

# Recent Advances in Theoretical and Physical Aspects of NMR Chemical Shifts

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In the first part of this review, theoretical aspects of nuclear magnetic shielding include (a) general theory, for example, newly developed approaches in relativistic theory of nuclear shielding, the relation between the spin-rotation tensor and shielding in relativistic theory, *ab initio* methods for treating open shell systems and a complete theory of chemical shifts in paramagnetic systems, the link between the definitions of the elusive concepts aromaticity and anti-aromaticity and the magnetic properties: the magnetizability tensor and the nuclear magnetic shielding tensor via delocalized electron currents and electron current maps, (b) *ab initio* and DFT calculations, both relativistic and non-relativistic, for various nuclei in various molecular systems using various levels of theoretical treatment. Physical aspects include (a) anisotropy of the shielding tensor, usually from solid state measurements, and calculations to support these, (b) shielding surfaces and rovibrational averaging, paying special attention to the sensitive relationship between shielding and bond angles or torsion angles that makes shielding such a powerful tool for structural/conformational determination in macromolecules, (c) chemical shifts that arise from isotopic substitution of NMR nucleus or neighboring nuclei, (d) intermolecular effects on nuclear shielding, and (e) absolute shielding scales.

**Keywords:** nuclear magnetic shielding; *ab initio*; relativistic; intermolecular effects; tensor; isotope shift

## THEORETICAL ASPECTS OF NUCLEAR SHIELDING

Chemical shifts that are observed in nuclear magnetic resonance spectroscopy are related to the difference between the fundamental quantities, the nuclear magnetic shielding, of

the nucleus in the sample and the nucleus in the reference substance. Theoretical calculations focus on the fundamental quantity, the nuclear magnetic shielding,  $\sigma$  relative to the bare nucleus, rather than the shielding differences obtained from experiment, that are based on a choice of reference substance.

$$\text{chemical shift, } \delta \equiv (\nu - \nu_{\text{ref}}) / \nu_{\text{ref}} = [\sigma_{\text{ref}} - \sigma_{\text{sample}}] / [1 - \sigma_{\text{ref}}] \quad (\text{Equation 1})$$

Here all quantities are tensors, in general, so the chemical shift tensor components  $\delta_{xx}$  can

be related to shielding tensor components  $\sigma_{xx}$ . Shielding is essentially a response of electrons

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to the presence of a magnetic field. Except for highly symmetric molecules, the observed shielding is expected to be dependent on the orientation of a molecule with respect to the magnet. However, due to the rapid and random tumbling of molecules in the liquid or gas phase, only the isotropic value of shielding, the average value, is observed. In the solid state where rapid tumbling does not occur, the orientation dependence or the anisotropy of the shielding manifests. The measurement of shielding as a tensor quantity obviously provides much more information than the isotropic value alone regarding the structure and dynamics of a molecule. *Ab initio* calculations of course yield the full shielding tensor. Thus, progress in understanding nuclear shielding, both its theoretical and physical aspects, has been dependent on measurements in the solid state.

The symmetric part of the shielding tensor is characterized by 6 numbers (components) for the nuclear site that has the lowest symmetry, some of these 6 numbers are either zero or are identical, depending on the symmetry at the nuclear site. The shielding tensor can be characterized by specifying the values of the principal components and the orientation of the principal axis system, again, in general requiring 6 numbers. The numbering of the principal components is such that  $\sigma_{33} \geq \sigma_{22} \geq \sigma_{11}$ , that is, the least shielded tensor component is called  $\sigma_{11}$  and the most shielded component  $\sigma_{33}$ .

The shielding tensor is also characterized by combinations of these numbers, the span and the skew. The span,  $\Omega$ , always a positive quantity, is the difference between the most shielded ( $\sigma_{33}$ ) and the least shielded tensor component ( $\sigma_{11}$ ), corresponding to the width of the resonance powder pattern in ppm. That is, where  $\sigma_{33} \geq \sigma_{22} \geq \sigma_{11}$

$$\Omega \equiv (\sigma_{33} - \sigma_{11}), \quad (\text{Eq 2})$$

and the skew  $\kappa$  is a signed dimensionless quantity, defined as

$$\kappa \equiv 3(\sigma_{\text{iso}} - \sigma_{22})/(\sigma_{33} - \sigma_{11}) \quad (\text{Eq 3})$$

