Understanding Temperature Dependent Hydrogen Bonding in Solids from NMR Chemical Shifts: Experimental and Periodic DFT Approaches

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Isak Rajjak Shaikh

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Understanding Temperature Dependent Hydrogen Bonding in Solids from NMR Chemical Shifts: Experimental and Periodic DFT Approaches

A Thesis

submitted to the committee composed of representatives from

Ecole normale supérieure de Lyon, France (Co-ordinating Institution),

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University of Rome "La Sapienza", Italy

in close association with CECAM (European Center for Atomic and Molecular Simulation)

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- From University of Amsterdam: *Master of Science in Chemistry*

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July 2008

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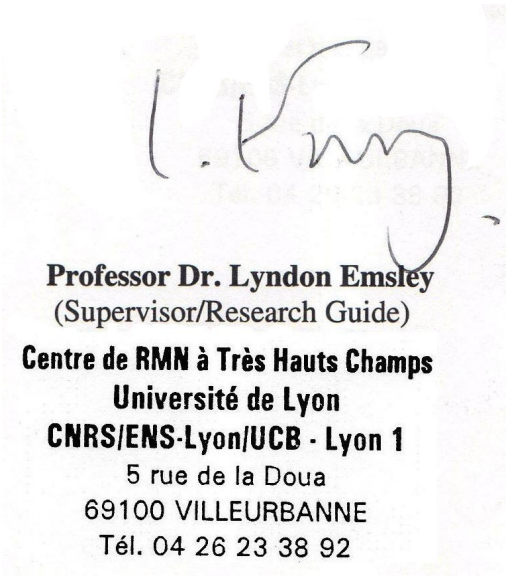
C E R T I F I C A T E

Certified that the research work incorporated in this master thesis entitled, "***Understanding Temperature Dependent Hydrogen Bonding in Solids from NMR Chemical Shifts: Experimental and Periodic DFT Approaches***" submitted by Mr. Isak Shaikh was carried out under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.



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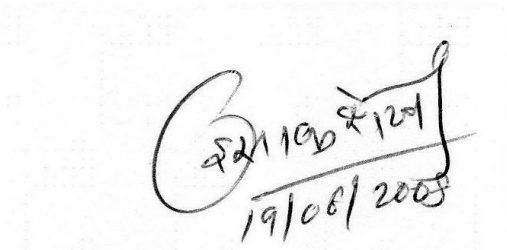
Declaration

The results presented in this thesis are based on my own research in the *Centre Européen de RMN à Très Hauts Champs de Lyon* and *Ecole Normale Superieure de Lyon*, France. All assistance received from other individuals and organizations has been acknowledged and full reference is made to all published and unpublished sources used. This thesis has not been submitted previously for a degree at any Institution. I defended this thesis on July 10, 2008 in the presence of an International jury at CECAM / ENS Lyon, France.



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PREFACE

The development of structural characterization methods for crystals is an area of immense research interest in chemistry. The establishment of links between structural information and Nuclear Magnetic Resonance (NMR) spectroscopy observables such as Chemical Shift (CS) is an important issue which has always concerned the solid-state NMR community. The NMR CS depends on molecular structure and also on other factors that affect those structural features. These important studies on structures answer the basic questions regarding bonding within the molecular crystal, and can explain the inter- and intra-molecular interactions that provide insight into the chemistry and properties (conformation, strength and directionality) of the crystalline component.

The proton is potentially an attractive nucleus for probing the molecular structures. It is pertinent considering hydrogen bond and methyl group dynamics, and any other examples one may have come across. One such example is the rationalization and understanding of hydrogen bonding patterns and motifs involved in some molecular organic crystals.

Although the ^{1}H nucleus has a very high natural abundance and intrinsic sensitivity, its utility in the solid state is limited by the strong homogeneous dipolar couplings which lead to spectral braodening whenever networks of protons are present. Consequently, special technique such as fast Magic-Angle Spinning (MAS) must be applied to obtain high resolution spectra. Increased resolution is also obtained by incorporating homo- and heteronuclear dipolar pulse sequences. I present you studies on temperature dependence of the ^{1}H

chemical shifts in molecular organic crystals using combination of solid-state NMR spectroscopy and CASTEP – a Density Functional Theory (DFT) code.

A series of CASTEP calculations of the X-ray (and or neutron diffraction) crystal structures were performed for some small organic bioactive molecules. The computations are carried out for essentially static atomic positions and therefore do not take account of intrinsic vibrations and molecular-level mobilities, if any. In this methodology, the experimental NMR chemical shifts were obtained at various temperatures and these values were further extrapolated to 0 K. The CASTEP, a first principles method, was used to compute the ^{1}H chemical shifts at 0 K from the static structure. The proton NMR chemical shift of the hydrogen-bonded proton tends to decrease with increase in temperature. This change is more noticeable than that for the other hydrogens. These studies are aimed at explaining the factor responsible for the discrepancy between the experimental and calculated ^{1}H chemical shifts. I observe that it is not the local electronic environment of a crystal that changes with temperature; but it is crystal structure or unit cell paramters and molecular dynamics that are sensitive to temperature which induce electronic changes in the crystal and (that) make the chemical shift temperature dependent. This approach also tries to validate crystal structures obtained from the diffraction studies. The difference between the experimental and computed ^{1}H CS is attributed to thermal motions in the H-bonds. I hope that the readers will be able to make sense of this research upon careful reading of this dissertation.

Lyon, France

June 2008 **ISAK RAJJAK SHAIKH**

"I give many thanks to Dr. Ms. Robin Stein

for her wonderful teaching….."

Dedicated To My Parents

and

the Memory of Mr. Nanhesaheb (who brought my Father up)

"I, for one, thoroughly believe that scientists are still very human and so they err and or, of course, have their own limitations; but the future ain't what it used to be. Mankind discovers intriguing findings that lead them to conclude that the human brain is apparently still evolving and a new day will come when researchers will "turn inward" to contemplate the discoveries and the people, I correct, good human beings will be able to free their inner selves and open themselves up to the higher powers of the universe. Meanwhile, our environment and the skills we need to survive in it are changing…. I'd expect the mankind try to develop their mind emanations and psychological power rather than materialistic means and anything will seem possible in the climate of a greater unity of mind, soul, body, and emotions. This, I believe, will discern metaphysical connections between the universe and spirituality."

Acknowledgement

Although it should be relatively simple, this part is an important part of my thesis. All the work presented here would not have been possible without the help, collaboration and encouragement of many people to whom I am very grateful.

This work was made possible in the available time (five months) at the Centre Européen de Résonance Magnétique Nucléaire (CRMN) à Très Hauts Champs and Ecole normale superieure (ENS) de Lyon, France under the eminent supervision of **Professor Lyndon Emsley**. My heart felt thanks go to my supervisor for giving me the opportunity to perform Master degree thesis under his guidance. During my work, I enjoyed the untiring discussion with him and **Dr. Ms. Robin Stein**. Much helpful advice and the moral support from them lead to the success of my dissertation work within stipulated time.

I thank Ms. **Elodie Salager** very much for helping me with the interpretation of ^{1}H NMR spectra of small organic molecules of biological /medical importance and for all the cooperation rendered during my stay in the CRMN Laboratory. I do also thank her for translating/writing the abstract in French. I would like to thank Dr. Anne Lesage for providing me with the useful temperature calibration data measurements for the NMR experiments.

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Finally, and importantly, I want to thank my family: My parents, grandparents, younger sisters, and brothers. I am deeply appreciative of their patience and buoyancy. Words are too poor to express all love for and gratitude to my parents!

Table of Contents

Abstract

This thesis presents an account of ^{1}H NMR experiments and chemical shift (CS) calculations for some small bioactive organic molecules using Solid-state Nuclear Magnetic Resonance (SS NMR) spectroscopy experiments and CASTEP a periodic Density-Functional Theory (DFT) code. The research project was initially motivated by the finding that while CASTEP generally reproduces ^{1}H chemical shifts well, it explains hydrogen bonding poorly. The discrepancy is here explained as a measure of temperature dependence of chemical shifts, since agreement is improved when calculation effectively performed at 0 K, are compared with experimental results extrapolated to 0 K. Variable temperature studies are a tool to study the nature and behavior of hydrogen bonding, and so could be useful to study the crystal lattice i.e. to understand the link between the molecule and the crystal from the intermolecular spaces and the interactions therein. The calculations may also be used to assign organic molecules at natural abundance to crystal structures.

Here we examine the effect of temperature on proton chemical shifts in ibuprofen, flurbiprofen, indomethacin, paracetamol and salicylic acid and show that often hydrogen-bonded ^{1}H- chemical shifts are the most strongly affected by temperature. This is explained in terms of known relations between chemical shifts and hydrogen bond strength. We also note that the application of computational approach leads to an estimate of an elongated O-H…O (through space) bond distance and a reduced O…H…O bond angle compared without using X-ray diffraction. The geometry obtained using CASTEP provides ^{1}H positions whose chemical shifts are in better agreement

with experiment than the chemical shifts of protons in positions determined by X-ray diffraction studies.

The CASTEP calculated proton chemical shifts are found to be in substantial agreement with the experimentally measured chemical shifts. Due to the effect of temperature, when the hydrogen will not necessarily be on the O-O line, a little bond angle variance is observed because crystal lattice vibrations place protons in new positions.

The difference between the theoretical and observed chemical shifts for hydrogen bonding protons is attributed to thermal motions of protons in the hydrogen bonds. The results also show that the experimental CS can be extrapolated to 0 K in order to compare them to the calculated CS at 0 K.

The underlying goal of this project is achieved by CASTEP calculations to show that the temperature dependence of hydrogen bonding is an important factor that explains the evolution of proton chemical shifts.

Abstract (in French)

Ce rapport présente une étude combinant des expériences de RMN du solide et des calculs de déplacements chimiques par DFT périodique (CASTEP) pour de petites molécules organiques biologiquement actives. Cette étude a été motivée par la volonté de comprendre pourquoi CASTEP, qui reproduit habituellement assez bien les déplacements chimiques du proton, prédit mal les protons impliqués dans des liaisons hydrogène. Cet effet est ici expliqué par une dépendance des déplacements chimiques avec la température, puisque l'accord est meilleur lorsque les calculs, effectués à 0 K, sont comparés avec les résultats expérimentaux extrapolés à 0 K. Les études en température variable sont utiles pour étudier la nature et le comportement des liaisons hydrogène. Ces liaisons sont donc importantes pour étudier le réseau cristallin car les interactions intermoléculaires sont le lien entre la molécule et le cristal. Les calculs pourraient aussi être utilisés pour attribuer une structure cristalline aux molécules organiques en abondance naturelle.

Nous examinons ici l'effet de la température sur les déplacements chimiques proton des poudres d'ibuprofen, indomethacin, paracetamol et acide salicylique, et nous montrons que les protons les plus affectés par la température sont ceux impliqués dans des liaisons hydrogène. Cela est expliqué grâce aux relations connues entre déplacement chimique et force de la liaison hydrogène. Notons également que ces calculs donnent une valeur plus élevée de la longueur de la liaison O-H....O (à travers l'espace) et un angle O....H....O plus petit que dans la structure obtenue par diffraction des rayons X. Les déplacements chimiques calculés sur la structure optimisée par CASTEP

sont en meilleur accord avec ceux calculés sur la structure déterminée par diffraction des rayons X. Ceci est dû à un repositionnement des protons lors de l'optimisation de géométrie.

Les déplacements chimiques proton calculés par CASTEP sont en très bon accord avec ceux mesurés expérimentalement. À cause de la température, le proton n'est pas nécessairement situé sur la ligne O-O et une légère variation de l'angle de liaison est observé, car les vibrations du réseau cristallin placent les protons dans de nouvelles positions.
La différence entre les déplacements chimiques calculés et observés pour les protons impliqués dans des liaisons hydrogène est attribuée à une dynamique du proton dans la liaison hydrogène. Les résultats montrent aussi que les déplacements chimiques expérimentaux peuvent être extrapolés à 0 K pour être comparés à ceux calculés à 0 K.

Le but de ce projet a été réalisé grâce à des calculs CASTEP : montrer que l'évolution des déplacements chimiques de certains protons avec la température peut être relié à des changements dans les caractéristiques de la liaison hydrogène.

(Translated from English to French by Ms. **Elodie Salager**)

Chapter 1

Introduction

This chapter provides the motivation and objective for the research presented in this thesis.

1.1 Hydrogen bonding – a structure and function determining phenomenon

Ever since the hydrogen bond (H-bond) was conceptualized by Latimer and Rodebush in 1920,[1] the H-bond fascinated researchers in the fields of physics, chemistry, biology and materials sciences. Linus Pauling[2] explained the term **hydrogen bond** as: *"Under certain conditions an atom of hydrogen is attracted by rather strong forces to two atoms, instead of only one, so that it may be considered as acting as a bond between them. This is called the 'hydrogen bond'."* *Pimentel and McLellan*[3] gave a very practical definition of the hydrogen bond: *A hydrogen bond is said to exist when (i) there is evidence of a bond; and (ii) there is evidence that this bond specifically involves a hydrogen atom already bonded to another atom.*

It was quite recently though when hydrogen bond was proven to originate from electrostatic interactions, (and was not due to electron sharing or covalent nature). Buckingham and Fowler had predicted the H bond geometry fairly accurately.[4] However, in 1949 Pauling[2] had empirically calculated that H-bond would have 5% covalent character in an O—H-----O bond. It took 50 years for experimentalists to verify Pauling's empirical estimate. The spin–spin

coupling between the two other nuclei involved in the H-bond was found using an NMR technique which gave convincing evidence that Pauling was right! [5]

The chemistry of hydrogen bonding

Hydrogen bonds are weaker than ionic or covalent bonds, but stronger than van der Waals interactions. Although they can be broken by *thermal fluctuations*, they govern the structure of a variety of systems. Many macromolecules, like DNA, proteins or cellulose, for instance, would not have stable conformations in the absence of this kind of interaction. Besides the conformation, they influence the dynamics of certain biological processes, for example, by assisting enzymes to bind to substrates. Life would not be possible without them. Therefore, scientists have been trying for decades to unravel the reasons behind specific behavior of hydrogen bonded systems.

Hydrogen-bonded molecules possess properties that differ from those of systems containing no such interactions. These properties arise as a consequence of electrostatic interactions of a hydrogen atom H, which is covalently bound to an electronegative atom X (the proton donor), and another electronegative atom Y (the proton acceptor). In the early investigations strong hydrogen bonds were mainly studied, with the donor and the acceptor being highly electronegative atoms, like fluorine, oxygen, or nitrogen. A few decades later, the definition was broadened, allowing less electronegative atoms, like carbon, silicon, phosphorus, to be considered as involved in hydrogen bonding. On the other hand, only hydrogen (and its isotopes) can play the role of such a bridge between two atoms or two atomic

groups. This is a consequence of hydrogen having only one electron pair that can be attracted by the donor X, leaving the hydrogen nucleus to a great extent free to interact with the electron cloud (lone pairs or electrons) belonging to the acceptor Y. Such strong deshielding of the nucleus has not been observed for any other element.

Various criteria have been used to classify an interaction as an H-bond. These criteria are geometrical, energetic, spectroscopic, or functional. These definitions concentrate on the borderline between a H-bond and a van der Waal's interaction.[6] However, H-bonds are most commonly classified[2,3,6] with respect to their energy: one distinguishes strong (15 - 40 kcal/mol), moderate (4 – 15 kcal/mol) and weak (1 - 4 kcal/mol) hydrogen bonds. **Strong** hydrogen bonds are also referred to as *low-barrier hydrogen bonds*. Strong hydrogen bonds are characterized by a short distance between the proton donor and the proton acceptor. Also, the donor/acceptor might have ionic character. If the donor is positively charged, it possesses deficiency in electron density, thereby attracting the hydrogen's electron, which leads to the deshielding of the proton. If the acceptor is negatively charged, that enhances Coulomb attraction with the proton. Usually, the proton is considered as located close to the midpoint between the donor and the acceptor, and in such case it is for sure that the hydrogen motion is restricted to a small volume. Although the hydrogen is in this case relatively rigid, it could be responsible, for instance, for the catalytic activity of certain enzymes. **Moderate** H-bonds are the most common kind of hydrogen bonds. The donor and the acceptor atom are neutral species with the donor being more electronegative than the hydrogen,

and the acceptor possessing lone electron pairs, that can interact with the proton. The transfer of the hydrogen atom is allowed from the donor to the acceptor atom and vice versa. This flexibility of the bond enables molecules to take part in various chemical reactions, as well as processes in biological systems. Medium-strong hydrogen bonds have been observed in all three phases. In solution, if the solvent is polar, additional hydrogen bonds can be formed between the solvent and the solute molecules. Also in crystals hydrogen bonds are recognized between neighboring molecules. **Weak** hydrogen bonds are characteristic of complexes in the gas phase, but have also been observed in crystal structures. The donor atom has a slightly higher electronegativity than the hydrogen atom, like C or Si, and the acceptor possesses electrons.

Hydrogen bonds play a fundamental role in structural chemistry. Hydrogen bonds are of great importance in stabilizing biomolecular structures. Moreover, in supramolecular chemistry, self-assembly is frequently driven by the formation of intermolecular hydrogen bonds.[7] Hydrogen bonding may provide us with unique structural and mechanistic consequences in chemistry and biology.[8]

Importance of hydrogen bonding in crystal structure

Hydrogen bonding is ubiquitous and almost universally present in organic molecular crystals.[9] Crystal structure is connectivity of the atoms in a compound and the molecular packing. From the exact connectivity of the atoms, the bond distances and angles between these atoms are known and

thus the solid state compound is completely defined. Crystal structure answers basic questions regarding bonding within the molecule, which can explain the chemistry and properties providing inter- and intra-molecular interactions which may provide insight into the chemistry and properties (conformation, strength and directionality) of the compound. Hydrogen bonding is also very important in the crystallization process. Hydrogen bonding is supposed to provide energy to the lattice and generally better packing (but not always). Such work is therefore centered on rationalizing and predicting hydrogen bonding patterns and motifs involved in the crystal structures.[10]

1.2 Study of hydrogen bonding by nuclear magnetic resonance (NMR)

We know that X-ray and neutron diffraction studies are far from accurate in placing the light atoms. NMR, by comparison, is very well placed to study hydrogen bonding because the ^{1}H nucleus has a very high natural abundance and intrinsic sensitivity. In solution state NMR of bio-macromolecules, it has recently been shown that *J* couplings (between two nuclear spins due to the influence of bonding electrons on the magnetic field running between the two nuclei) can be observed across hydrogen bonds.[11,12] Lyndon Emsley et al. demonstrated, for the first time, a direct evidence for the existence of a hydrogen bond in the solid state, by detecting a hydrogen bond mediated *J* coupling observed in a molecular crystal.[13] Other solid-state NMR techniques had already been used in the investigation of hydrogen bonding; for example, the ^{1}H chemical shift and the 2H quadrupolar coupling constant are sensitive indicators of hydrogen bonding strength,[14] while the measurement of dipolar couplings allows the quantitative determination of H-bond distances.[15-18]

Experimental chemical shifts can be related to structure and strength of H-bond in a crystal.

1.3 ^{1}H chemical shift as NMR observable for hydrogen bonds

Protons are difficult to study in solids, and this is one of the major challenges facing solid-state nuclear magnetic resonance (NMR) research. Although the ^{1}H nucleus has a very high natural abundance and intrinsic sensitivity, its utility in the solid state is limited by the strong homogeneous dipolar couplings which lead to spectral broadening whenever networks of protons are present. Consequently, special technique such as fast magic angle spinning (MAS) must be applied to obtain high resolution spectra. This is generally the case in organic molecular crystals and in many inorganic compounds. It is known that homonuclear couplings can in principle be removed by homonuclear dipolar decoupling.[19] and high-resolution spectra can be obtained in combination with sample rotation at the magic angle in CRAMPS approach.[20, 21] However, most information based on ^{1}H as a probe in solid-state NMR so far comes from simple very fast MAS experiments, [22] and so fast MAS is the technique applied here in this research project.

Proton chemical shifts have been much less used in computational approaches than ^{13}C.[23-30] Firstly, because they have only very recently become available from experiments and secondly, since the range of chemical shifts is smaller (in ppm), the calculation methods need to be relatively more accurate to provide useful information. Indeed, most previous studies of proton chemical shifts have made used of highly shifted protons that were identifiable at the edges of

relatively low resolution fast magic angle spinning (MAS) spectra, often involved in specific hydrogen bonding configurations.[22]

The isotropic chemical shift is directly observable, and can be obtained from the spectrum as the difference between the resonance position and a reference chemical shift. H-bond formation usually results in chemical shift changes for all the nuclei involved in the H-bond, because of a redistribution of the electron density upon H-bond formation. For H-bonding to an electronegative acceptor atom such as oxygen or nitrogen, there is *always* a change in the isotropic chemical shift of the H-bonded hydrogen nucleus to higher frequencies (downfield shift). This downfield shift is a result of a number of not yet fully understood and partially competing factors, including a decrease in the electron density around the hydrogen nucleus and deshielding effects from the electronic currents of the acceptor atom.

