that occur upon hydrogen bonding.

Reporting in the Journal of Physical Chemistry A[4] , a recent paper describes how researchers used DFT and the gauge-including projector-augmented wave (GIPAW) method[5] to calculate the ^{17}O chemical shifts and EFG parameters for four polymorphs of glutamic acid. Using these results, it was possible to assign the chemical shifts with certainty and so demonstrate how hydrogen bonding affects the shielding parameters.

Use of the advanced quantum mechanical software, NMR CASTEP, allowed predictive calculations to assign the shifts to specific oxygen atoms. The assignments were later confirmed by experiment.

CALCULATIONS

The calculations were carried out using the GIPAW method[5]. The DFT calculations used norm-conserving pseudopotentials[6]; the exchange-correlation functional of Perdew, Burke and Ernzerhof (PBE)[7]; and a plane wave energy cutoff of 80 Ry (1088 eV) was used.

The chemical shielding tensor, σ, is the ratio between an external magnetic field, B_{ex}, and the induced magnetic field at a nucleus, B_{in}:

$$B_{in} = - \sigma B_{ext}$$

The isotropic shielding, σ_{iso}, is defined as the trace of σ: $\sigma_{iso} = (\sigma_{xx}+\sigma_{yy}+\sigma_{zz})/3$, and may be computed using NMR CASTEP. Experiments, however, generally measure a chemical shift δ_{iso} relative to some reference value σref: $\delta_{iso} = \sigma_{ref} - \sigma_{iso}$. For ^{17}O, the reference is liquid water. Rather than compute σ_{ref} explicitly, it is inferred as described below.

Besides the chemical shifts, the researchers also computed the electric field gradient (EFG) tensor. From the diagonalized EFG it is possible to extract two experimentally determined parameters:

- the quadrupolar coupling constant, $C_Q = eV_{zz}/h$ and
- the asymmetry parameter, $\eta_Q = (V_{xx} - V_{yy}) / V_{zz}$

where *h* is Plank's constant and V_{ii} are the components of the diagonalized EFG.

RESULTS

The glutamic acid molecule contains 2 hydroxyl and 2 carbonyl oxygen atoms. The experimental results for L-glutamic acid•HCl easily distinguish the hydroxyl oxygens from the carbonyls. Within each pair, however, there is no clear evidence to distinguish O1 from O4, or O2 from O3. (See Fig. 1). The computed results, however, provide an unambiguous assignment.

Rather than compute σ_{ref} for water, it is obtained by reference to experiment: a least-squares fit of computed σ_{iso} vs. observed chemical shifts provides the optimum value of σ_{ref}: 255.0 ppm. Using this value, it is possible to compare computed and observed shifts, summarized in Table 1.

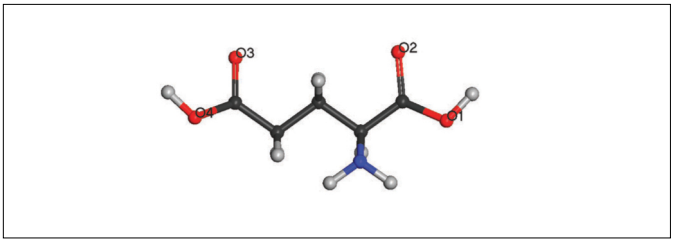


Figure 1. *Glutamic acid molecule illustrating naming convention for O-atoms*

Furthermore, this same reference value may be used to compute δ_{iso} for all the polymorphs of glutamic acid. The assignment in Table 1 has been further supported by recent experimental evidence[8].

Species	Calculated δ	Observed δ
O1	177.6	172.5
O2	316.9	322
O3	311.0	315
O4	198.0	187

Table 1. *Calculated vs. observed chemical shifts for L--glutamic acido•HCl (from reference 4)*

Yates and coworkers[4] next looked for a correlation between the degree of hydrogen bonding and the ^{17}O chemical shifts. Quantifying the strength of a hydrogen bond is rather difficult, but a related parameter is the length of the carbonyl bond itself, which will vary depending upon the strength of the hydrogen bonds.

Figure 2 shows effect of the C=O bond length on the calculated σ_{iso}. This confirms a general trend: increased hydrogen bond strength results in increased shielding of the carbonyl oxygen. Similar trends can be observed for C_Q and η_Q[4]. Although a linear regression provides a good fit, note that an empirical rule based on this line would not be accurate enough to assign resonances reliably. In order to achieve that level of certainty a full quantum mechanical calculation is required using NMR CASTEP.

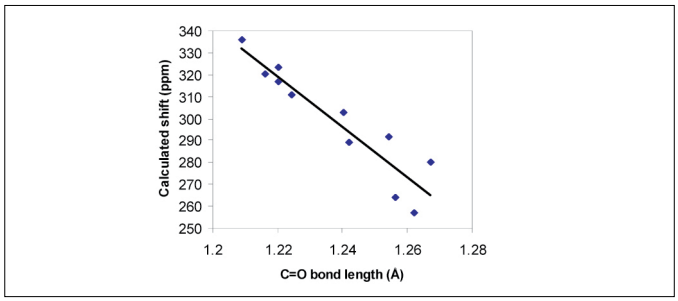


Figure 2. *Calculated ^{17}O isotropic chemical shift vs. C=O bond length*

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