The skew ranges from  $-1$  (for  $\sigma_{22} = \sigma_{33}$ ) to  $+1$  (for  $\sigma_{11} = \sigma_{22}$ ). Experimentally, the skew is independent of the reference substance used in defining the chemical shift,

$$\kappa \equiv 3(\delta_{\text{iso}} - \delta_{22})/(\delta_{33} - \delta_{11}) \quad (\text{Eq 4})$$

but the span cannot be determined exactly purely from experiment because

$$\begin{aligned} \Omega &\equiv (\sigma_{33} - \sigma_{11}) \\ &= (\delta_{11} - \delta_{33})/(1 - \sigma_{\text{ref}}) \end{aligned} \quad (\text{Eq 5})$$

and  $\sigma_{\text{ref}}$  is not always negligible compared to 1, considering the level of accuracy that chemical shifts can be measured nowadays. The  $(1 - \sigma_{\text{ref}})$  factor is usually incorrectly left out in converting chemical shifts from one reference to another (which should not happen if one thinks always in terms of the fundamental molecular electronic property, shielding, from which chemical shifts are derived). We should note the  $(1 - \sigma_{\text{ref}})$  factor here and always be conscious of our inability to know span exactly from measuring the width of the resonance powder pattern ( $\delta_{11} - \delta_{33}$ ).

**General Theory.** As an introduction to some of the ideas and terms used in this review, it would benefit the reader to first look at the lucid and accessible introduction to relativistic effects by Jochen Autschbach in a Perspective, ending with special attention to NMR quantities: electric field gradients, chemical shifts and J coupling (Autschbach, 2012). The reason that relativistic effects are so important for these NMR quantities is that  $r^{-3}$  appears in the mathematical operators for calculations of these quantities, heavily weighting the electron contributions very close to the nucleus where consequences of Einstein's special relativity in quantum chemistry, the relativistic effects, are large. For low atomic numbers, we can still approximately use non-relativistic theory but many NMR experiments use nuclei below the first and second row of the Periodic Table, where non-relativistic theory becomes inadequate.

Wenjian Liu continues to re-cast and explain the basic ideas of relativistic quantum chemistry at various levels of exposition: comprehensive advances (Liu, *Advances*, 2014; Liu, *Perspectives*, 2014), and tutorial (Liu, 2015), (these are only the most recent ones), so as to answer these fundamental questions: (a) what is the appropriate relativistic many-electron Hamiltonian, (b) how to make explicit representation of relativistic wavefunctions, (c) how to formulate relativistic molecular electronic properties, and (d) how to interface relativistic quantum chemistry and quantum electrodynamics. These fundamental issues are to be addressed from both conceptual and methodological standpoints, so as to establish the 'big picture' of relativistic molecular quantum mechanics. In particular, a more general formulation of the so-called exact two-component (X2C) relativistic Hamiltonians is given where various kinetic and magnetic balances are incorporated in a unified manner (Liu, *Advances*, 2014). In a manner of speaking, Liu comments that X2C serves as a seamless bridge between the Schrödinger (non-relativistic) and Dirac (relativistic) equations. In these expositions, special mention is made of electric and magnetic properties, nuclear magnetic shielding, in particular.

For systems where spin-orbit couplings are very weak, it is highly desired to separate the algebraic exact two-component (X2C) relativistic Hamiltonian into spin-free and spin-dependent terms, such that scalar relativistic effects can be treated variationally to infinite order, whereas spin-orbit couplings can be treated order by order either perturbatively or variationally (Li et al., 2012). This is done by *a priori* partitioning the Dirac matrix into spin-free and spin-dependent terms. Recently, this idea is extended to both electric and magnetic molecular properties (Li et al., 2014). Explicit expressions are derived for these properties as well as two-electron spin-orbit couplings. The spin-dependent terms are treated via analytic derivative technique. Whereas here the spin-orbit coupling can be treated order by order, as needed, in an earlier version, the full X2C-

NMR formulation of nuclear magnetic shielding, the mixed second-order energy is of first order in both the external magnetic field  $\mathbf{B}_0$  and the nuclear moment  $\boldsymbol{\mu}_N$  but is of infinite order in spin-orbit coupling (Sun et al., 2012). This is one extreme. At the other extreme, sf-X2C-NMR is zeroth order in spin-orbit coupling (Cheng et al., 2013). Both the full X2C (Jameson and de Dios, 2014) and the sfX2C formulations (Jameson and de Dios, 2015) have been reviewed by us earlier.

The well-known nonrelativistic mapping of the nuclear magnetic shielding tensor and the nuclear spin-rotation coupling tensor proposed by Ramsey in 1950 and made generally useful by Flygare since 1964, had been in wide use for establishing absolute shielding scales for light nuclei in molecules containing light atoms (Ramsey, 1950; Flygare, 1964). The direct relativistic mapping between nuclear magnetic shielding tensor and the nuclear spin-rotation coupling tensor (Xiao et al., 2012) [reviewed by us earlier (Jameson and de Dios, 2013)] permits accurate determination of absolute shielding scales for nuclei in relativistic systems. What is new is the employment of rotational London orbitals in the basis set for the 4-component relativistic calculations of the nuclear spin-rotation coupling tensor (Xiao et al., 2014). These orbitals are the counterpart of GIAO (gauge-including atomic orbitals) in nuclear magnetic shielding calculations. This is to help overcome the slow convergence with basis set size in relativistic calculations of spin-rotation tensors. It is well known that the advantages of using London orbitals in NMR shielding calculations are that (a) the unphysical dependence on the gauge origin can be eliminated completely, (b) the slow basis set convergence problem is greatly alleviated. At first glance the nuclear spin-rotation tensor does not have a gauge origin problem since the tensor is defined physically relative to the position of the nucleus in question, but the transformation of the origin of the electronic orbital angular momentum to an arbitrary origin holds only in the limit of a complete basis set and therefore leads to an origin dependence with a finite basis set. Thus, the