Temperature dependence of hydrogen bonding

There does not appear to be much information about the temperature dependence of the chemical shifts for hydrogen bonded systems. We therefore undertook such a study ourselves, the motivation stemming basically from two interests. First, to show that isotropic chemical shift of the hydrogen bonding is quite sensitive to temperature, as may be expected due to the change in local electronic environment caused by the thermal vibrations in hydrogen bonded structures. Second—we were motivated to make CASTEP ^{1}H chemical shift computations agree with the experimental ^{1}H chemical shifts. The experimental chemical shifts were obtained at various temperatures and

these values were further extrapolated to 0 K. We used CASTEP, a periodic DFT program, to calculate the proton chemical shifts at 0 K from a static structure. (This periodicity implies a more accurate calculation of solids).

1.4 Motivation

The development of structural characterization methods for crystals is an area of great research interest in chemistry due to their widespread applications.[31] Despite significant advances in the X-ray diffraction and or neutron diffraction methods, it is challenging to investigate intermolecular interactions in the crystal structures of drug molecules. Solid-state NMR is an increasingly important technique for the physical characterization of active pharmaceutical ingredients that allows direct investigation of solid pharmaceutical products in their final dosage and dispensed forms, revealing possible physicochemical modifications induced by the processing or manufacturing steps.[32] Understanding hydrogen bonding is a topic of interest in academia,[33] and it is very important from a pharmaceutical point of view to characterize a drug in final form.[34] Indeed, small differences with the structure or polymorphism of a drug may lead to different physical and chemical properties, including color, morphology, stability, dissolution, and bioavailability, that have to be considered with regard to regulatory aspects when developing new dosage forms.[34] Among the different solid-state spectroscopic techniques, NMR spectroscopy has become an essential technique for the solid-state characterization of pharmaceuticals.[35,36]

Structural characterization in natural isotopic abundance is still a formidable challenge for spectroscopy.[37-41] Very recently, it has become possible to combine measured solid-state NMR chemical shifts and first principles calculations to validate the known structure of organic crystals.[42] In order to place the light atoms in their correct places, S. J. Clark et al. used geometry optimization by the CASTEP program and then calculated the NMR observable, chemical shielding.[43] The crucial difference for the application here between this code and other quantum chemical techniques is that the charge density and wave functions are described using a plane wave basis set and so the translational symmetry of the system is implicit. This method allows for a fully solid-state treatment of the system under investigation. The accuracy of plane wave DFT for the structural parameters is found to be excellent.[44,45]

We apply solid state nuclear magnetic resonance spectroscopy to probe structural and dynamic properties of hydrogen bonded solids, focusing in particular on organic molecular materials. Use of DFT optimization procedure for the calculation of chemical shifts and its comparison to experimental chemical shift data is essential to validate the resulting structures.

1.5 Outline of the research work

In this work the dynamics of hydrogen bonded system in the crystalline organic molecules was investigated with reference to the temperature dependence of proton chemical shifts. The purpose of the project was to validate the X-ray and neutron diffraction crystal structures of small organic

(bioactive) molecules and to examine the temperature dependence of ^{1}H chemical shifts.

Here we have tried to show that with fast MAS proton spectra, proton chemical shifts can be assigned to crystal structures especially in the case of hydrogen bonded powdered solids at natural isotopic abundance. The computational calculations of the proton chemical shifts suffice to assign the structure.

Considering the widely recognized importance of hydrogen bonding for the structure and properties of crystals, there is surprisingly little experimental information available on the temperature dependence of hydrogen-bonded systems. Our aim here is to provide this missing information. We chose chemical shift (C.S.) as an important NMR observable needed to study the nature and temperature dependent behavior of hydrogen bonds.

In principle, by using a combination of experimental and computational NMR calculations, we should be able to explain the temperature dependent behavior of hydrogen bonding in terms of proton chemical shifts. We will discuss the results in the following section (Chapter 3, 4) to see whether this is possible. We report our studies on ibuprofen, flurbiprofen, indomethacin, paracetamol, and salicylic acid. This approach could easily be extended to other such organic crystalline molecules.

This thesis outlines two techniques for understanding temperature dependent hydrogen bonding in molecular crystals:

(i) NMR experiments at variable temperatures, and

(ii) CASTEP chemical shift NMR calculations at 0 K

Chapter 1 introduces the readers to the motivation and objectives for this research project.

In Chapter 2, a background to the density-functional theory is presented. Special attention is paid to CASTEP (Cambridge Sequential Total Energy Package), the DFT code used here for the calculations of chemical shifts.

The following chapter, Chapter 3, describes the experimental and computational methods used to understand hydrogen bonding and validate organic molecular structures with the temperature dependence of proton chemical shifts.

The fourth chapter contains results and discussion on the data obtained from the temperature dependence of ^{1}H-chemical shifts for ibuprofen, flurbiprofen, indomethacin, paracetamol, and salicylic acid. Finally, the research work is summarized in the conclusion, Chapter 5.

Chapter 2

CASTEP – a Periodic DFT Program

This chapter provides background information on CASTEP, a versatile Density Functional Theory (DFT) code whose periodic nature allows us to calculate ^{1}H chemical shifts accurately in the solid state.

Background:

Density functional theory has long been the mainstay of electronic structure calculations in solid-state physics, and has recently become popular in quantum chemistry. It provides a way to solve the Schrodinger equation numerically by replacing wavefunctions with density functionals. As it is implemented to CASTEP, it allows the calculation of chemical shifts.

The establishment of links between structural information and NMR observables such as chemical shifts is an interesting issue, which has concerned the solid-state NMR community in recent time.[45,46] This is complicated in powdered solids, where long-range range effects and inter-molecular interactions may significantly change the isotropic chemical shifts from their solution state values. As a consequence, computational methods have been developed to predict the chemical shifts from a given structure, including in particular long-range interactions. The implementation of first principles calculations, using plane waves and pseudo-potentials, in the presence of an external magnetic field was first addressed by Mauri and co-workers[47] who developed a theory later adapted to codes based on norm-

conserving pseudo-potentials. Few applications of this method had been proposed because of the limitations inherent to norm-conserving pseudopotentials, and because it has long been expected that the approaches using pseudo-potentials would not be suitable for the prediction of chemical shifts, as this property requires an accurate description of the wave function at the nucleus. However, the use of the Projector Augmented Wave (PAW) approach may overcome this problem, as demonstrated by Pickard and Mauri, who implemented a gauge-including PAW formalism (GIPAW) for the accurate calculation of NMR chemical shifts from periodical DFT calculations. [48, 49]

Here, we have focused specifically on CASTEP, *a first principles method* with GIPAW, to develop it for the validation of crystal structures obtained from the diffraction studies.

First Principles Calculations:

The term *condensed matter* describes matter that has condensed to form stable systems of atoms and molecules, is found in solid or liquid phases. The large variety of ways in which these systems can take form leads to a rich diversity of physical phenomena that is practically endless in scope. Because of this, approaching the field of condensed matter physics from a theoretical or computational angle can be a very challenging task to undertake. A good method to use calculations for condensed matter systems is to pick a particular macroscopic phenomenon, which has been well studied experimentally, and to build empirical, or semi-empirical, models to describe the experimentally observed results. This often provides a good understanding of the physics of the system under study, and it is often possible to interpolate

or extrapolate these models in order to predict the behavior of systems under conditions not yet tested experimentally. However, due to the complexity of condensed matter systems, and the difficulty in building accurate models, the predictive power of such an approach can be severely limited. The *first principles* approach to condensed matter theory is entirely different from this. It starts from what we know about all condensed matter systems - that they are made of atoms, which in turn are made of a positively charged nucleus, and a number of negatively charged electrons. The interactions between atoms, such as chemical and molecular bonding, are determined by the interactions of their constituent electrons and nuclei. All of the physics of condensed matter systems arises ultimately from these basic interactions. If we can model these interactions accurately, then all of the complex physical phenomena that arise from them should emerge naturally in our calculations. The physics that describes the interaction of electrons and nuclei that is relevant to most problems in condensed matter is actually relatively simple. There are only two different types of particle involved, and the behavior of these particles is mostly governed by basic quantum mechanics.

In theory, quantum mechanics provides a reliable way to calculate what electrons and atomic nuclei do in any situation. The behavior of electrons in particular governs most of the properties of materials.[50,51] This is true for a single atom or for assemblies of atoms in condensed matter, because quantum mechanics describes and explains chemical bonds. Therefore we can understand the properties of any material from *first-principles*, that is, based

on fundamental physical laws and without using free parameters, by solving the Schrodinger equation for the electrons in that material.[52]

2.1 Density functional theory

The basis for *density functional theory* (DFT) is the proof by Hohenberg and Kohn[53] that the ground state electronic energy is determined completely by the electron density. If we find the ground state density, then we can calculate the energy. In other words, there exists a one-to-one correspondence between the electron density of a system and the energy. The significance of the Hohenberg–Kohn theorem is perhaps best illustrated by comparing it with the wave function approach. A wave function for an *N* electron system contains 4*N* variables; three spatial and one spin coordinate for each electron. The electron density is the square of the wave function, integrated over $N - 1$ electron coordinates, and each spin density only depends on three spatial coordinates, independent of the number of electrons. The electron density has the same number of variables, independent of the system size. The "only" problem is that although it has been proven that each different density yields a different ground state energy, the functional connecting these two quantities is not known. Though this functional is not known, but it turns out that even relatively crude approximations can give excellent results. The goal of DFT methods is to design functionals connecting the electron density with energy.[54-59]

Many-Body Wavefunctions In order to study a system of interacting electrons and nuclei, we must find the density. This requires us to construct a suitable

many-body wavefunction for the system. In principle this wavefunction is a function of time and all nuclear and electronic coordinates. While the complexity of a wave function increases exponentially with the number of electrons, the electron density has the same number of variables, independent of the system size.

The Born-Oppenheimer Approximation We can decouple the electronic and nuclear motion and assume that the electrons respond instantaneously to any change in nuclear coordinates move to after coordinates. This approximation allows us to rewrite the full many-body wavefunction as the product of a nuclear and an electronic wavefunction. Since the electronic wavefunction only depends on the instantaneous nuclear configuration, and not on time, we can describe its behavior with the time-*independent* Schrodinger equation. The nuclei are massive enough to be treated as classical particles, responding to the electronic forces according to Newton's laws. This semi-classical approximation, coupled with adiabatic separation of variables, is called the *Born-Oppenheimer approximation*.

Bloch's Theorem simplifies our problem. Bloch's theorem says that any wavefunction of a periodic system must be the product of a cell-periodic part and a phase factor, in order to preserve the translational symmetry of the density. The phase factor takes the form of a plane wave, whose wave vector is a linear combination of reciprocal lattice vectors.

Thus, the electronic and geometric structures can be computed in the solid-state by using the planewave pseudopotential DFT framework.[60,61] It is often

constructed with the formalism given by Kohn and Sham.[62] Herein, a fictitious system of non-interacting electrons that yields the same electronic density as the real system is introduced. This leads to a set of equations for monoelectronic wave functions ϕ_i that have to be solved self-consistently:

$$-\frac{\hbar^2}{2m}\nabla^2\phi_i + V_H\phi_i + V_{ext}\phi_i + V_{xc}\phi_i = \varepsilon_i\phi_i \qquad V_{xc} = \frac{\delta E_{XC}}{\delta n}$$

where V_H is the Hartree potential, V_{ext} is the external potential, and E_{XC} is the exchange correlation functional. E_{XC} contains contributions to the kinetic energy and the electron-electron interaction energy. Local density approximation (LDA) and generalized gradient approximation (GGA) exchange correlation functionals are most commonly found, and hybrid functionals are rarely used. Among several possible sets of functions available.

Plane Waves We use a plane-wave basis in order to express the wavefunction as a whole (both the phase factor and the cell-periodic part). This has the additional advantage that the basis functions are orthogonal, and that operations on them are computationally efficient. In particular, it is straightforward to Fourier transform our wavefunction from real to reciprocal space or vice versa. (For studies in extended periodic systems such as ours, plane waves are particularly favorable, as they are delocalized and periodic.)

For example, according to Bloch's theorem, the wavefunction is written as the product of a cell-periodic part and a wavelike part.

$$\Psi_{\mathbf{k}}^{n}(\mathbf{r}) = e^{i\mathbf{k}\cdot\mathbf{r}}u_{\mathbf{k}}^{n}(\mathbf{r})$$

where *n* is the band index. The possible values for **k** depend on the size of the crystal. The periodic part can itself be expanded using plane-waves, whose wave vectors **G** are reciprocal lattice vectors of the crystal, so that:

$$\Psi_{\mathbf{k}}^{n}(\mathbf{r}) = \sum_{\mathbf{G}} c_{\mathbf{k}}^{n}(\mathbf{G}) e^{i(\mathbf{k}+\mathbf{G}).\mathbf{r}}$$

The calculation of an infinite number of wave functions (corresponding to an infinite number of electrons) is turned into that of a finite number of functions at infinite values for **k**, called **k**-points. However, the actual calculation can be limited to a very small number of carefully chosen **k**-points because wave functions corresponding to **k**-points that are close together are almost identical.

Basis sets The plane wave basis sets (composed of sets of plane waves down to a cut-off wavelength) are often used, especially in calculations involving systems with periodic boundary conditions. The cut-off energy is the only parameter determining size of the basis set. The energy for a plane wave describing a free electron is given by:

$$E = \frac{\hbar^2 |\mathbf{k} + \mathbf{G}|^2}{2m}$$

Physical quantities to be calculated can be converged systematically, with respect to basis size set, by increasing E_{cut}. The expansion of wave functions that have a high curvature requires planewaves with short wavelength, i.e. a

high cutoff energy. This problem of basis set size can however be overcome by the use of pseudopotentials.

Pseudopotentials Every electronic state of our system must be orthogonal to every other state. As we fill higher and higher states, this orthogonality condition forces the wavefunctions of these states to have increasing numbers of nodes. This dramatically increases the width of the Fourier spectrum, and hence the number of plane waves we need to adequately represent our wavefunction. Many of the nodes of the atomic states lie in a "core region" close to the nucleus. The wavefunctions in this core region are relatively unchanging, regardless of the chemical environment of the atom, and many of the lower energy states are localised in this region. In the pseudopotential approximation, the electrons whose wavefunctions are localised in the core region are removed ("pseudised"), and replaced with an effective potential which, when combined with the nuclear coulomb potential, is called the *pseudopotential*. This means that the remaining electrons' wavefunctions only have to be orthogonal to each other, so the number of nodes is reduced. The pseudopotential is constructed such that the wavefunctions outside the core region are unchanged. The use of pseudopotentials dramatically reduces the number of plane waves required to represent the wavefunctions, whilst still giving excellent results.

Although pseudopotentials are necessary for plane-wave calculations to be tractable, they are not logically adapted to compute NMR shieldings. Shieldings must be computed at the location of the nuclei, which is not

properly described by pseudopotentials. As a consequence, a reconstruction scheme has been developed to obtain, with a pseudopotential method, all-electron accuracy: the gauge-including projector augmented wave method (GIPAW).[63]

Gauge-including projector augmented-wave method

There are two problems when computing NMR shieldings with pseudopotentials. First, as core electrons are not considered explicitly, their direct contributions to shielding cannot be obtained from the calculation. Then, as pseudo-wave-functions are smoothed near the nucleus, the contribution from valence electrons is not necessarily correct. The first issue was solved by Gregor, Mauri and Car in 1999.[63] They showed that, for a gauge-invariant separation of core and valence contributions, core contributions are rigid; i.e., they do not depend on the environment of the atom. Full shielding values can thus be obtained by adding a constant term, which depends only on the nature of the atom, to the contribution of valence electrons. The second issue is also relevant for other physical quantities computed at the nuclei, such as hyperfine parameters or electric field gradients. In 1993, Blöch introduced a method that allows the computation of expectation values with all-electron accuracy, from pseudo quantities: the projector augmented-wave method (PAW).[64]

The PAW method, which considers a polyatomic system in a uniform magnetic field, was not developed for the calculation of NMR shieldings. It was later modified to do so.[65, 49] GIPAW operator moves, for each atom, the gauge origin

at the centre of the nuclei. This reduces the number of partial-waves needed to correctly pseudize all-electron quantities, by minimizing the effect of the magnetic field and the interaction between core and valence electrons. The PAW method and the other details but will NOT be discussed here.

The GIPAW method,[66] by explicitly taking into account the effect of pseudopotentials on the calculation of chemical shieldings, allows accurate studies of heavier nuclei in extended systems to be performed. Applications for oxygen, silicon, sodium, magnesium and boron atoms have been published.[67-69] In those studies, the predictions of NMR spectra can be combined with experimental data for structural studies.

Ultrasoft pseudopotentials

Vanderbilt introduced a new class of pseudopotentials, called ultrasoft pseudopotentials (USPP).[70] For USPP, the norm-conservation constraint for the pseudo-wave-function is relaxed when building the pseudopotential. Smoother pseudo-wave-function can thus be obtained. A smaller number of plane-waves are then necessary to expand the wave functions, meaning that a lower cutoff energy can be chosen. This eventually reduces the computational cost of calculations. The original PAW method does not impose norm-conservation for the pseudization step, and can therefore be implemented with ultrasoft pseudopotentials, by using a modified PAW operator. The relationship between USPP and the PAW method has been analysed in detail.[71] The GIPAW operator can also be expressed by relaxing the norm conservation constraint. This method is still under development.[72-74]

2.2 CASTEP – an application

First principle calculations allow researchers to investigate the nature and origin of the magnetic resonance properties of a system without the need for any empirical parameters. NMR CASTEP provides a tool for predicting accurate NMR chemical shift tensors, isotropic shifts, and electric field gradients for any material with descent reliability: relative isotropic shifts can be predicted to within a few ppms. Using computed chemical shifts, users can perform assignment of the observed NMR spectra. Comparing the accurate results of NMR CASTEP with experiment makes it possible, for example, to assign chemical shifts to atoms unambiguously; to discriminate between crystal polymorphs; or to analyze the degree of disorder in crystalline materials. It has been recently reported that the CASTEP is a partial empirical methodology to hypothesize the behavior of hydrogen bond.[13]

We use CASTEP, which incorporates planewaves, pseutopotentials and GIPAW into a DFT package.

The advantage of CASTEP is that, contrary to Gaussian which uses only a single molecule, it uses a periodic calculation all around the crystal. Recently using the CASTEP program, NMR calculations have been successfully applied to various chemical problems in combination with solid-state NMR studies.[60, 75-78]

Calculation of NMR Chemical Shifts by CASTEP:

It is well known fact that chemical shifts are very sensitive to non-covalent interactions in crystals, such as hydrogen bonds or Van der Waals interactions.[79] The availability of truly periodic NMR shielding calculations, which have precisely the advantage of properly taking into account

intermolecular interactions, has recently led to many studies to further characterize noncovalent interactions (such as hydrogen bonding) in solids. It has for example become possible to compare calculated NMR parameters for the crystal and for the corresponding isolated molecule, thus identifying packing effects. Such a strategy has been applied to characterize quantitatively so-called strong hydrogen bonds, i.e. O-H…O, N-H…O hydrogen bonds. Recently, bulk chemical shifts, the chemical shift difference between the full solid and the isolated molecule, were computed for a series of simple hydrogen-bonded systems.[80]

Chemical shifts (CS) are the most readily available data from an NMR experiment. For solids, NMR is in many ways complementary to X-Ray diffraction studies. No simple relation is known, however, which links CS values and geometrical parameters. Many empirical rules to correlate CS values with structural information have been derived from experiment, but empirical analyses are limited. Computational method for chemical shifts can better bridge the gap between experimental observations and microscopic information. Several methods have thus been developed, within different electronic structure calculation theories, to predict chemical shifts from a given molecular structure.[81-84] The combination of high-resolution NMR spectroscopy and accurate calculations now allows for the emergence of powerful methods for structural studies.[14] The agreement between CS calculated for a given structure and experimental values can be evaluated for compounds under study. The results obtained allow for structure validation by solid-state NMR to become a possibility.

The accuracy of *ab initio* calculations, either in the liquid or the solid state, is however still limited by the fact they most often consider static systems.[13,37] Such static calculations formally correspond to experiments performed at zero Kelvin, while actual measurements are carried out at finite temperature. We believe that the accuracy of calculations can be improved by taking into account the effects of temperature. Thus, the aim is to calculate NMR shieldings, and the corresponding chemical shifts, for compounds that show temperature-dependant chemical shifts.

First of all, we carry out calculations on single static structures, which formally would only correspond to spectra recorded at 0 K. However, experimental spectra are recorded at non-zero temperature, and therefore correspond to systems where molecules are in motion. One may doubt that this is only obvious in the liquid state, where molecules have large relative motions; however it is also true for solids, where molecules, although they have a well-defined average configuration, can have instantaneous positions and geometries which differ significantly from their average value. As NMR shieldings are very sensitive probe for molecular geometry and environment, they show strong variations with timescales corresponding to molecular motion. When those timescales are significantly shorter than the duration of an NMR scan, experiments yield an average value. One can never guarantee beforehand that the value computed for a static, equilibrium structure at 0 K will be the same as the experimental one.

In practice, for solid-state NMR, static calculations by periodic DFT often lead to accurate results,[13,23] but there are cases where accuracy could be improved by taking motion into account. Deviations between experimental and computed values are for example sometimes observed for nuclei in aromatic rings, or for hydrogen-bonded atoms, and it is suspected those deviations arise from temperature effects.

It would be very important to take into account the temperature effect on these calculations in the solid-state; we will therefore present examples for few organic crystals, where motional averaging is often compulsory to obtain an accurate validation of structures. The one we will describe first aims at including the effect of the evolution of interactions during molecular motion, by such DFT calculations.

Here we combine experiments and calculations of the chemical shifts to understand the temperature-dependent interactions in the solid state. Thus the results obtained allow for structure validation by solid-state NMR and CASTEP. If calculations are shown to be reliable, they could be used to extend the studies of structure-property relationships to larger sets of molecules, thus bypassing experimental measurements, which can be time consuming. Some deviations were observed in the studies cited above, and were attributed to the difference between static structures at 0 K, considered for calculations, and the actual solid at finite temperature. Theoretical predictions that take

temperature effects into accounts could improve the agreement between calculated and measured data.

NMR studies on the chemical nature of the molecule:

NMR studies on the small organic molecules were performed at finite temperature.[85,86] Although all the compounds were solid (well below their melting point), the molecules were not fully static. By contrast, DFT calculations did not include any thermal energy or zero-point vibrational energy. To examine whether the difference in thermal energy between *temperatures at which NMR spectra were acquired* and the *that of effectively at 0 K temperature of the DFT calculations* could account for discrepancies between calculated and experimental chemical shifts (CS), we measured CS at different temperatures and extrapolated to 0 K.

Chapter 3

Experimental Section

This chapter describes the source and structure of the chemical compounds under study, experimental methods, computational methods and other software used for this study.

3. 1 Chemical substances

Small drug molecules

In order to study the hydrogen bonding in solids, we selected a few bioactive organic compounds with known crystallographic structures. Understanding the structural parameters by measuring the temperature dependence of its chemical shifts was our main goal. We searched the Cambridge Structural Database (CSD)[87] for known X-ray diffraction and or neutron diffraction structures. All the compounds chosen had the following interesting structural characteristics:

(i) Structure with OH----O hydrogen bond

(ii) The increase in temperature of the molecule could set the proton oscillating between the two oxygens and thus have an intermediate position that is not the original position below the thermal change; [88] thus the substances (may) have non-linear hydrogen bonds (iii) Carboxylic acid dimers, though weakly ordered, are useful model systems for understanding the hydrogen bonding. Among the molecules we chose, few are carboxylic acids; and it is well known fact that hydrogen bonding is one of the most important

interactions responsible for dimerization of carboxylic acids (except formic acid).[89]

(iv) Hydrogen bonding is one of the principal interactions that determine biomolecular structures and assemblies.[90]

The compounds under study are described in Table 1.

3.2. Methods – Experiment and Computation

Solid-state NMR spectroscopy: ^{1}H chemical shifts for ibuprofen, flurbiprofen and indomethacin were obtained using a Bruker 700 MHz NMR spectrometer employing a 2.5 mm probe at an MAS rate between 28 and 33 kHz. The ^{1}H chemical shifts of salicylic acid were measured on a Bruker 700 MHz spectrometer using a 3.2 mm probe and an MAS rate of 22 kHz. There measurements were at temperatures that had been calibrated previously. The ^{1}H chemical shifts of paracetamol were measured in a Bruker 900 MHz spectrometer using a 1.3 mm probe and an MAS rate of 60 kHz. Although an effort was made to control the temperature, it was unsuccessful, as will be discussed below. All spectra were referenced against adamantane as an external chemical shift standard.

CASTEP – A Computational Method

CASTEP stands for Cambridge Sequential Total Energy Package (Academic Release CASTEP; Version 4.2; © 2000-2007). CASTEP is an *ab initio* Total Energy program, developed in the mid 1980's by *Mike Payne* of Cambridge University, UK and is still under constant development.[65,49,73] CASTEP is a DFT program that uses planewaves, pseudopotentials, and the GIPAW method to

make chemical shift calculations of periodic material tractable. This is being used here to calculate ^{1}H chemical shifts. CASTEP is a software package which uses density functional theory to provide a good atomic-level description of all manner of materials and molecules. A method to describe the exchange correlation interactions within density functional theory then has to be chosen, and we chose Perdew-Burke-Erznehof (PBE)[91] here. Generally, CASTEP gives information about total energies, forces and stresses on an atomic system, as well as calculating optimum geometries, band structures, optical spectra, phonon spectra and much more.

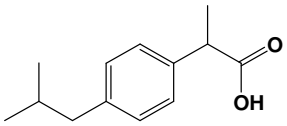
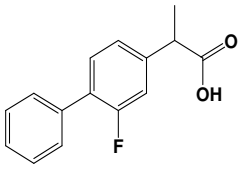
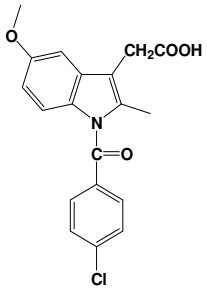
We use CASTEP to perform three tasks. The first of these is a single point energy calculation, which gives the total ground state energy of the system along with the forces and stresses on the atoms. The second is a geometry optimization where the atoms are allowed to move, and from this the program calculates the geometry of the molecule which minimizes the energy and stress to some set level of tolerance. The third task that can be defined is NMR chemical shift calculations.

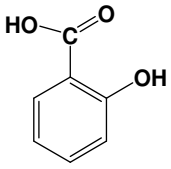
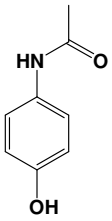
As CASTEP uses plane waves, these also have to be defined. It is known that the basis set of the electronic wave functions at each ***k*** point can be expanded in terms of a discrete plane wave basis set, according to *Bloch's theorem*. In principle, an infinite plane wave basis set is needed to expand these wave functions. However, the coefficients for plane waves with a small kinetic energy are more important than those with a large kinetic energy. This means that the plane wave basis set can be truncated to include only plane waves

with a kinetic energy that is less than a specified cutoff energy. Using the interface there are few settings for the cutoff. These cutoff values correspond to the total energy convergence and this determines the accuracy of the results.

The crystal structures for the small organic bioactive molecules (ibuprofen, flurbiprofen, indomethacin, paracetamol, and salicylic acid) were obtained from the Cambridge Crystallographic Database (CSD).[87] The electron-ion interaction of the core electrons is represented by a pseudo-potential, the use of which greatly enhances the computational efficiency of the approach. In all of our calculations the electron correlation effects are modelled using the generalised gradient approximation of Perdew, Burke and Ernzerhof (PBE).[91] For the geometry optimisation, we employ "ultrasoft" pseudopotentials,[70] a planewave converged cut-off energy of 500eV and a k point density of 0.07 A^0. The NMR calculations were performed using the Gauge Including Projector Augmented Wave approach (GIPAW) at the cut-off energy of 500eV and the k-point density of 0.07 A^0 using CASTEP.[75] This method allows for a fully solid-state treatment of the system under investigation for it is periodic.

Table 1 | The list of molecular crystals under study (X-ray / Neutron diffraction data were collected from the Cambridge Structural Database)

Compound / **CSD reference code**	Molecular formula, chemical structure and IUPAC name	Citation: *Reference Number* [†] and *Deposition No.* from CSD	Comments
Ibuprofen **IBPRAC** (X-ray structure, Obtained at 283-303 K)	$C_{13}H_{18}O_2$  2-(4-Isobutylpheny) propionic acid	Ref. 92	Forms a ***dimer***
Flurbiprofen **FLUBIP** (X-ray structure, Obtained at 283-303 K)	$C_{15}H_{13}FO_2$  (+-)-2-(2-Fluoro-4-biphenyl)propionic acid	Ref. 93 Deposition: IUCr A12054	Forma a **dimer**
Indomethacin **INDMET03** (X-ray structure, Obtained at 120 K) **INDMET** (X-ray structure, Obtained at 283-303 K)	$C_{19}H_{16}ClNO_4$  1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid	Ref. 94 Deposition:IUCr CF6262 Ref. 95	The crystal structure of γ-indomethacin is supported, not only by O-H---O interactions, but also by C-H…π and π-π interactions. The indole, *p*-chlorophenyl, and carboxylic acid groups are each nearly planar. The relative orientation of the *p*-chlorophenyl and indole groups

			are unusual and may play an important role in the chemistry of indomethacin. The crystal structure exhibits the expected hydrogen bonding of the carboxylic acid group about centers of inversion to form molecular dimers.
Salicylic acid **SALIAC12** (neutron diffraction ; unconstrained refinement, Obtained at 283-303 K) **SALIAC16** (X-ray diffraction, Obtained at 90 K)	$C_7H_6O_3$  2-Hydroxybenzoic acid	Ref. 96 Ref. 97 Deposition: IUCr LC5044	The intramolecular hydrogen bonding is postulated to weaken the dimeric hydrogen bond in salicylic acid.[111]
Paracetamol **HXACAN13** (neutron diffraction structure, Obtained at 20 K) **HXACAN15** (neutron diffraction structure, Obtained at 80 K)	$C_8H_9NO_2$  *N*-(4-hydroxyphenyl)acetamide	Ref. 98 Deposition: CCDC 150966 Ref. 98 Deposition: CCDC 150968	

HXACAN16 (neutron diffraction structure, Obtained at 150 K)		Ref. 98 Deposition: CCDC 150969	
HXACAN17 (neutron diffraction structure, Obtained at 200 K)		Ref. 98 Deposition: CCDC 150970	
HXACAN18 (neutron diffraction structure, Obtained at 250 K)		Ref. 98 Deposition: CCDC 150971	
HXACAN19 (neutron diffraction structure, Obtained at 330 K)		Ref. 98 Deposition: CCDC 150972	

[†] *Reference Number* (from this thesis section: References); *Deposition No.* is from CSD

The positions of only the hydrogen atoms were allowed to relax since location of heavy atoms by diffraction methods is significantly more accurate than those for hydrogen. However, it is well known that, even for nuclear positions

determined by neutron diffraction, reported errors in atomic locations significantly influence computed chemical shifts. To compare directly with experiment, the absolute shielding must be converted to the chemical shift using an appropriate reference shielding. To determine the reference shielding, we perform a linear regression against the experimental shifts, imposing a slope of unity.

As the temperature of a crystal is increased, the magnitude of thermal fluctuations becomes larger, which results in an increase in the average distance between atoms. As is shown below, protons move upfield shifts as the temperature is increased. This is normally explained as a weakening of the hydrogen bonding, which results from an increase in the average distance between hydrogen bond donor and acceptor. The lengthening of the average hydrogen bond distance will be greater for intermolecular hydrogen bonds than for intramolecular hydrogen bonds.[99]

The ^{1}H MAS-NMR spectra have been recorded for all the bioactive molecular crystals under study. Chemical shifts were extracted from the spectra and assigned to different protons in the structure. The CS of the hydrogen-bonded proton was found to be between 8-14 ppm.

Stepwise procedure for the calculations of ^{1}H chemical shifts:

We begin NMR ^{1}H chemical shifts calculations by inputting the diffraction data of .cif file (obtained from CSD).

1. The first of these steps is single point energy (SPE) calculation, which gives the total ground state energy of the system along with the forces and stresses

on the atoms. We observed that a planewave converged cut-off energy of 500eV and k point density of $0.07A^0$ for ibuprofen (Figure 1 and 2) was necessary for convergence of the single-point energy.

2. The positions of the hydrogen atoms were adjusted in a constrained DFT geometry optimization using CASTEP.

3. The NMR calculations were performed using the Gauge Including Projector Augmented Wave approach (GIPAW) using CASTEP.

4. CASTEP is used to calculate the isotropic chemical shielding for each ^1H nuclei. Proper conversion of chemical shielding data to referenced chemical shifts is an important issue. This is solved as follows: (i) The chemical shielding values are converted to chemical shifts, by multiplying by -1. (ii) Make the average calculated shifts equal to the average experimental shifts by adding the appropriate constant amount to each calculated chemical shifts.

The **rmsd** (root-mean square deviation), which are frequently-used measure of the differences between CS values predicted by a computation and the values actually observed from the NMR spectrometer, are obtained and compared to find whether the calculated chemical shifts fit in good agreement with the experimental ones.

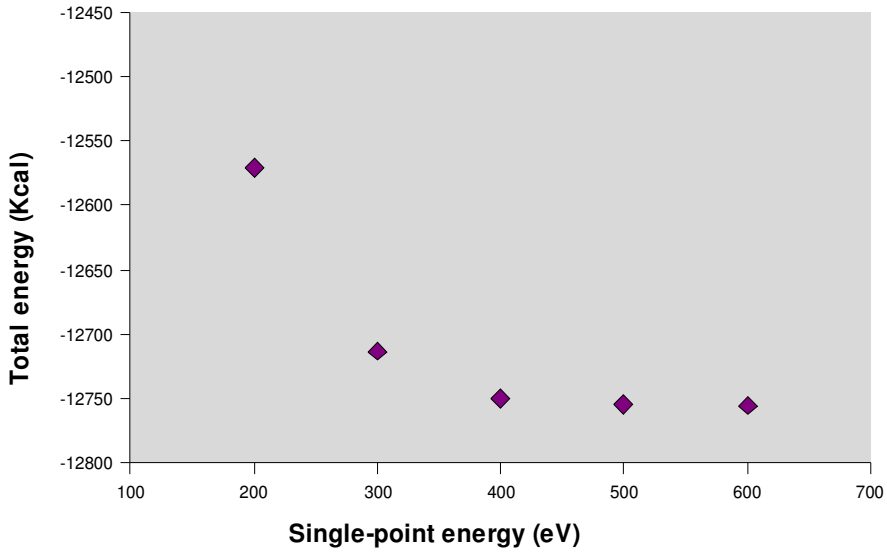


Figure 1 | CASTEP computation for Ibuprofen shows the planewave cut-off energy converged at 500 eV.

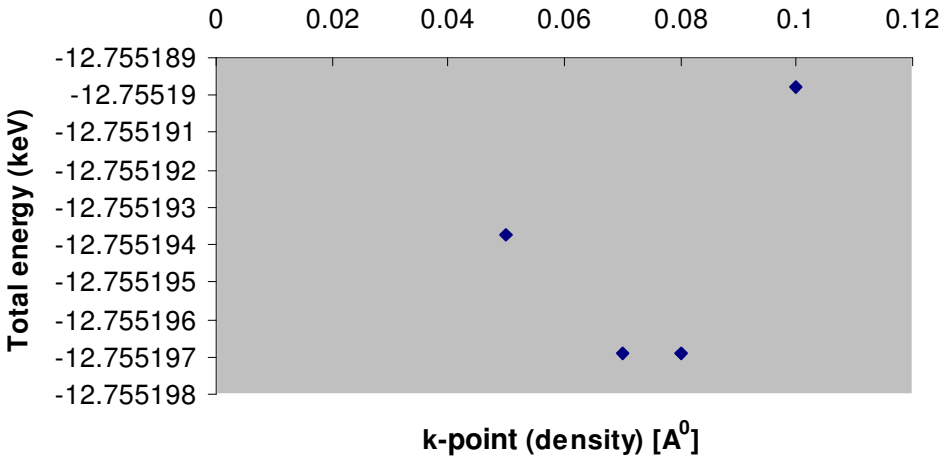


Figure 2 | CASTEP computation for ibuprofen shows k-point density convergence at 0.07 A

Chapter 4

Results and discussion

The temperature dependence of the ^{1}H NMR chemical shifts of ibuprofen, flurbiprofen, indomethacin, paracetamol and salicylic acid will be discussed in this chapter. The general protocol consists of two steps. First, the experimental chemical shifts are obtained at various temperatures, and then extrapolated to 0 K for each proton peak. Secondly, for each temperature, we compare these experimental chemical shifts with those calculated by CASTEP. The NMR chemical shift is strongly dependent on molecular structure and on the inter- and intra-molecular interactions that exist within a crystalline framework. Hence NMR is an extremely important tool for structural determination of matter. We have undertaken a series of CASTEP calculations on the X-ray crystal structures of ibuprofen, flurbiprofen, indomethacin and salicylic acid. We performed CASTEP CS calculations on neutron structures of paracetamol and salicylic acid. The computations are carried out for essentially static atomic positions and therefore do not take account of molecular level mobility, if any.

4. 1 Proton chemical shifts extracted from the spectra and computations

First of all, the NMR peaks seen in the ^{1}H NMR spectra are assigned. The resonance of the hydrogen bonded proton is identified and assigned. As the hydrogen bonded protons are expected to exhibit the largest chemical shift of all lines in each of the spectra, this assignment is rather simple. The typical range for hydrogen bonded ^{1}H chemical shift is 8-12 ppm and their lines are usually broad. In the following, we discuss the ^{1}H NMR spectra of the systems

identified in Chapter 3 in order to understand and relate / categorize the hydrogen bonding as strong, moderate or weak based on the temperature dependence of ^{1}H chemical shifts.

All data obtained are assembled in Figures, Charts and Tables.

Table 2 | The **rmsd** between calculated and experimental chemical shifts at various temperatures for all the compounds studied here. Since paracetamol chemical shifts were not determined accurately, as will be discussed below, they are not included here.

Temperature (K) / Compounds	0 K (not real) Ref.[124]	250 K	260 K	270 K	280 K	290 K	300 K	310 K	320 K	330 K
Ibuprofen										
(Without G.O.)*	1.33	-	-	1.53	1.53	1.53	1.54	1.54	-	-
(After G.O.)*	0.78	-	-	0.81	0.82	0.82	0.82	0.82	-	-
Flurbiprofen	1.00	1.07	1.08	1.08	1.08	1.08	1.08	1.08	-	-
Indomethacin (Indmet03)										
Normal fridge	0.24	0.54	0.54	0.55	0.56	0.56	0.57	0.58	-	-
Small fridge	0.25	-	-	-	-	0.59	0.57	0.58	0.59	0.59
(Indmet)										
Normal fridge	0.22	0.49	0.49	0.50	0.51	0.51	0.52	0.52	-	-
Small fridge	0.25	-	-	-	-	0.54	0.52	0.53	0.54	0.54
Salicylic acid										
(**SALIAC12**)	1.75	1.00	1.03	0.99	0.98	0.98	0.98	0.98	-	-
(**SALIAC16**)	1.67	0.95	0.97	0.95	0.95	0.94	0.94	-	-	-

* G.O. = Geometry Optimization (using CASTEP)

The difference with the structures for indomethacin and salicylic acid are summarized in Table 1. The comparison between the calculated and experimental proton chemical shifts was made for all of those compounds; and also the comparison between **rmsd** at variable temperatures with that of at 0 K show the agreement between calculations and experiments.

4.2 Discussion over results obtained for organic molecular crystals under study

Ibuprofen

Ibuprofen (IB; (*rac*)-2-(4-isobutylphenyl)propionic acid, melting point 75-77ºC, (for structure see Table 1) is a non-steroidal anti-inflammatory, analgesic, and antipyretic drug widely used in the treatment of rheumatic disorders, pain, and fever. It has an estimated annual global production of several kilotons, and it is the third most popular drug in the world. The crystals of ibuprofen are reported to be more plastic than brittle.[100] Ibuprofen contains one polar group, the carboxylic acid group, which can form a strong bond with many functional groups via an acid–base reaction. The geometry optimization favors the formation of the hydrogen bond to the hydrogen acceptor when one tries to place the hydrogen bond to the hydrogen acceptor of C=O. Here, during the process of geometry optimization, we fix the heavy atoms and allow hydrogens to relax. This helps us locate H-positions which are not properly placed in diffraction studies.

High resolution solid state NMR experiments were performed on ibuprofen to yield ^{1}H CS. These are assigned to aliphatic, aromatic and hydrogen bonding protons. (See the NMR spectrum, Figure 3). The chemical shifts obtained at

various temperatures are plotted (Figure 4). Proton chemical shift variations with temperature are observed.