use of London orbitals endows the same two-fold advantage here as use of GIAOs does to NMR shielding. The use of kinetically balanced rotational London orbitals (KB-RLO) ensures that the relativistic treatment gives rise to the correct nonrelativistic limit, even with a finite basis set. Also, the use of KB-RLO and GIAO together gives rise to a direct relativistic mapping between nuclear magnetic shielding and nuclear spin-rotation coupling tensors that is identical to the one derived previously without these pre-factors in the basis set, as it has to be, because the mapping is insensitive to one-particle basis sets, as shown previously (Xiao et al., 2012).

Relativistic formulations with various approximations have recently been reported (Reynolds and Shiozaki, 2015; Yoshizawa and Hada, 2015). One is a non-perturbative implementation of the 4-component Dirac-Hartree-Fock (DHF) method for molecules in magnetic fields using the Dirac-Coulomb-Gaunt Hamiltonian (Reynolds and Shiozaki, 2015). The DHF wavefunction is constructed from GIAOs; restricted magnetic balance is used to generate 2-spinor basis functions for the small component. The molecular integrals for the Coulomb and Gaunt interactions are computed using density fitting. Timings for an 85- and a 112-atom molecule are given. The other is a second-order Douglas-Kroll-Hess method where the magnetic operators are replaced with the Breit-Pauli magnetic operators and GIAOs are used (Yoshizawa and Hada, 2015). Shielding tensors for HXeCCH molecule are reported as an example, in addition to diatomic molecules containing iodine, IX (X = F, Cl, Br).

In a holistic review article, Lazzarotti shows that the non-relativistic quantum mechanical theory of magnetic properties can be proposed in terms of electronic current densities induced by an external magnetic field and permanent magnetic dipole moments at the nuclei. The molecular response to magnetic perturbations is reformulated in terms of electron current density induced by magnetic fields and nuclear magnetic dipoles. Theoretical relationships are derived for the

evaluation of magnetizability, nuclear magnetic shielding, and nuclear spin-spin coupling, proving that the whole theory can be reformulated via the equations of classical electromagnetism, provided only that the current density is evaluated by quantum mechanical methods. Emphasis is placed on the invariance of response properties in a translation of the coordinate system as a basic requirement for measurability. In principle, only origin-independent atomic and molecular macroscopic observables can be experimentally accessible: A measurement is not generally conceivable for quantities which change in a translation of coordinate system. For the same reason, translationally invariant theoretical definitions are needed for a meaningful evaluation of response properties via computational procedures of quantum mechanics. In this review, the connections among translational invariance, gauge invariance, and electron charge conservation are outlined, showing that they can be illustrated via quantum mechanical sum rules, in typical Lazzarotti fashion (Lazzarotti, 2014). He employs the Bloch gauge to define electric and magnetic multipole electron operators. Including the terms in cubic response to magnetic field  $\mathbf{B}$ , he also derives the expressions for hypershielding (the quadratic term in the  $\mathbf{B}$  dependence of nuclear magnetic shielding) and for hypermagnetizability. The sum rules are not necessarily obeyed in calculations using the algebraic approximation, that is, within a finite basis set, but the closeness to following the sum rules is a measure of basis set completeness.

The electron density of atoms is set in rotation by an external magnetic field and thus, by continuity of the flow, peripheral delocalized electron currents are expected for any molecule. The interest in delocalized electron currents and electron current maps is intimately linked with definitions of the elusive concepts of aromaticity and anti-aromaticity through the magnetic properties: the magnetizability tensor and the nuclear magnetic shielding tensor. It had been assumed that delocalized currents require a ring of chemically bonded atoms to sustain