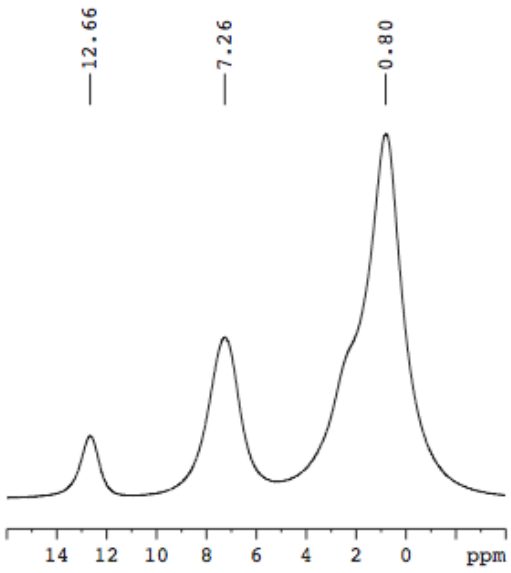


Figure 3 | ^{1}H Spectrum of ibuprofen (NMR 700 MHz, at 270 K, under MAS at 33 kHz)

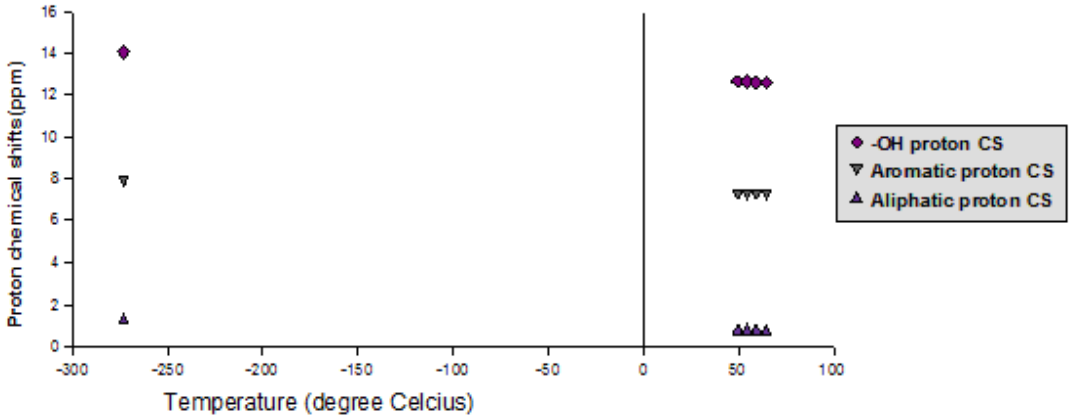
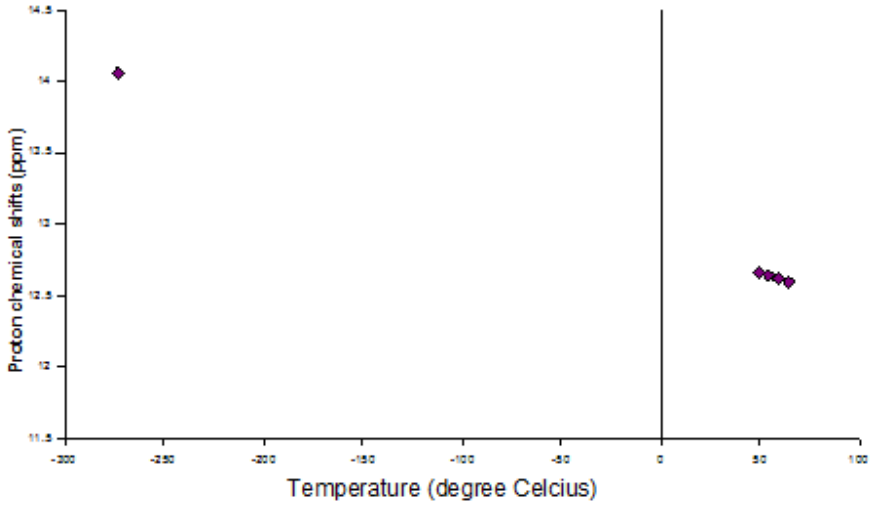
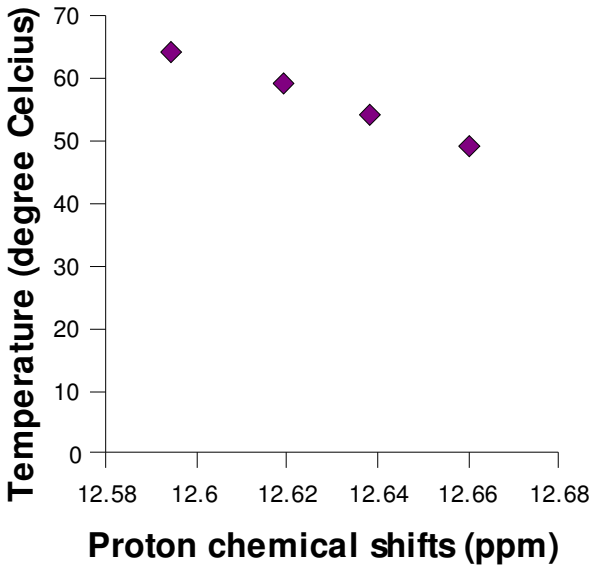


Figure 4 | Temperature dependence of ^{1}H chemical shifts for hydrogens of ibuprofen

The proton NMR chemical shift for hydrogen-bonded (OH) proton tends to go upfield with increase in temperature. This change is more noticeable than that for the other hydrogens (Figure 5). We extrapolated these chemical shifts to 0 K. The ^{1}H-CS observed for OH at 300 K is 12.59 ppm whereas at 0 K, it was extrapolated to 14.06 ppm.



[a]



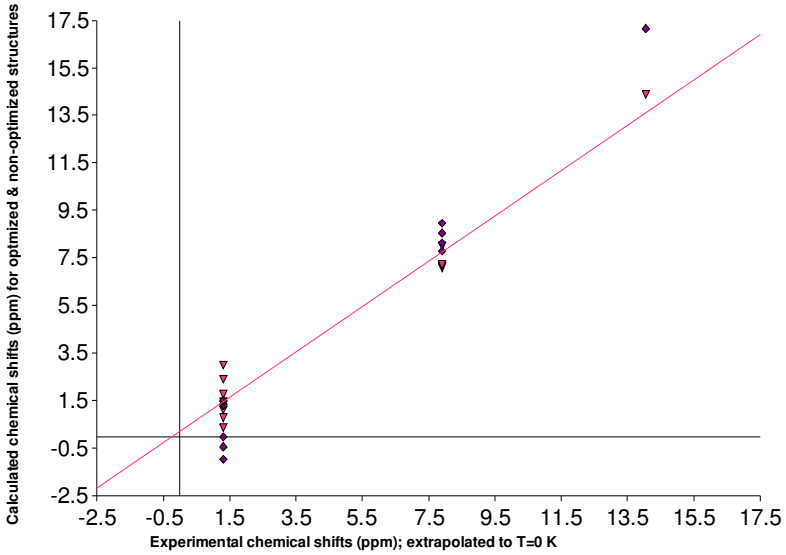
[b]

Figure 5 | NMR experiments on ibuprofen show the temperature dependence of ^{1}H-chemical shifts for the hydrogen bonded proton (OH). [a] All the experimental ^{1}H-CS along

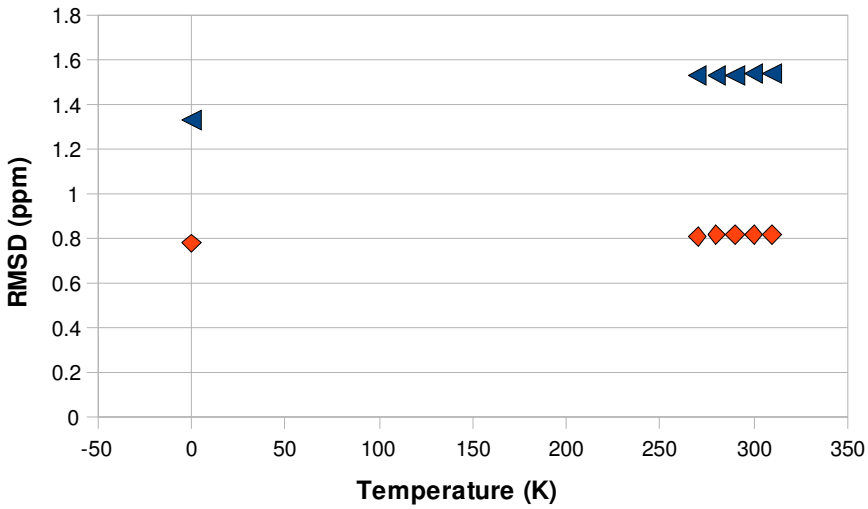
with the one extrapolated down to 0 K. [b] The experimental ^{1}H-CS for the hydrogen bonded proton (OH).

A relationship between the H-bond distances with the H-bond strength was reported by Berglund and Vaughan.[99] A correlation has been noted between lower chemical shift values of ^{1}H in $(H_2O)_2$ dimers and longer H-bond distances. Robin K. Harris et al. reported a clear relationship between proton isotropic chemical shifts and hydrogen-bond distances using proton combined rotation and multiple-pulse spectroscopy (CRAMPS) approach.[14] In view of the aforementioned literature reports, we correlate the proton chemical shifts to the behavior and strength of the hydrogen bond. For ibuprofen, it appears as if the H-bond is weakened as temperature is increased. Our experimental and calculated CS shows that CS values are lowered as we increase the temperature.

Chemical shifts are calculated for ibuprofen structures both before and after optimization of hydrogen positions. The calculated ^{1}H chemical shifts for the geometry optimized ibuprofen structure are in good agreement with the experimental chemical shifts; whereas the non-geometry optimized structure does not reflect chemical shifts in agreement with the experimental CS. The diagonal line represents the perfect agreement between the calculated and experimental chemical shifts, as shown in figure 6[a]. CASTEP calculated RMSD i.e. root-mean square deviation (before and after geometry optimization) are compared with calculations at 0 K (Figure 6[b]).



[a]



[b]

Figure 6 | Ibuprofen: [a] Chart for the comparison of CASTEP calculated ^{1}H-chemical shifts (before and after geometry optimization) to the experimental ^{1}H-CS. The diagonal line represents perfect agreement of calculated and experimental chemical shifts. [b] Chart for the comparison of CASTEP calculated RMSD (before and after geometry optimization) compared with calculations at 0 K {blue colored points indicate **rmsd** for non-geometry

optimized structures; orange colored points indicate after geometry optimized structures which show better agreement between the calculated and experimental CS}.

Ibuprofen (structure without geometry optimization) yields an **rmsd** in the range of 1.53 to 1.54 ppm (from temperature 270 K to 300 K) and at 0 K, rmsd is 1.33 ppm. Rmsd values in the range of 0.81 to 0.82 ppm (from 270 K to 300 K) were obtained, and at 0 K, the rmsd is 0.78 for the optimized structure. Calculated chemical shifts, both before and after the partial geometry optimization of ibuprofen, are fit to each of the set of experimental chemical shifts. The best agreement between calculated and experimental chemical shifts was found for the values at 0 K (Figure 7).

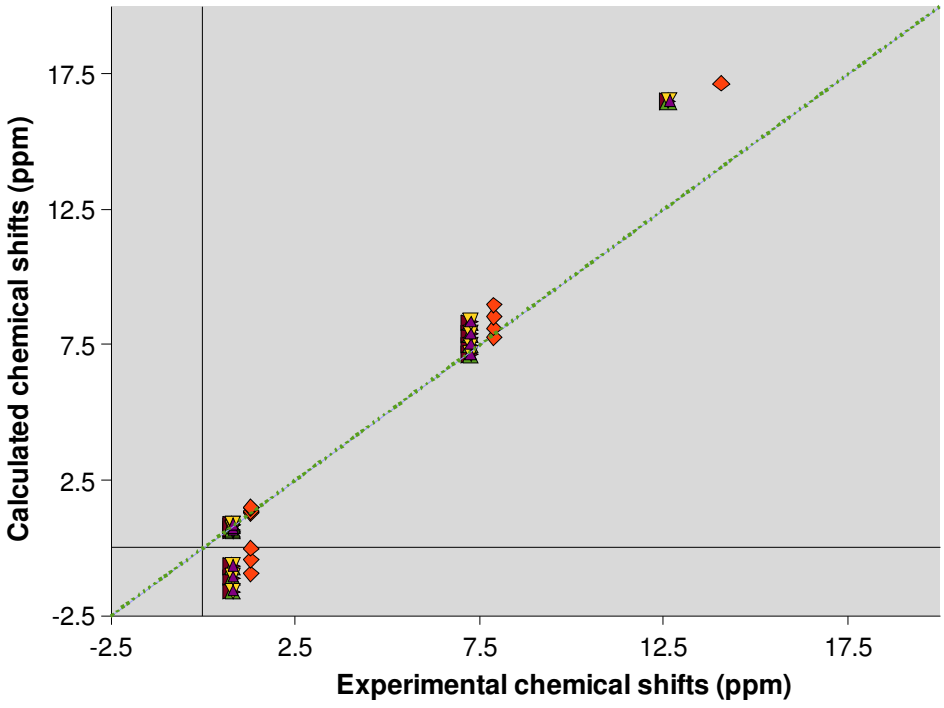
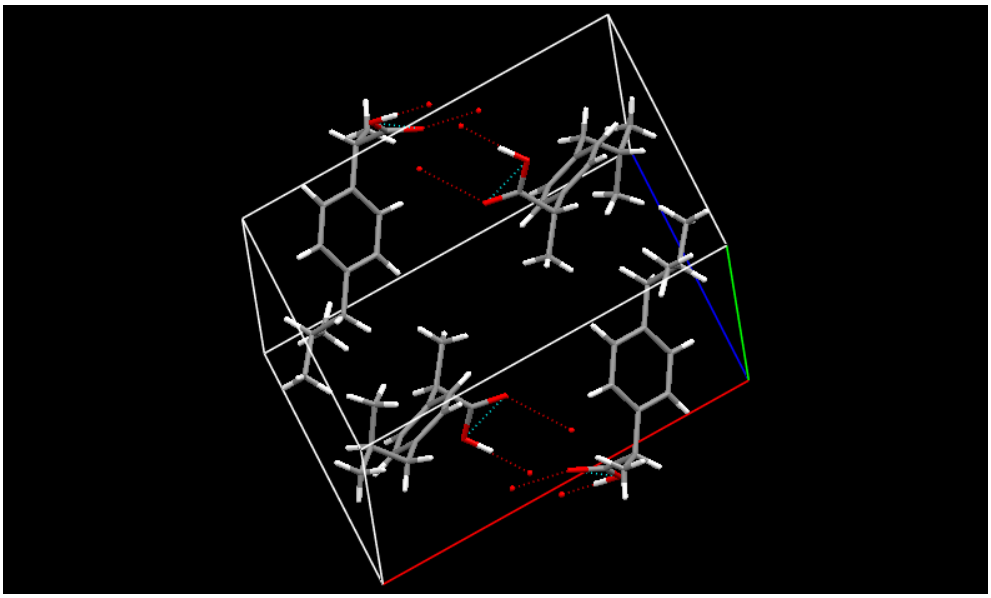
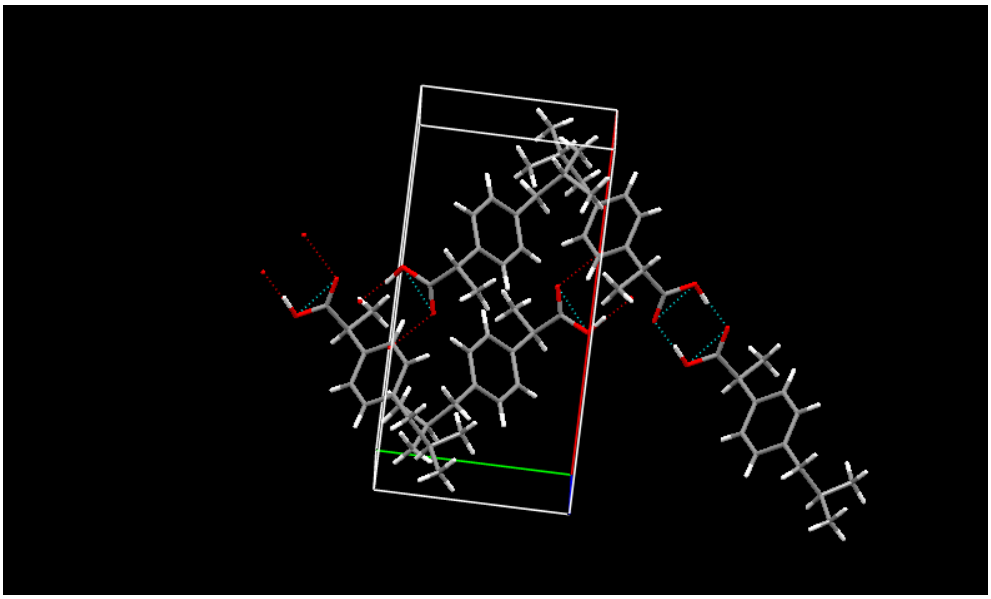


Figure 7 | Ibuprofen: Chart for the experimental ^{1}H-chemical shifts versus the CASTEP calculated ^{1}H-chemical shifts at various temperatures

The CASTEP geometry optimized ibuprofen structure was then compared with its calculated CS to that of non-geometry optimized ibuprofen. The geometry optimization relaxes the protons and fixes the heavy atoms; thus it gives the information about locations of protons which are not necessarily accurately given by X-ray studies (Figure 8).





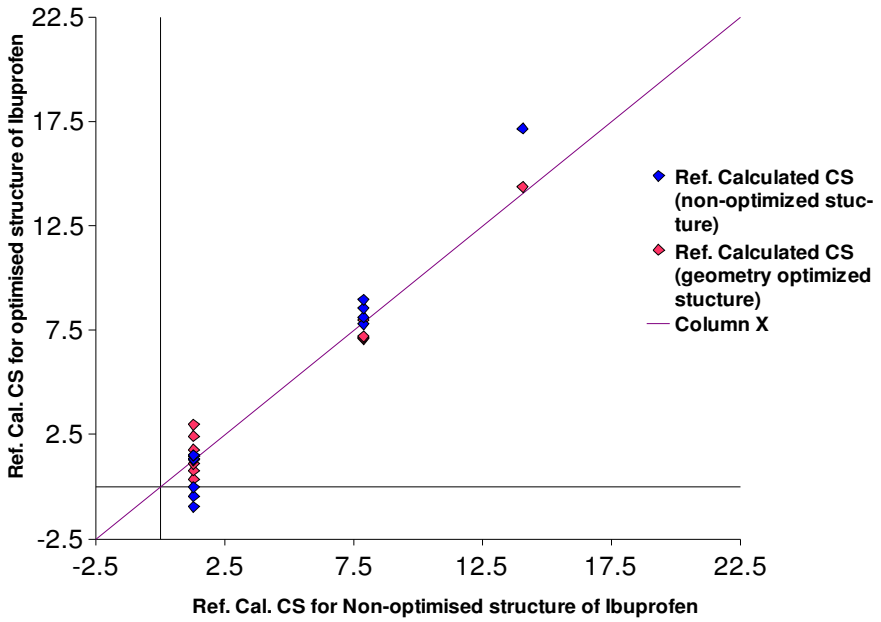


Figure 9 | Ibuprofen: Chart for the comparison between calculated ^{1}H chemical shifts for ibuprofen (x-ray) structure without geometry optimization (blue) and with geometry optimization (red).

Table 3 | Ibuprofen: Bond distances and bond angle

Chemical bond	Bond distances (in Angstrom)	
	Before CASTEP	After CASTEP
O-H	1.036	1.021
OH----O	1.624	1.636
C-H	0.969	1.097
C-H aromatic	0.966	1.089

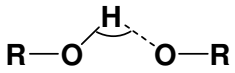
Bond Angle (in degrees)	Before CASTEP	After CASTEP
	179.10	174.61

Table 3 shows the bond distances and bond angle before and after geometry optimization. Better chemical shift rmsd calculated for the geometry optimized structures indicate that hydrogen atoms are better placed for NMR measurements using CASTEP. In other words, it just shows that in X-ray diffraction data, the hydrogen positions are poor. More information could be used to explain the conformation of the molecular structure, and geometry of the hydrogen bond. In this case of ibuprofen, we find that O-H…O angle is reduced; and thus an evidence for a stronger intermolecular H-bonding (interaction) in the crystal lattice. We see the close contact between H and the O (OH…O) in two different ibuprofen molecules i.e. the geometry optimization favors the formation of the hydrogen bond between the hydrogen donor (OH) and the hydrogen acceptor (O of C=O) (Figure 9, 10).

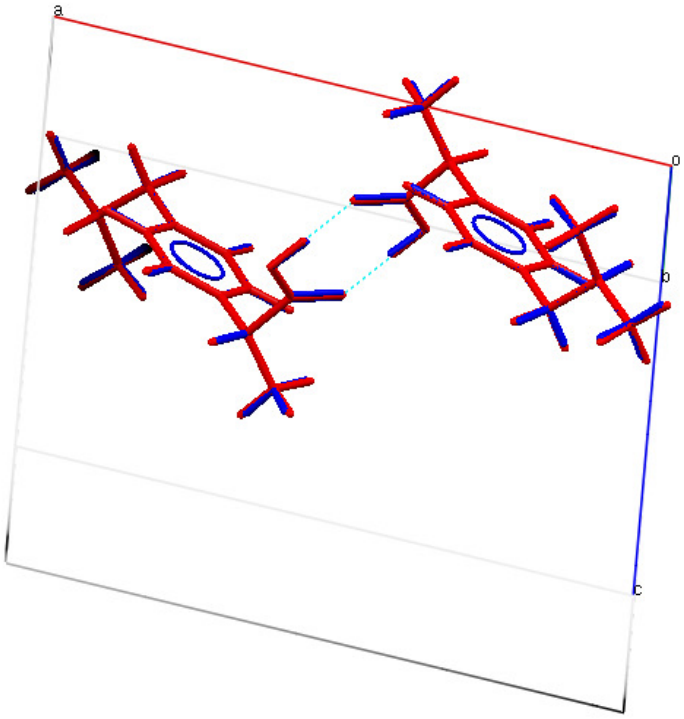


Figure 10 | The close contact between H and the O (OH…O) in ibuprofen molecule and this figure also shows the comparison between ibuprofen structures before (blue) and after geometry optimization (red). We find positions of protons placed differently than that of the structure before geometry optimization (blue). Thus geometry optimization helps us relax protons and place them at correct positions; which is not well explained by X-ray diffraction.

The temperature dependence of H-bond is observed in ibuprofen. As the temperature is increased the OH…O distance is increased, and consequently the H-bond gets weaker. At lower temperature, the H-bond is stronger than at higher temperature. The lower chemical shift values are thus related to the weak H-bond resulting from an increase in temperature.

Flurbiprofen

Flurbiprofen ((M.P. 114-117°C)) is a well-known chiral nonsteroidal anti-inflammatory agent with analgesic and antipyretic activity.[101] Flurbiprofen contains a polar carboxyl acid. We expect that this group always favors the formation of a hydrogen bond to another carboxylic acid as the hydrogen acceptor.

Solid state high resolution NMR experiments were performed on flurbiprofen to yield ^{1}H-spectra that show chemical shifts (CS) characteristic of four different hydrogens present in its molecular structure. These are assigned to two aliphatic, one aromatic and one hydrogen bonding site (See the NMR spectrum, Figure 11). The chemical shifts obtained at various temperatures are plotted (Figure 12). Proton chemical shift variations due to their temperature dependence are observed. The proton NMR chemical shift for hydrogen-bonded (OH) proton tends to go upfield with increase in temperature. This change is more noticeable than that for the other hydrogens (Figure 13).

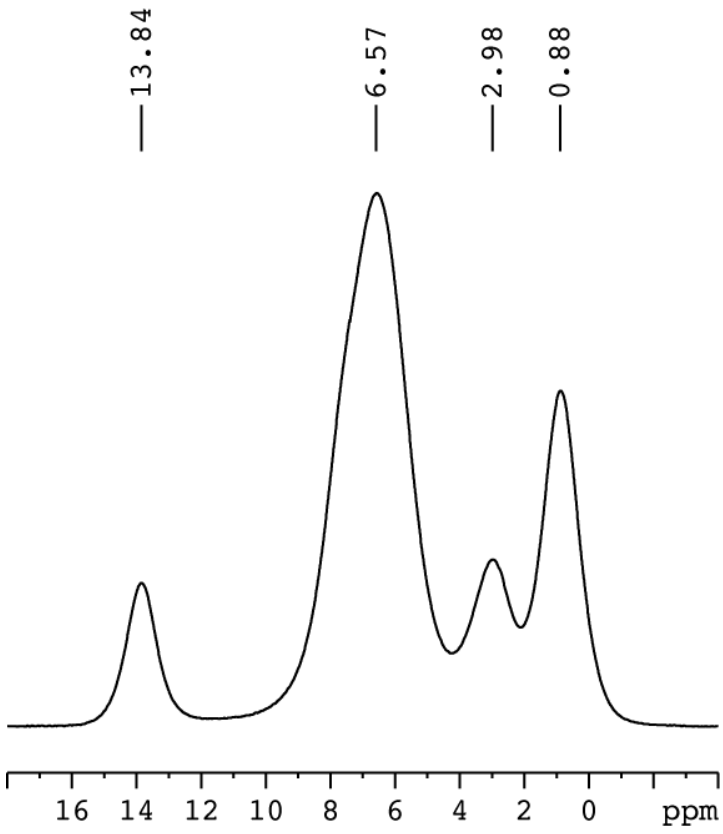


Figure 11 | ^{1}H spectrum of flurbiprofen (MAS NMR 700 MHz, at 250K, under MAS 33 kHz)

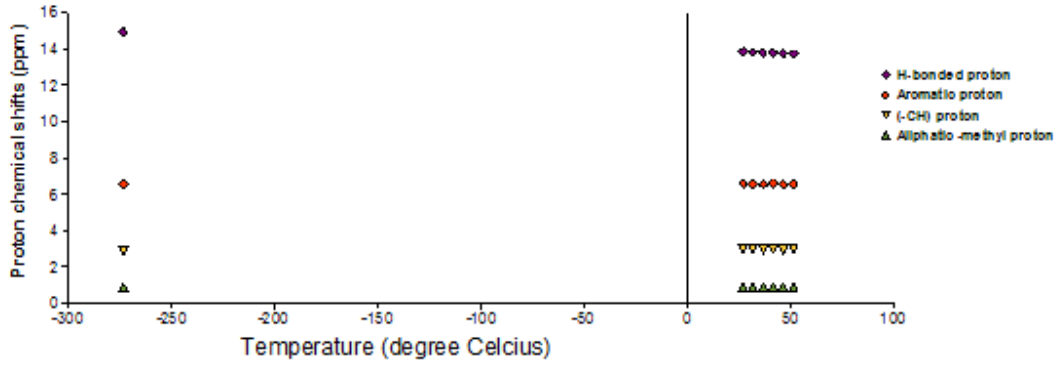


Figure 12 | NMR experiments on flurbiprofen show a temperature dependence of ^{1}H-chemical shifts for all hydrogens.

Experimental CS were obtained by performing NMR experiments at various temperatures; and then the CS is extrapolated to 0 K. The above figure shows the temperature dependence of ^{1}H-chemical shifts for all of its hydrogens.

We extrapolated these chemical shifts to 0 K. The ^{1}H-CS observed for OH at 250 K (27.64 C) is 13.84 ppm whereas at 0 K (-273.15 C), it was extrapolated to 14.96 ppm. This trend is shown clearly in the Figure 13. This tends to go in agreement with the literature where the H-bond strength was correlated with the H-bond distances; and here we suggest a correlation between the lower proton chemical shifts with the increasing temperatures and a weaker H-bond with an increase in temperature. In other words, at lower temperature the hydrogen bond is strong, and the bond distance and angle is lowered (e.g. at 0 K). This relationship between the H-bond distances with CS is in good agreement with the literature. The calculations reproduce the experiments well.

A partial CASTEP geometry optimization of the structure was performed. We fixed the heavy atoms, and allowed the hydrogen atoms to relax. The CASTEP hydrogen bond distances and angle give calculated chemical shifts that are consistent with the experimental NMR chemical shift calculations (Figure 15).

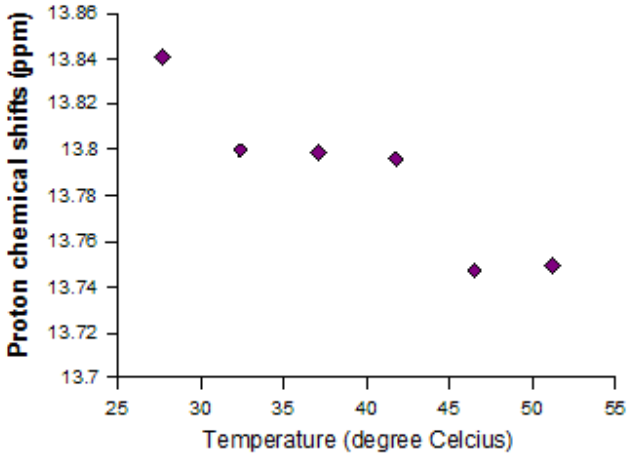


Figure 13 | NMR experiments on flurbiprofen shows the temperature dependence of ^{1}H-chemical shifts for the hydrogen bonded proton (OH).

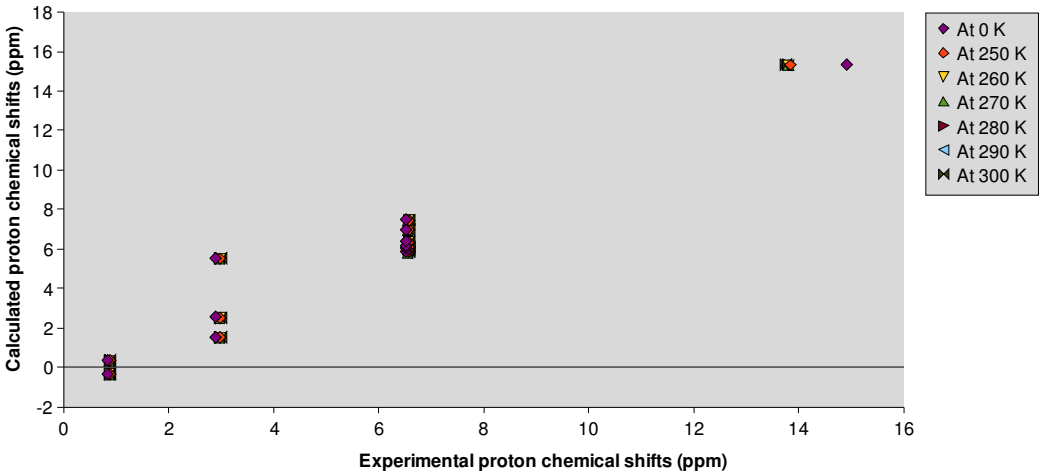


Figure 14 | Flurbiprofen: Chart showing the experimental ^{1}H-chemical shifts versus calculated ^{1}H-chemical shifts at variable temperatures.

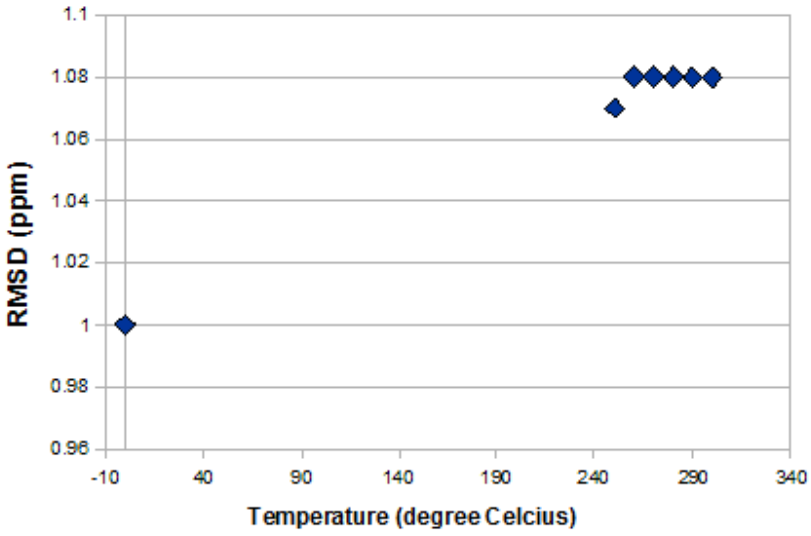


Figure 15 | Flurbiprofen: Chart showing the calculated chemical shift RMSD as a function of temperature.

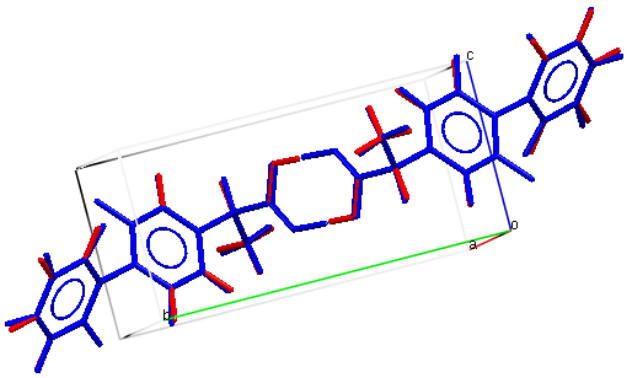
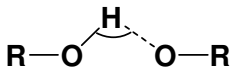


Figure 16 | The close contact between H and the O (OH…O) in flurbiprofen molecule and this figure also shows the comparison between flurbiprofen structures before (blue) and after geometry optimization (red). We find positions of protons placed differently than that of the structure before geometry optimization (blue). Thus geometry optimization helps us relax protons and place them at correct positions; which is not well explained by X-ray diffraction.

Table 4 | Flurbiprofen: Bond distances and bond angle

Chemical bond	Bond distances (in Angstrom)	
	Before CASTEP	After CASTEP
O-H	1.021	1.026
OH----O	1.636	1.616
C-H	1.097	1.096
C-H aromatic	1.092	1.089

Bond Angle (in degrees)	Before CASTEP	After CASTEP
	179.10	178.94

The above table shows bond distances and bond angle for structures before and after geometry optimization. This indicates that the hydrogen atoms are differently placed in X-ray studies. The chemical shift agreement (RMSD) between calculated and experimental CS shows whether their placement agrees with what is measured by NMR. In this case of flurbiprofen, we find that O-H…O angle is reduced upon geometry optimization; and hereby gives an evidence for a stronger intermolecular H-bonding (interaction) in the crystal lattice. We see the close contact between H (of OH) and the O (of C=O) in two different ibuprofen molecules (Figure 16). The temperature dependent

behavior H-bond is observed in flurbiprofen. As we can from the trend shown in charts, it is clear that the H-bond gets weaker upon increase in temperature, and well reflected by the lower chemical shift values.

Indomethacin

Indomethacin (melting point 155 - 161 ^{0}C) or indometacin is a non-steroidal anti-inflammatory drug commonly used to reduce fever, pain, stiffness, and swelling. It works by inhibiting the production of prostaglandins, molecules known to cause these symptoms. It is marketed under many trade names, including Indocin, Indocid, Indochron E-R, and Indocin-SR.[102, 103] Indomethacin is a methylated indole derivative, and it contains - COOH carboxyl acid group. We expect that this group always favors the formation of a hydrogen bond to another carboxylic acid as the hydrogen acceptor.

Solid state high resolution NMR experiments were performed on indomethacin to yield ^{1}H-spectra that show the proton chemical shifts (CS) characteristic of different hydrogens present in its molecular structure. These are assigned to one peak each for aliphatic, two aromatic and hydroxyl (hydrogen-bonded proton) protons. (See the NMR spectrum, Figure 17)

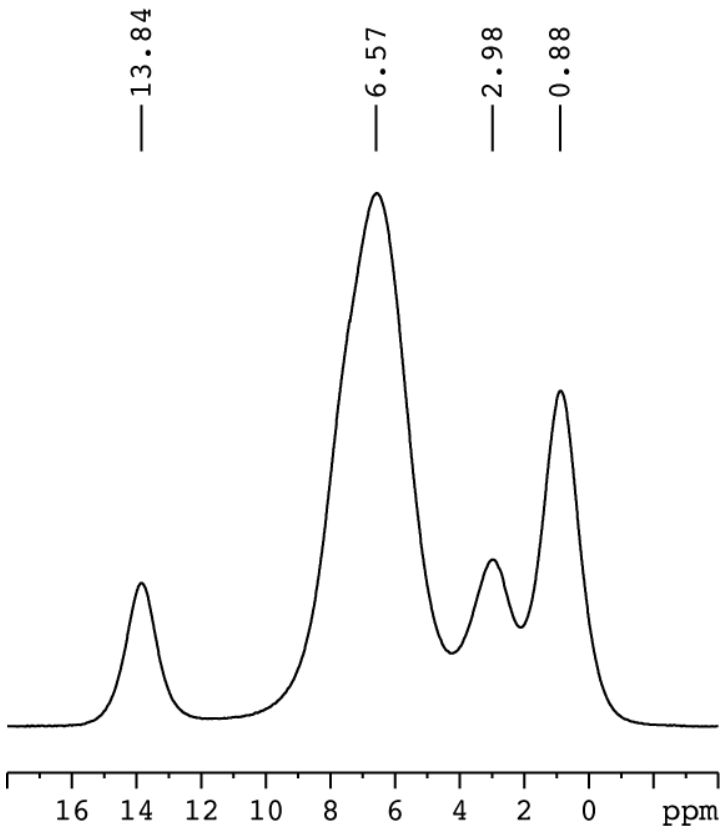


Figure 17 | ^{1}H Spectrum of indomethacin (MAS NMR 700 MHz, at 280 K under MAS 33 kHz)

A partial CASTEP geometry optimization of the structure was performed. We fixed the heavy atoms, and allowed the hydrogen atoms to relax. The CASTEP hydrogen bond distances and angle give calculated chemical shifts that are consistent with the experimental NMR chemical shift calculations (Figure 19).

The chemical shifts obtained at various temperatures are plotted (Figure 18). Proton chemical shift variations with temperature are observed. The proton NMR chemical shift for hydrogen-bonded (OH) proton tends to go upfield with an increase in temperature. This change is more noticeable than that for the

other hydrogens (Figure 19). We extrapolated these chemical shifts to 0 K and compared with that of the CASTEP calculations (effectively done at 0 K). The ^{1}H CS observed for OH at 250 K (26.7 C) is 13.01 ppm whereas at 0 K (-273.15 C), it was extrapolated to 14.44 ppm. This trend is shown clearly in the charts. This result can be interpreted in light of literature reports where the H-bond strength was correlated with the H-bond distances; and here we show a correlation between the lower proton chemical shifts with the increase in temperature. The H-bond is apparently weakened upon an increase in temperature. In other words, at lower temperature the hydrogen bond is stronger, and the bond distance and angle is lower (e.g. at 0 K) according to the CASTEP geometry optimization. This relationship between the H-bond distances with CS is in good agreement with the literature. Thus, the effect of the hydrogen bonding on the chemical shift is decreased with an increase in hydrogen bonded (distance). The calculations reproduce the experiments well. We performed temperature variable experiments on NMR spectrometer by using two different types of cooling systems (one of which is indicated as “small fridge” in table 1, effecting in different temperature range); and we confirmed the cooling rate or method do not much affect the proton chemical shift values obtained for indomethacin (Figure 20).

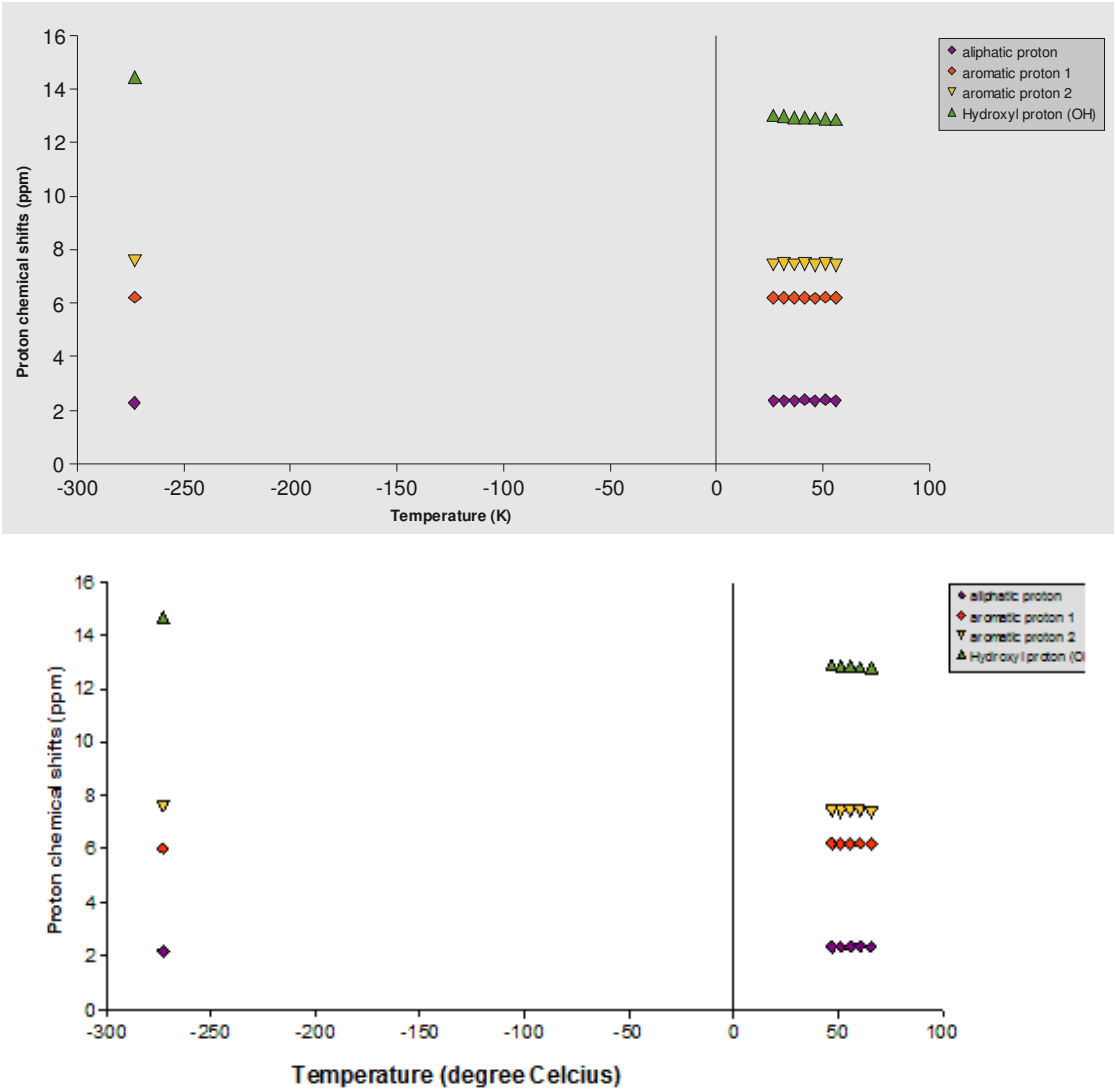


Figure 18 | NMR experiments on indomethacin shows the temperature dependence of ^{1}H-chemical shifts for all of its hydrogens. These two figures indicate the NMR experiments done under two different air flow (670 l/h and 800 l/h, two different figures above); which does not seem to affect the measurements of ^{1}H chemical shifts. (See figure 20)

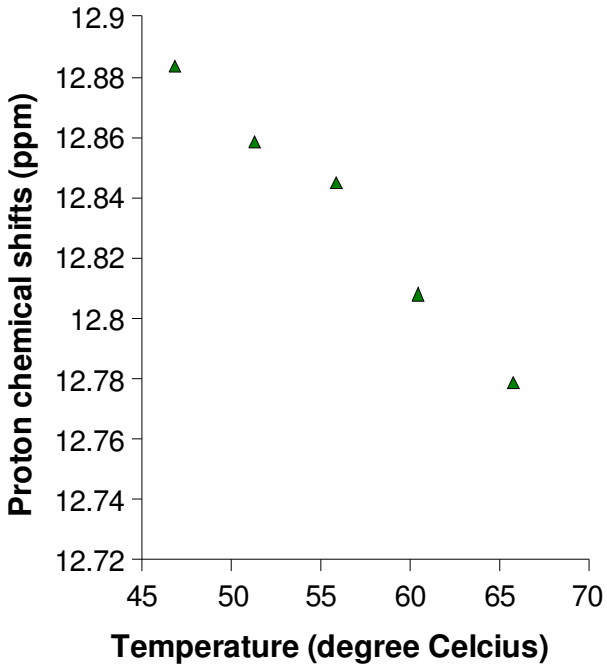


Figure 19 | NMR experiments on indomethacin shows the temperature dependence of ^{1}H-chemical shifts for the hydrogen bonded proton (OH).

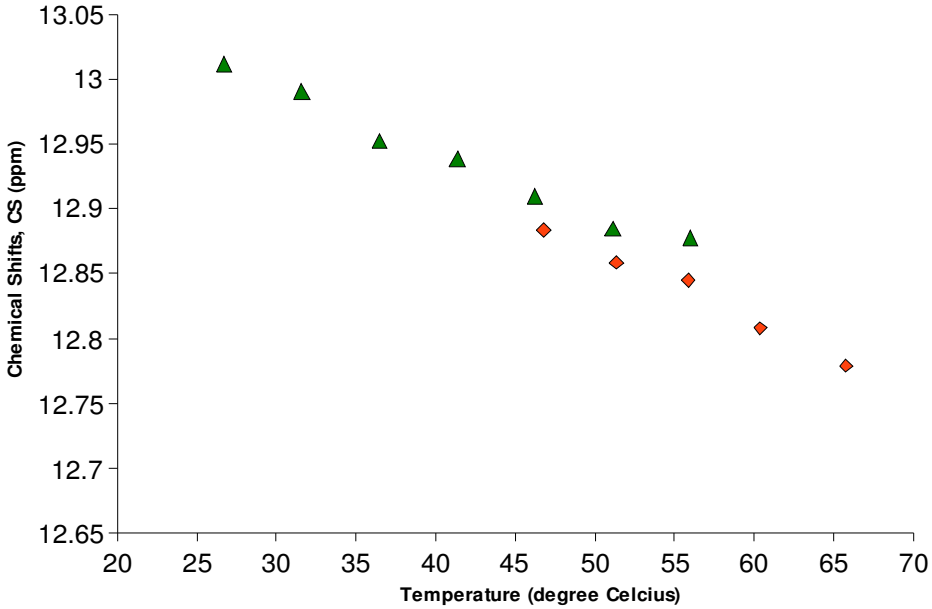
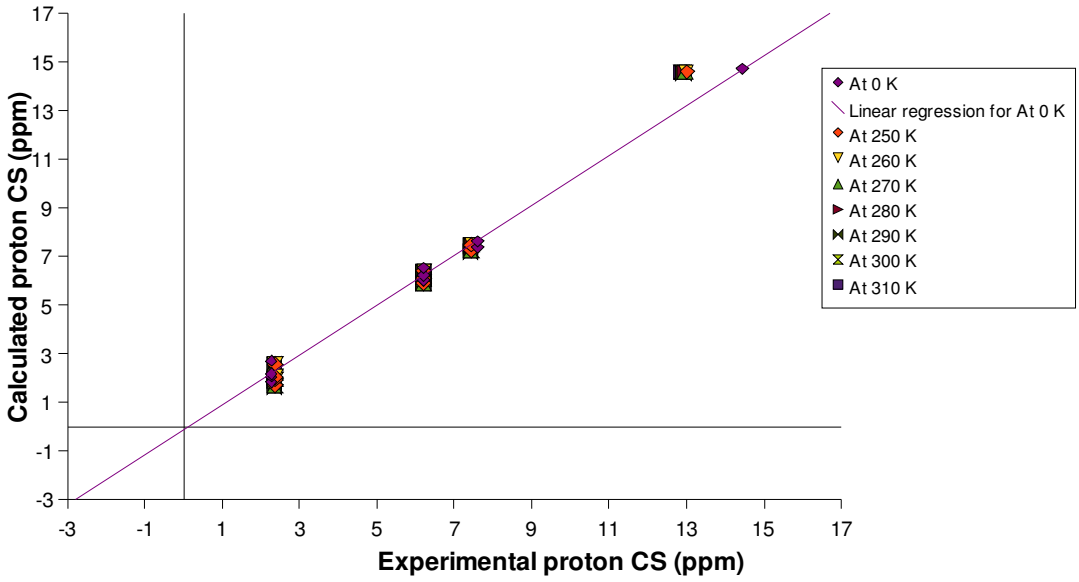
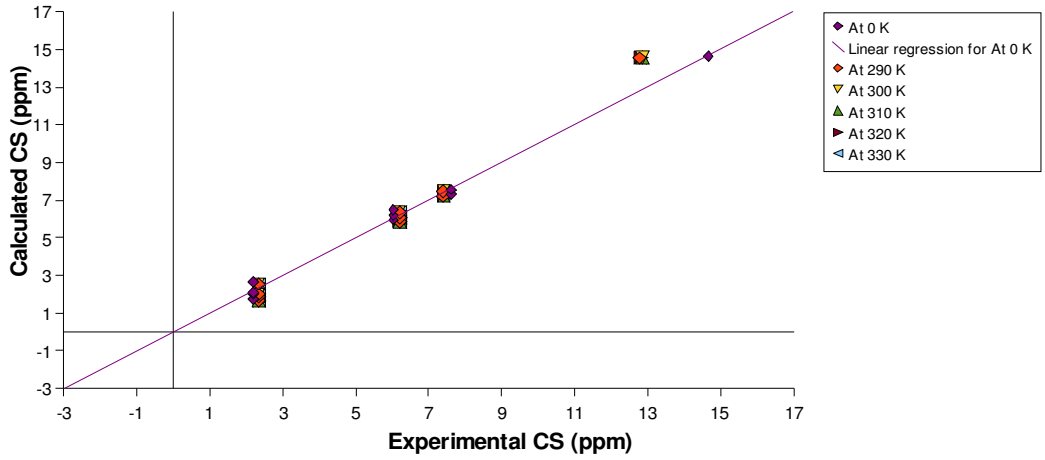


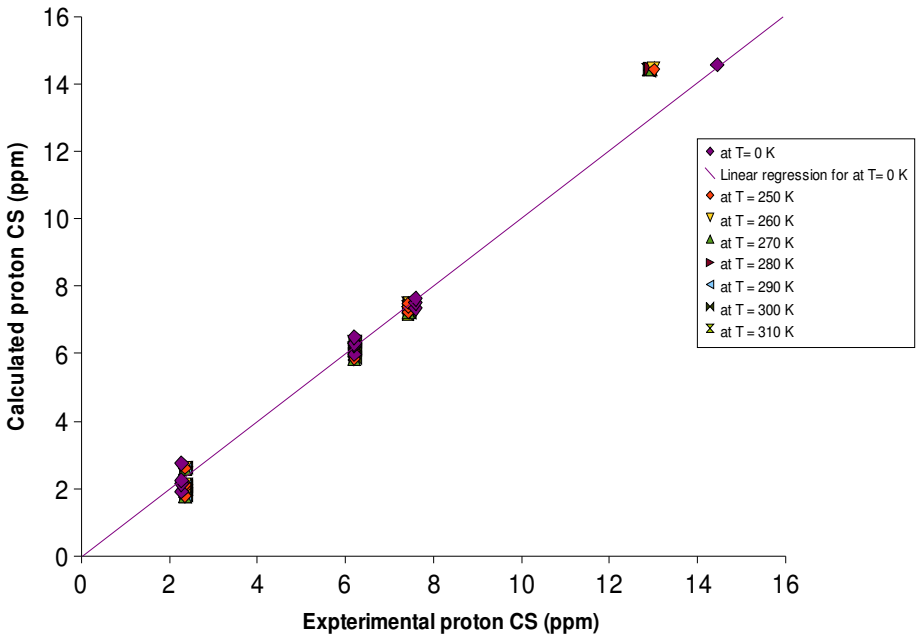
Figure 20 | NMR experiments on indomethacin under two different air flow rate (535 l/h and 800 l/h) shows no remarkable discrepancies with their experimental chemical shift values (six green triangles are for big fridge, and rest red diamonds are for small fridge).


Calculated proton CS (ppm)
Experimental proton CS (ppm)
At 0 K
Linear regression for At 0 K
At 250 K
At 260 K
At 270 K
At 280 K
At 290 K
At 300 K
At 310 K

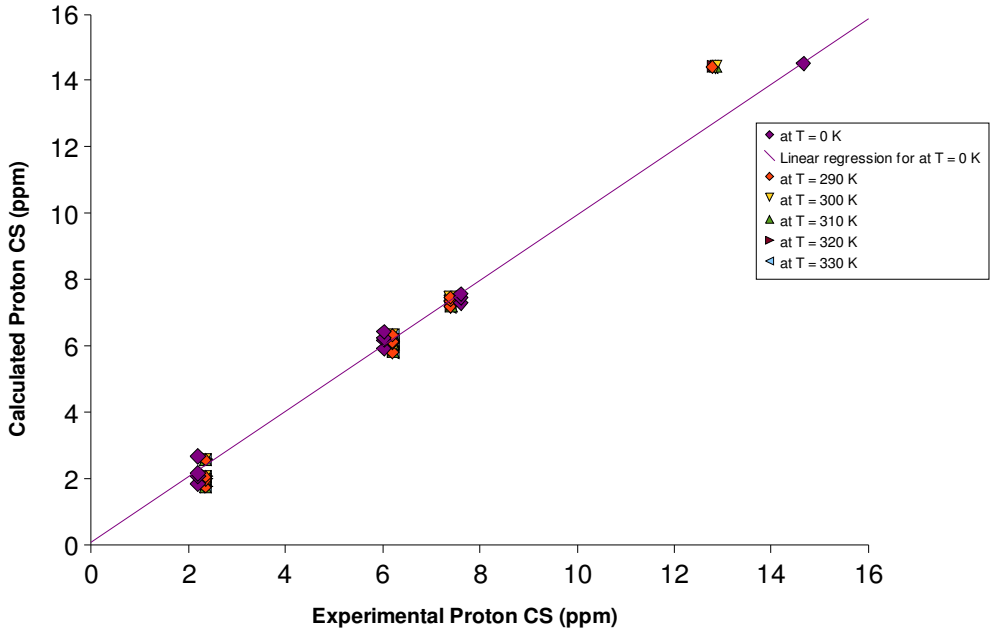
[a]


Calculated CS (ppm)
Experimental CS (ppm)
At 0 K
Linear regression for At 0 K
At 290 K
At 300 K
At 310 K
At 320 K
At 330 K

[b]



[c]



[d]

Figure 21 | Charts showing the calculated ^{1}H-chemical shifts versus the CASTEP calculated ^{1}H-chemical shifts at variable temperatures for indomethacin (CSD Ref. codes: INDMET03

and INDMET) at various temperatures; the figures 21 [a] and 21 [b] are for INDMET03 under different cooling systems (Refer to normal, and small fridge; See the Table 1), and the figures 21 [c] and 21 [d] are for INDMET under different cooling systems (Refer to normal, and small fridge; Please refer to the Table 1). The agreement between the experimental and calculated CS does not depend much on the temperatures at which the structures (INDMET03 & INDMET) were determined.

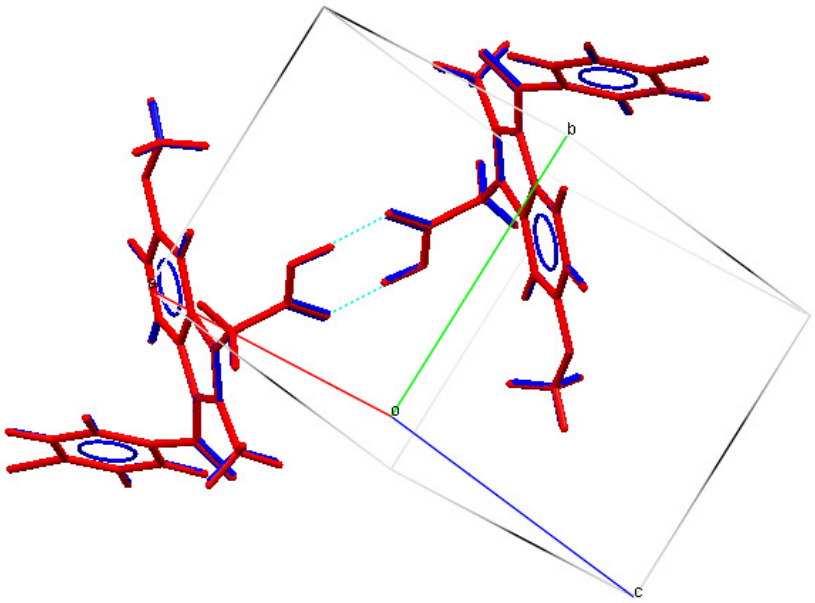


Figure 22 | The close contact between H and the O (OH…O) in the indomethacin (INDMET03) crystal; before geometry optimization (blue) and after geometry optimization (red) of INDMET03 structures

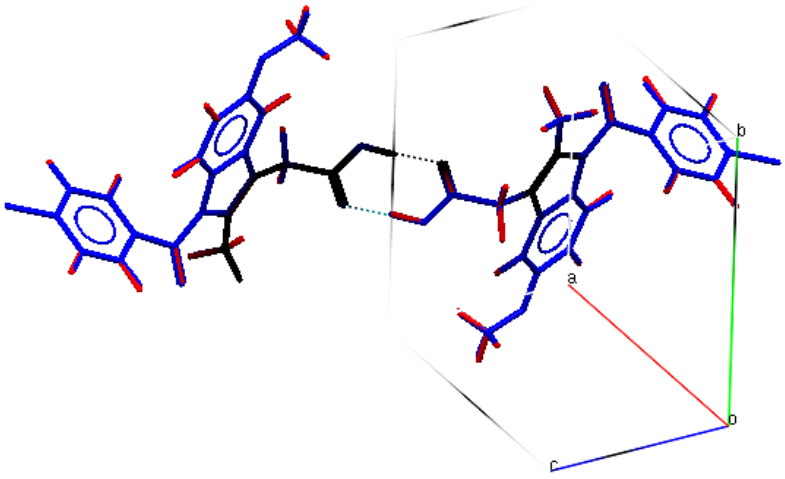


Figure 23 | The close contact between H and the O (OH…O) in the indomethacin (INDMET) crystal; before geometry optimization (blue) and after geometry optimization (red) of INDMET structures

Table 5 | Bond distances and bond angle (INDMET03)

Chemical bond	Bond distances (in Angstrom)	
	Before CASTEP G.O.	After CASTEP G.O.
O-H	0.908	1.022
OH----O	1.748	1.633
C-H	0.980	1.096
C-H aromatic	1.950	1.088

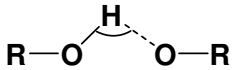
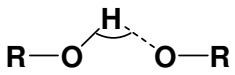
Bond Angle (in degrees)	Before CASTEP G.O.	After CASTEP G.O.
	172.54	173.24

Table 6 | Bond distances and bond angle (INDMET)

Chemical bond	Bond distances (in Angstrom)	
	Before CASTEP	After CASTEP G.O.*
O-H	1.061	1.021
OH----O	1.608	1.650
C-H	0.967	1.097
C-H aromatic	0.951	1.089

Bond Angle (in degrees)	Before CASTEP G.O.	After CASTEP G.O.
	174.72	173.08

* G.O. = geometry optimization

Tables 5 and 6 show the bond distances and bond angle before and after geometry optimization for two different indomethacin (INDMET03, INDMET) structures. This indicates that the hydrogen atoms are differently placed in X-ray studies. The chemical shift agreement (RMSD) between calculated and experimental CS shows that their placement after geometry optimization agrees with what is measured by NMR. More information could be used to explain the conformation of the molecular structure, and geometry of the hydrogen bond upon CASTEP geometry optimization (Figure 22, 23). In this case of two indomethacin structures, we find that O-H…O angle is reduced; and thus an evidence for a stronger intermolecular H-bonding (interaction) in the crystal lattice. We see the close contact between H and the O (OH…O) in two different indomethacin molecules (Figure 22, 23). INDMET03 is an X-ray

structure studied at 120 K and the other one INDMET was studied by X-ray at room temperature. From the calculated chemical shift data, we conclude that indomethacin gave higher chemical shift values due to the stronger hydrogen bond and less OH…O distance at lower temperature. This trend agrees with the earlier report in literature.[99,14]

Paracetamol (melting point 169 - 172 ^{0}C)

Paracetamol or acetaminophen is a widely-used analgesic and antipyretic.[104,105] It consists of a benzene ring core, substituted by one hydroxyl (OH) group and the nitrogen atom of an amide group in the para pattern. It is an extensively conjugated system, as the lone pair on the hydroxyl oxygen, the benzene π cloud, the nitrogen lone pair and the *p* orbital on the carobonyl carbon are all conjugated. The conjugation greatly reduces the basicity of the oxygens and the nitrogen, while making the hydroxyl acidic thorough delocalization of charge developed on the phenoxide anion. These polar groups in paracetamol always favor the formation of hydrogen bonds.[106]

In paracetamol, the temperature dependence of some of the amide proton is observed by invoking N...H...O instead of a covalent representation NH...O which results in a lengthening of the N–H separation and the peptide structure is intermediate between amide-like (–OCNH) and imidol-like (HOCN).[106]

Solid state high resolution NMR experiments were performed on paracetamol at various temperatures to yield ^{1}H-spectra. Five resolved peaks characteristic of five different hydrogen sites present in its molecular structure were obtained. These are assigned to aliphatic methyl group, aromatic-H and two undistinguishable hydrogen bonded protons each one from amide (-NH) and hydroxyl (OH) group. (See the NMR spectrum, Figure 24) However, in variable temperature experiments run on a new 900 MHz spectrometer, the CS (Figure 25) from these experiments change too much with temperature to be believed.

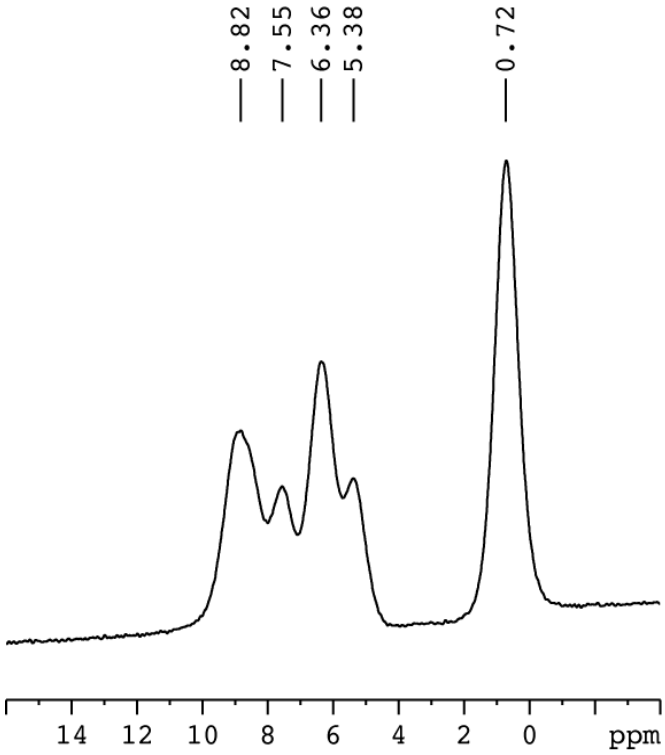


Figure 24 | ^{1}H Spectrum of paracetamol (MAS NMR 900 MHz, at 247K)

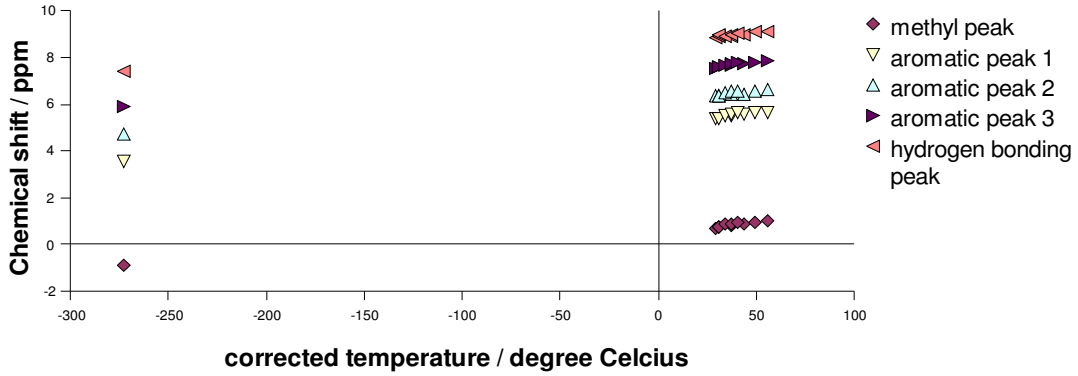


Figure 25 | The experimental CS (not believable) for the inconsistent temperature dependence of chemical shifts in paracetamol; error correction was made by using reference chemical shift variation, adamantane, and displayed in Figure 26.

Variable temperature experiments were run on the same NMR spectrometer for adamantane, whose ^{1}H chemical shift is normally insensitive to temperature. However, on the 900 MHz NMR spectrometer, chemical shifts for adamantane also change as a function of temperature. This confirms that experiments performed on paracetamol were wrong not because of the samples, but because of a problem with the shim coil in spectrometer. A correction was made to this error by performing the variable temperature experiments on adamantane. We found the change in the CS with change in temperature; which is surely because of the bad shim coil. We tried to correct the error and plotted new experimental data (Figure 26). The temperature calibration and chemical shift correction are still not certain, so when the problems with the shim coils are fixed, the variable temperature experiments will be repeated.

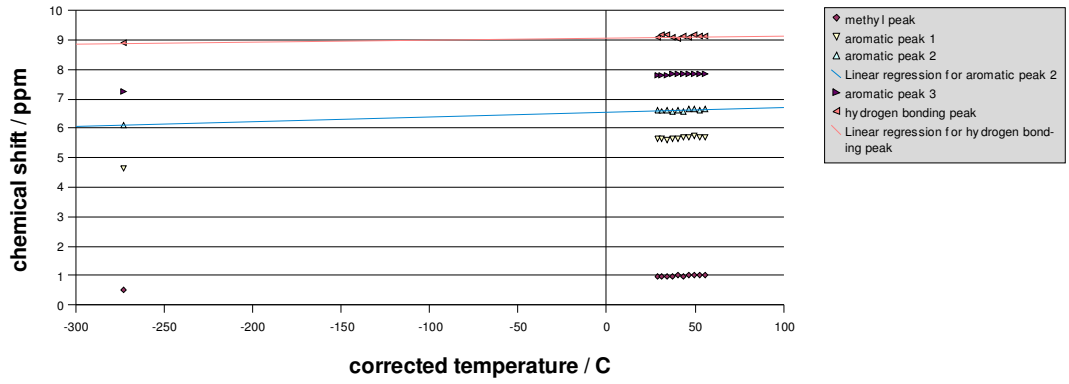


Figure 26 | NMR experiments on paracetamol shows the temperature dependence of ^{1}H-chemical shifts for all of its hydrogens (including that for the hydrogen bonded proton); since the previous experimental CS (Figure 25) were not believable for its inconsistent temperature dependence values, these experiments were obtained from the corrected

temperature, and corrected chemical shifts (using adamantane as reference) to find the believable experimental data (error correction for bad shim-coil in NMR spectrometer).

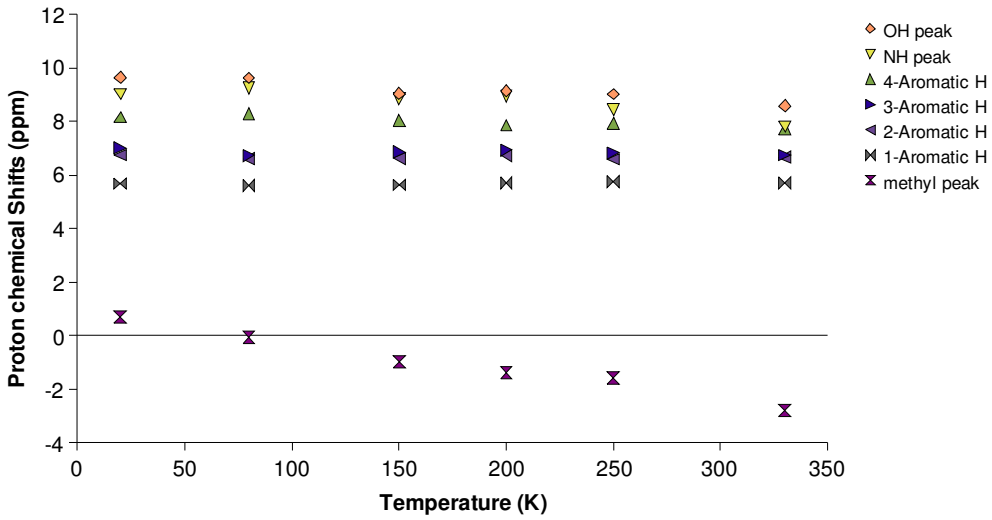
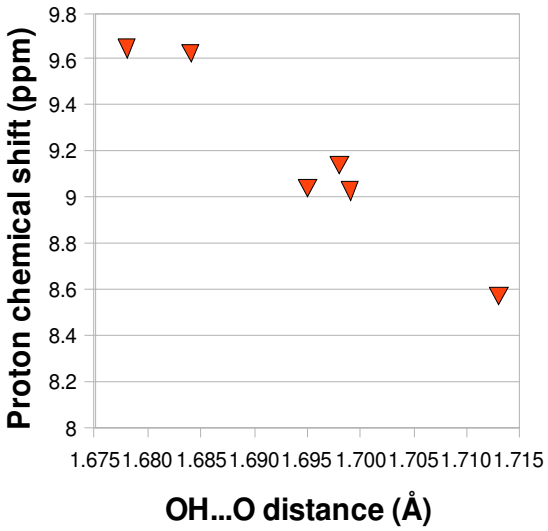
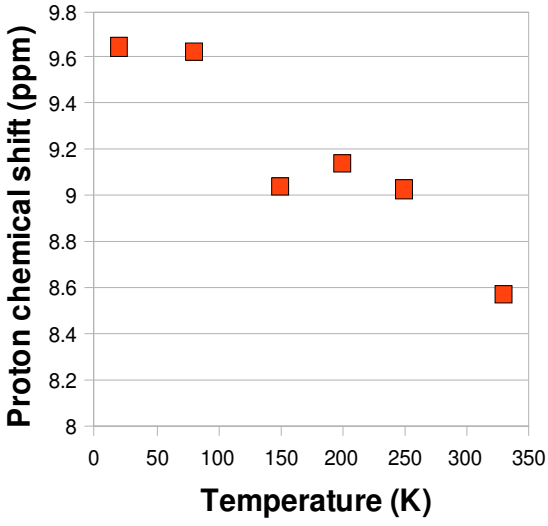


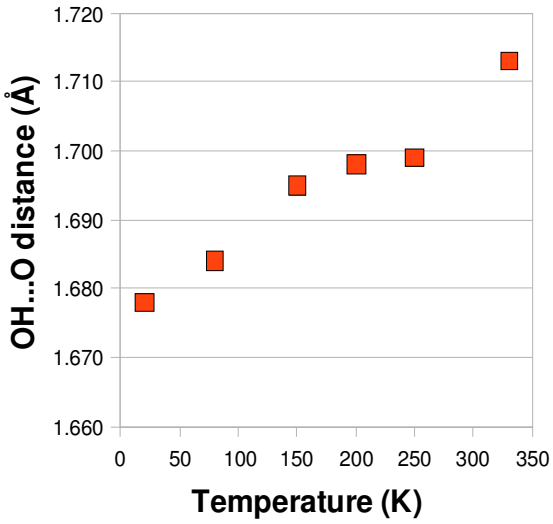
Figure 27 | Paracetamol: Chart for the temperature dependence of ^{1}H-chemical shifts calculated with reference to the "averaged reference value"

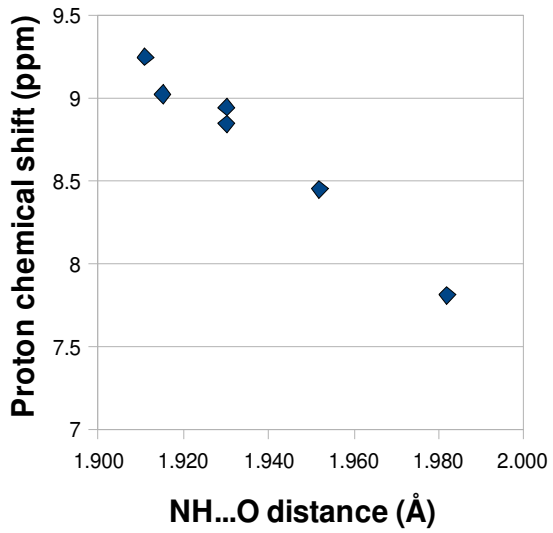
The structures of paracetamol used in calculations in this study were obtained from the CSD. The reference codes are HXACAN13, HXACAN15, HXACAN16, HXACAN17, HXACAN18, and HXACAN 19. Wilson C. C. reported these structures resulted from the neutron diffraction studies at various temperatures.[98] We consider that the neutron diffraction study is advantageous over the X-ray diffraction in placing light atoms in their proper positions. So we did not perform the geometry optimization using CASTEP; instead we directly calculated a set of chemical shifts for the selected structures of paracetamol.[98] In order to reference the chemical shifts obtained

from CASTEP, we used an appropriate “averaged referenced value” (30.91 ppm) equal to the average reference value from three other data sets (ibuprofen, flurbiprofen, and indomethacin). Since the paracetamol structure is very interesting for studying hydrogen bonding, we decided to continue using CASTEP to correlate the H-bond distances and strength with calculated chemical shifts at different temperatures.






1.720
1.710
1.700
1.690
1.680
1.670
1.660
OH...O distance (Å)
0
50
100
150
200
250
300
350
Temperature (K)


9.5
9
8.5
8
7.5
7
Proton chemical shift (ppm)
1.900
1.920
1.940
1.960
1.980
2.000
NH...O distance (Å)

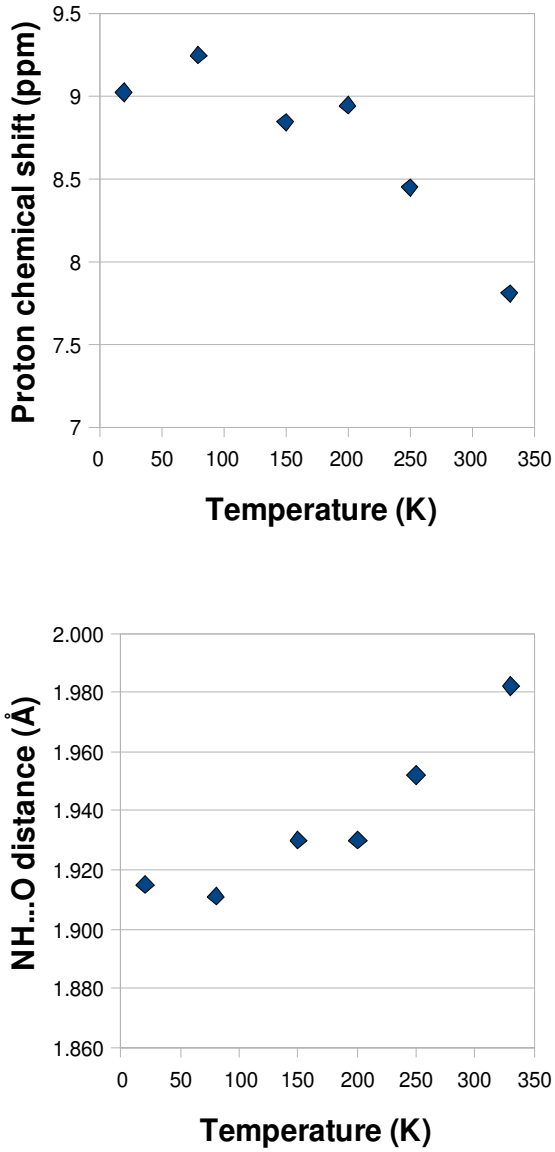


Figure 28 | NMR calculation on paracetamol shows the relationship between temperature dependence of ^{1}H-chemical shifts and the bond distances that involve hydrogen bonded protons; bond distances were measured on the neutron crystal structures obtained at various temperatures (Table 1). Please refer to Fig. 24 & 25, for the peaks for NH and OH which are not well resolved in experiments and not well distinguished in NMR spectrum.

We found that the H-bond is weakened upon an increase in temperature. In other words, at lower temperature the H-bond is strong, and the bond distance and angle is lowered. Thus, the effect of the hydrogen bonding on the chemical shift is decreased with an increase in through-space hydrogen bond distance (Figure 28,29). We anticipate the experiments will reproduce well our "average referenced" calculated chemical shifts at various temperatures.

In paracetamol, tunneling and librational excitations for the methyl group were invoked to explain the NMR observables related to H-bonds quantitatively. But the agreement between molecular mechanics calculated and measured methyl group observables were not as good as expected.[106] In our case study, we expect to reproduce the NMR trend calculated by CASTEP. These calculations confirm the validity of the crystal structures.

Table 7 | The following data is obtained from the CSD; and these structures were studied by Neutron diffraction at various temperatures. This data clearly shows that the light atomic positions are surely not well explained by the neutron diffraction studies.

Part I:

Paracetamol Structures (CSD Codes)	**OH bond distance**	**OH...O**	**C=O...O**	**O-H...O bond angle**
HXACAN13 (at 20 K)	**0.989**	**1.678**	**2.646**	**165.31**
HXACAN15 (at 80 K)	**0.988**	**1.684**	**2.654**	**166.38**

HXACAN16 (at 150 K)	**0.973**	**1.695**	**2.652**	**166.94**
HXACAN17 (at 200 K)	**0.979**	**1.698**	**2.669**	**166.79**
HXACAN18 (at 250 K)	**0.976**	**1.699**	**2.659**	**166.66**
HXACAN19 (at 330 K)	**0.964**	**1.713**	**2.660**	**166.77**

Part II:

Paracetamol Structures (CSD Codes)	**NH bond distance**	**HO…HN bond distance**	**OH…HN**	**O-H...N bond angle**
HXACAN13 (at 20 K)	**1.006**	**1.915**	**2.621**	**163.89**
HXACAN15 (at 80 K)	**1.005**	**1.911**	**2.605**	**162.97**
HXACAN16 (at 150 K)	**1.004**	**1.930**	**2.608**	**163.20**
HXACAN17 (at 200 K)	**1.010**	**1.930**	**2.614**	**163.52**
HXACAN18 (at 250 K)	**0.994**	**1.952**	**2.625**	**162.61**
HXACAN19 (at 330 K)	**0.978**	**1.982**	**2.640**	**162.66**

The table 7 (part I, II) show the bond distances and bond angles of different structures obtained at different temperatures by using neutron diffraction.[98]

We calculated the ^{1}H chemical shifts from CASTEP without any geometry optimization of these structures.

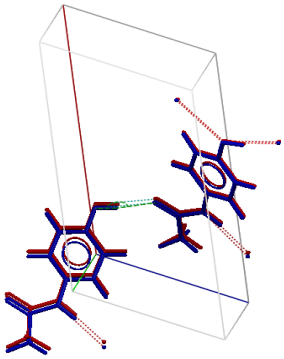


Figure 29 | The close contact shown for the H-bonded atoms in paracetamol structures at two different temperatures (blue: 20 K; violet: 330 K) studied under neutron radiations. Prominent change in (hydrogen bond) structures is observed with respect to change in temperature.

For the physico-chemical properties of phenolic carboxylic acids, intra- and intermolecular hydrogen bonding is very important, even structure-determining.[107, 108,8] Information gained from FT-IR and NMR spectroscopies certainly help clarify the influence of structural parameters on the physico-chemical properties of H-bonded compounds.[109] We studied temperature dependence of H-bonded intermolecular contacts in the form of chemical shifts in the structure. Those examined are close contacts of hydrogen atoms to oxygen and nitrogen atoms with (H…O, H…N distances of in the range of 1.678-1.713 A^{0} and 1.915-1.982 A^{0} respectively at temperatures rising from 20 K to 330 K (Table 7). This data explains the temperature dependence of bond distances, bond angle for paracetamol structure. The similar trend is

correlated between chemical shifts and the distances in order to explain the strength of H-bonds.

The ^{1}H chemical shifts are obtained by performing CASTEP calculations on paracetmol structures.[98] The CS data set support our hypotheses:

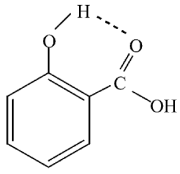
(i) Chemical shifts of hydrogen bonding protons decrease as temperature increases

(ii) Chemical shifts of hydrogen bonding protons increase as hydrogen bond strength increases (or the distance between hydrogen and hydrogen- bond acceptor decreses)

Please see the trend in figure 28 and table 6 and 7.

Salicylic acid (melting point 159 °C)

The pharmacological effects, as well as the physiological side-effects of salicylic acid (SA), are due to its structural features, so the active moiety for the cyclooxygenase (COX) inhibition appears to be the salicylate anion, while side-effects appear to be associated with the carboxylic acid functional group.[110]



SA

In SA molecule, the functional groups –COOH and –OH are adjacent, which make it form a strong intramolecular hydrogen bond in a six-membered ring. This intramolecular hydrogen bond has previously been postulated to weaken the dimeric hydrogen bond in salicylic acid[111] and this leads to the non-formation of stable enough SA–SA dimer in the crystal packing. It could be interesting to find this trend reflected in our experimental and calculated chemical shifts with respect to temperature. The effects of the structural features on the physico- chemical properties and on the bioactivity of these compounds are very important and are already investigated in numerous theoretical and experimental studies.[112-116]

High resolution solid state NMR experiments were performed on salicylic acid to yield ^{1}H CS. These are assigned to aromatic, OH, and COOH (hydrogen bonding) protons. (See the NMR spectrum, Figure 30). The chemical shifts obtained at various temperatures are plotted (Figure 31). Proton chemical shift variations with temperature are observed. This change is more noticeable than

that for the other hydrogens. In the literature,[99] the H-bond distance is correlated to the chemical shift values. When we increase the temperature, the H-bond distance is increased; and consequently the hydrogen bond becomes weaker and ^{1}H chemical shift values are lowered. On the contrary our CASTEP ^{1}H CS calculations for the neutron structures of salicylic acid does not support the literature trend.[99] The ^{1}H-CS observed for COOH and OH at 300 K is 11.96 ppm and 9.28; whereas at 0 K, those were extrapolated to 9.88 and 9.28 ppm respectively. A relationship between the H-bond distances with the H-bond strength was reported by Berglund and Vaughan.[99] We see that as we increase the temperature, the OH…O bond distance is increasing and thus the H-bond is weakened. In addition to this, the intramolecular H-bonding in salicylic acid is supposed weaken the dimeric bonding in its crystal structure.[111] This is well reflected by the higher chemical shifts observed for OH than that of the COOH and the strength of the H-bond with respect to change in temperature and bond distances (Figure 31).

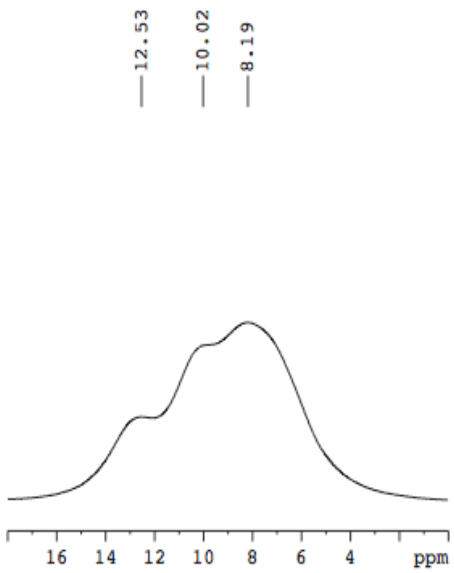


Figure 30 | ^{1}H Spectrum of salicylic acid (NMR 700 MHz, at 250K, MAS rate 22 kHz)

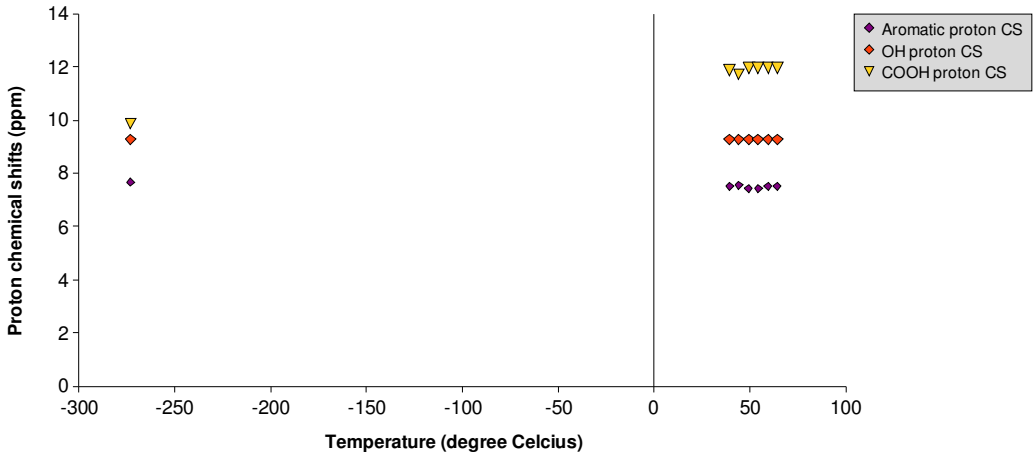


Figure 31 | NMR experiments on salicylic acid shows the temperature dependence of ^{1}H-chemical shifts for all of its hydrogens.

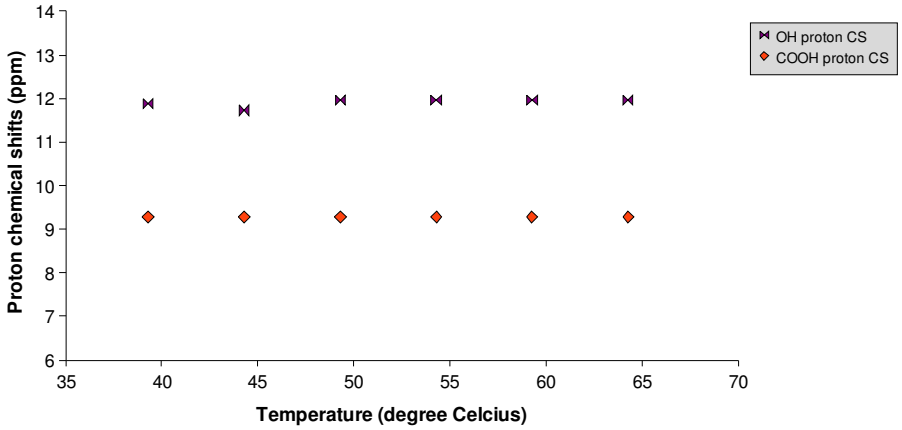


Figure 32 | NMR experiments on salicylic acid shows the temperature dependence of ^{1}H-chemical shifts for the hydrogen bonded protons.

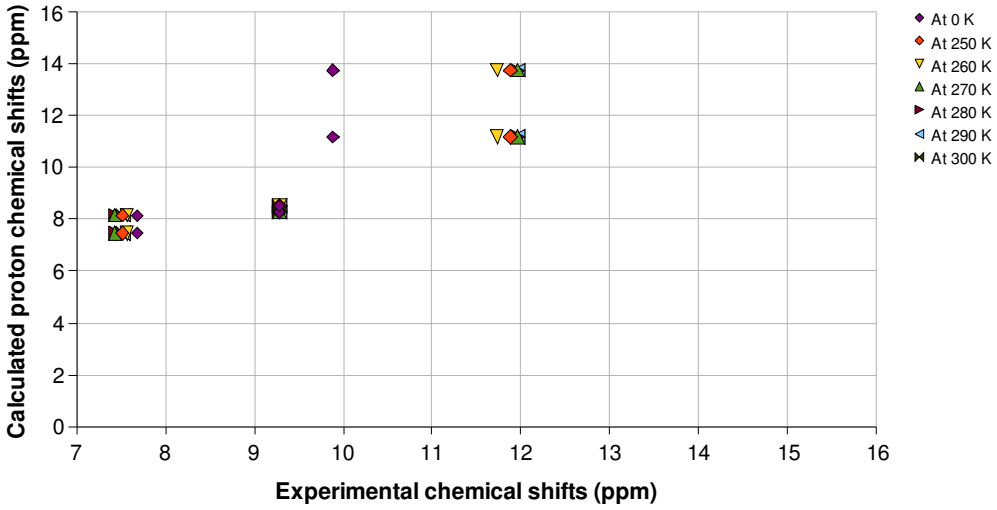


Figure 33 | Salicylic acid (CSD RefCode-SALIAC12): Chart for the comparison of experimental and calculated ^{1}H-chemical shifts at various temperatures

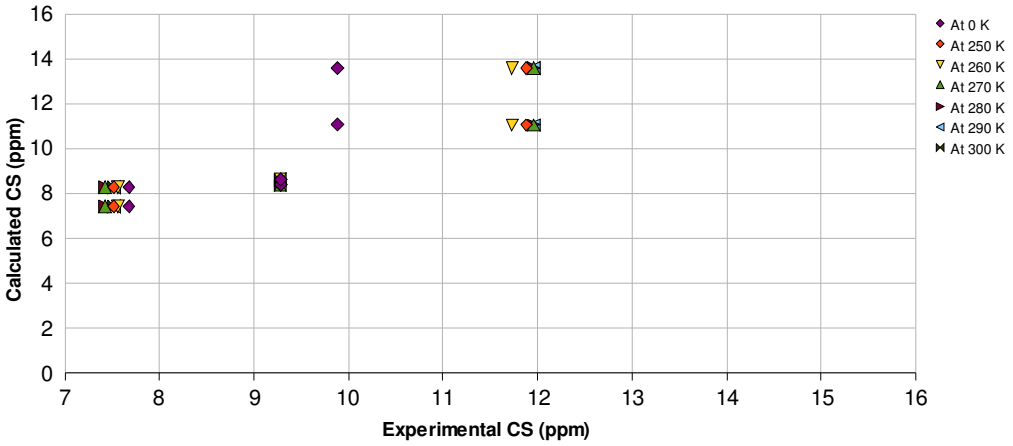


Figure 34 | Salicylic acid (CSD RefCode-SALIAC16): Chart for the comparison of experimental and calculated ^{1}H-chemical shifts at various temperatures

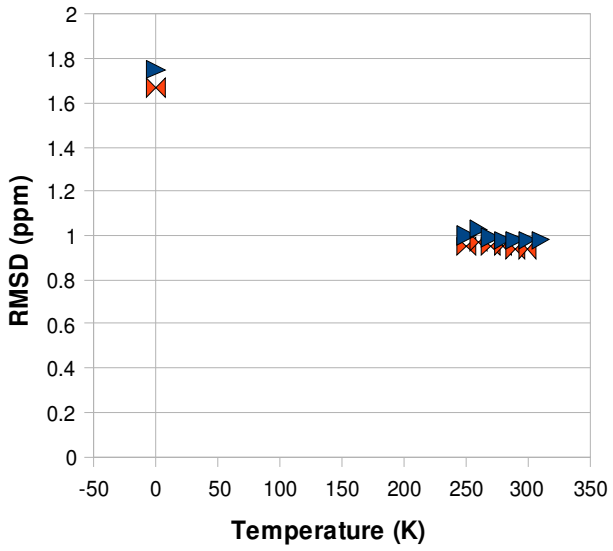


Figure 35 | Salicylic acid (CSD Ref. Code-SALIAC12&16): Chart for the comparison of rmsd for two different salicylic acid structures (blue: SALIAC12, orange: SALIAC16); but not good agreement was found with that of the 0 K calculations. This failure is caused due to the low MAS rate.

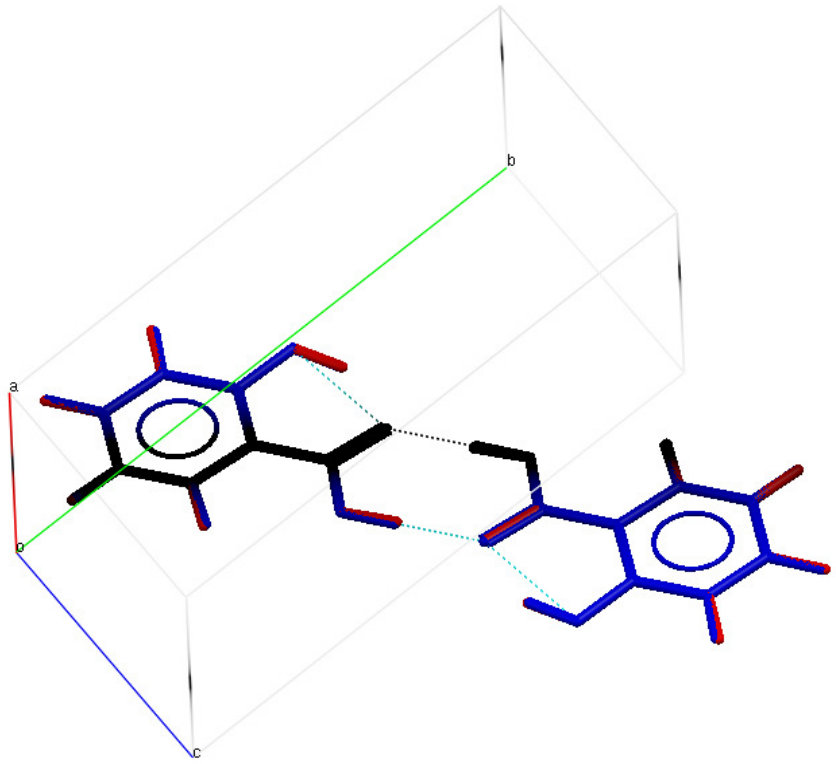


Figure 36 | The close contact shown for the H-bonded atoms in salicylic acid (SALIAC12) structures studied under neutron radiations. Prominent change in (hydrogen bond) structures is observed with geometry optimization (red) and without geometry optimization (blue).

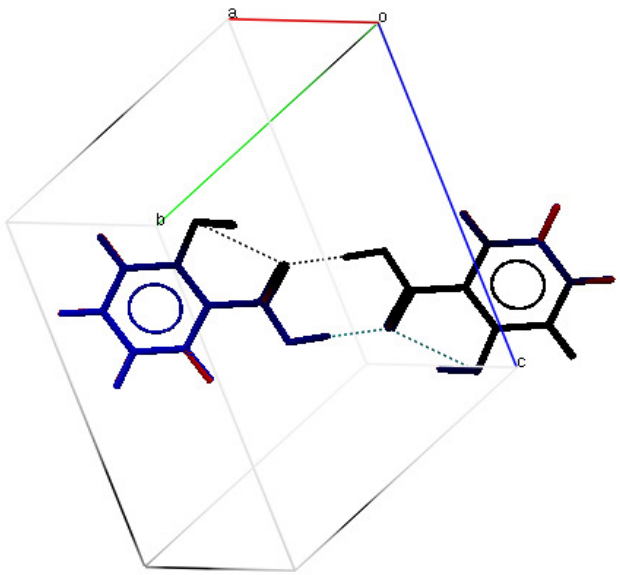


Figure 37 | The close contact shown for the H-bonded atoms in salicylic acid (SALIAC16) structures studied under neutron radiations. Prominent change in (hydrogen bond) structures is observed with geometry optimization (red) and without geometry optimization (blue).

The reason for the much noticeable difference between the rmsd at 0 K and variable temperature experiments could be accounted for the limitations of NMR spectrometer which used very low MAS rate of only 22 kHz. And at such spinning rate, one can really not expect very well resolved proton peaks in the spectra. Consequently, the averaged experimental CS values were not precise which led us to the different in rmsd values. This is suffice to say that even under such poor NMR experimental conditions, we are able to find the relationship between chemical shifts and the temperature; and their comparison with the static DFT calculations at 0 K. Though we reproduce the

trend, we failed to get precise measurements from NMR experiments due to the slow magic angle spinning.

4.3 Scope and applications

There is much current interest in short, strong hydrogen bonds. The possible transfer of protons through such linkages enables charge and energy to be transferred between molecules in solid chemical and biological systems and has widespread implications for issues as diverse as ferroelectrics, electrochemical processes, crystal engineering, and enzyme action.[117] In contrast to normal and weak hydrogen bonds, very strong hydrogen bonds have a quasi-covalent character. In the resulting three-center four-electron bond, the H-atom is involved in two partial covalent bonds of comparable bond orders (i.e., X-H-Y); In these, a rich variety of short, strong hydrogen bonds is found to be present in a relatively simple framework and is therefore very suitable for in-depth study by experimental and computational methods.

Much effort has been devoted in the past decade to the study, design, and understanding of the aggregation of organic molecules.[118-120] The considerable interest in the field has been based on the fact that crystal engineering, the ability to predict the strength or direct the molecular arrangements, can be used to tailor materials of biological or technological importance. In this context, intermolecular hydrogen bonds are an effective tool for organizing organic molecules. Furthermore, some packing forces and intermolecular interactions in the crystal play a crucial part in the final macroscopic properties of these materials. So, understanding these intermolecular interactions should

help toward understanding the nature of the macroscopically produced effects.[121-122]

Our study employing NMR and DFT calculations of ^{1}H chemical shifts is very promising to understand the temperature dependent behavior of H-bonds existing in molecular crystals. This approach is applied as a probe to understand the structural features and behavior of solids, and find their usage as from crystal structure validation to their applications in many fields such as the ones mentioned in previous two paragraphs.

Chapter 5

Conclusion

The main goal of the present project is to study the temperature dependence of ^{1}H chemical shifts and relate them to structural changes in the molecule or crystal. The NMR studies indicate that the systems studied have hydrogen bonds in which the proton gradually becomes disordered or move as the temperature is increased. In principle, bond-distances can also be related to correlate the hydrogen bonding chemical shifts at different temperature.

The work presented here is aimed at understanding strong hydrogen bonding in crystalline organic molecules. By complementing experimental measurements with theoretical calculations, we try to build a more complete picture of the electronic effects governing the description of such hydrogen bonds.

High resolution solid state NMR experiments were performed on ibuprofen, flurbiprofen, and indomethacin to yield ^{1}H chemical shifts (CS). The peaks were assigned to different protons including the ones in hydrogen bonds. The chemical shifts obtained at various temperatures were plotted and the proton chemical shift variations with temperature were observed. The proton NMR chemical shift for the hydrogen-bonded (OH) proton was seen to tend upfield with increase in temperature. This change was more noticeable than that for the other hydrogens. We extrapolated these chemical shifts to 0 K. We show that the ^{1}H chemical shifts computed by CASTEP (effectively at 0 K) from the X-

ray and the experimental ^{1}H CS extrapolated to 0 K [124] from those obtained by variable temperature NMR experiments are comparable and in good agreement.

We fail to get a good agreement between the calculated and experimental proton chemical shifts for salicylic acid for we could not get well resolved proton peaks in the spectra upon a very poor magic angle spinning rate in NMR experiments. But the calculated CS were helpful to validate the dimeric structure.

In an another case study, we employed CASTEP to perform the ^{1}H chemical shift calculations of neutron structures of paracetamol obtained at different temperatures.[98] The trend for the proton chemical shift variations with temperature were reproduced, and the correlation with OH…O and NH…O distance is as expected. By comparing the paracetamol structures studied by neutron diffraction at various temperatures (Table 1) and their calculated proton chemical shifts, we conclude that as the hydrogen bond gets weaker, the ^{1}H CS have lower chemical shift values.

The ^{1}H chemical shifts calculations using CASTEP on neutron structures of paracetamol support our hypotheses:

(i) Chemical shifts of hydrogen bonding protons decrease as temperature increases

(ii) Chemical shifts of hydrogen bonding protons increase as hydrogen bond strength increases (or the distance between hydrogen and hydrogen-bond acceptor decreases)

Proton transfer or proton disorder has been studied by variable-temperature diffraction studies and reflaxometry.[89,123] Our research approach is unique for it proposes a method to validate X-ray and neutron crystal structures at variable temperatures by the combination of NMR experiments and CASTEP calculations so as to understand the ^{1}H position at high temperatures and intermolecular interactions. In view of the literature,[99,14] our application of CASTEP reproduced a relationship between the H-bond distances with the H-bond strength for ibuprofen, flurbiprofen, and indomethacin (all X-ray crystal structures); and also for paracetamol (neutron structures at low to high temperatures). This was done by exploiting the temperature-dependent disorder in hydrogen bonds. We used a novel approach addressing the concept of hydrogen bonding for structural study as a measure of temperature-dependence of proton chemical shifts.

The investigation of the intermolecular short hydrogen bond in small organic molecules using plane-wave density functional theory suggests *dynamics*. Simulations indicate that the strength of hydrogen bonding is well explained by behavior of the proton which is temperature-dependent. Inspired by our computations and SS NMR experiments, we offer a possible explanation for the hydrogen bonding and proton migration phenomenon in organic crystal (dimer) structures. As the temperature is increased, the proton chemical shifts tend to move upfield. This suggests that the hydrogen bond gets weaker upon an increase in temperature.

Explaining Hydrogen Bonds with Temperature-Dependent Protons:

We suggest that a possible explanation for the proton migration effect is due to coupling between the thermal influences on electronic bridging modes with the O-H standard hydrogen bond stretch. In almost all the organic molecular crystals under study (except salicylic acid), dimers contain slightly elongated O-H bonds than the usual, suggesting that the hydrogen atom could potentially exhibit disorder. It could now be recognized that the thermal anomalies of crystals are related to their hydrogen-bond network. And therefore the variable temperature studies help us rationalize organic compound from a basic understanding of the nature and behavior of hydrogen bonding (O-H---O), which could provide pathways for structure-activity correlation, packing in the lattice and assign organic molecules at natural abundance to crystal structures.

This study has shown that we observe temperature-dependent proton mobility in the solid state as evidenced by evolution of chemical shifts for the protons involved in hydrogen bonding. The combination of MAS solid-state NMR spectroscopy and CASTEP chemical shift calculations presents an interdisciplinary approach towards understanding hydrogen bonding and crystal structure validation of small organic molecules. In particular, DFT calculations are achieved using CASTEP by taking into account finite temperature effects in proton chemical shift calculations. This development opens a promising way to the study the *dynamics in solids* with such an interdisciplinary approach. *The underlying goal of this project is achieved by CASTEP calculations to find the "temperature dependence of hydrogen bonding*

as an important factor" that explains the "evolution of proton chemical shifts" in order to suggest the existence of dynamics in molecular crystals.

One could also intend to quantify the temperature-dependent behavior of H-bonds accurately with DFT studies in near future. The effect of perturbing the geometry of the molecules on the possible presence of proton dynamics could also be studied, which is a first step toward being able to quantify such effects.

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Highlights from the literature

"***The discovery of the Hydrogen Bond could have won someone the Nobel Prize, but it didn't***." George A. Jeffrey, Wolfram Saenger

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and the fascination continues ….

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