them. Pelloni *et al.* show that delocalized currents are induced by magnetic fields without a ring of bonded atoms or cyclic system (Pelloni *et al.*, 2014). Fairly large delocalized electron flow is calculated for any molecules containing at least three atoms, such as H<sub>2</sub>O or NH<sub>3</sub>. They conclude that the ability to sustain delocalized currents is not exclusive to molecules characterized by a ring structure. They have documented electron motion all over an interatomic circuit, induced by a magnetic field in a series of neutral or charged molecules via the quantum mechanical current density. For example, for H<sub>2</sub>O in two different orientations, the total electron stream is comparable to that in benzene molecule (116% and 105% of the benzene value). The delocalized currents are less intense in species such as CO<sub>3</sub><sup>2-</sup> and NO<sub>3</sub><sup>-</sup> because of electron withdrawing exerted by electronegative peripheral atoms. This work brings into question the use of NICS<sub>||</sub> (the parallel component of the NICS calculated at the center of the benzene ring) for the molecule as a reliable quantifier of absolute aromaticity based on the magnetic criterion. On this basis one would call H<sub>2</sub>O, NH<sub>3</sub>, CH<sub>4</sub>, H<sub>3</sub>O<sup>+</sup>, NH<sub>4</sub><sup>+</sup> and ethane more aromatic than benzene itself. Of course, the paradox is quickly dispelled by noting that the loop about the hydrogen atoms in H<sub>2</sub>O, NH<sub>3</sub>, or CH<sub>4</sub> has a much smaller radius than the radius of the benzene ring.

An *ab initio* method for treating open shell systems combined with an *ab initio* treatment of the paramagnetic chemical shifts has been proposed by Autschbach *et al.* (Gendron *et al.*, 2015). Where spin-orbit coupling is not significant, it had been sufficient to use electron paramagnetic resonance (EPR) pseudospin Hamiltonian parameters (*g* and *A* tensors, usually calculated using DFT methods) to calculate the contact and pseudo-contact contributions to shielding in a paramagnetic molecule. The Fermi contact contribution arises from the isotropic part and the pseudo-contact contribution arises from the anisotropic part of the hyperfine coupling tensor. In the general case where spin-orbit coupling is strong, an *ab initio* theoretical

approach that treats the open shell system that may have orbital degeneracies, low-lying excited states, in addition to strong spin-orbit coupling, is needed. Autschbach *et al.* (Martin and Autschbach, 2015) start from the concept proposed by Soncini *et al.* (Van den Heuvel and Soncini, 2013), that the temperature dependence of the shielding tensor could be defined by using the bi-linear derivative of the Helmholtz free energy with respect to the magnetic field and the nuclear magnetic moment. The operators which are the linear and bilinear derivatives of the Hamiltonian (with respect to the field **B**, with respect to the nuclear moment  $\mu^N$  and the bilinear derivative with respect to **B** and  $\mu^N$  are expressed as usual and the temperature dependent shielding tensor from the Helmholtz free energy) is written in terms of these derivative operators. With the ensemble average carried out before the integration from 0 to  $\beta$  ( $= 1/k_B T$ ), subsequent integration leads to sum-over-states like expression for the shielding tensor components in terms of *Q*, the canonical partition function in the absence of the external field or the fields from nuclear moments. This expression is general in the sense that the wavefunctions and operators may include relativistic effects to all orders. Autschbach *et al.* find that contrary to conventional ideas, the temperature dependence of contact contribution to shielding is  $1/T$  and the pseudo-contact contribution to shielding is  $1/T^2$  only in the cases where  $S \geq 1$  and zero-field splitting is appreciable, and only if *g* is isotropic (Martin and Autschbach, 2015). Otherwise the temperature dependence is not so simply separable for the two contributions. In a subsequent paper, Autschbach *et al.* (Gendron *et al.*, 2015) start with the general expression in the sum-over-states form in the previous paper and consider the various parts. The operator, that is the derivative with respect to the nuclear moment of the nucleus of interest, has three contributions: Fermi contact, spin-dipole, and paramagnetic spin-orbital. The Fermi contact mechanism is isotropic and the contact shift arises from a net magnetization around and at the probe nucleus. One should note their use of the more general term net

magnetization rather than “spin density”, because in the general case both spin and orbital angular momenta are important, that is, contributions from all three mechanisms arise. When SO coupling is significant, then the association of the FC operator with contact paramagnetic shifts and spin-dipole operator with dipolar paramagnetic shifts no longer applies, and also, the electronic states are not pure spin multiplets. They explicitly state the conditions under which the general expression morphs into the commonly used equations in terms of EPR parameters: orbitally non-degenerate ground state, absence of low-energy excited states, and relatively weak SO coupling. They consider an example where none of these explicit conditions apply: the paramagnetic shifts of ligand nuclei ( $^{13}\text{C}$ ) in actinide complexes  $[\text{UO}_2(\text{CO}_3)_3]^{3-}$  and  $[\text{NpO}_2(\text{CO}_3)_3]^{4-}$ . They use restrictive active space (RAS) calculations and include SO coupling in the actinide 5f shell via state interaction. They find that inclusion of higher-lying unoccupied orbitals in the active space improves the convergence, especially for the Np complex (Gendron et al., 2015).

For systems where the spin-orbit coupling is weak, and excitations only within the ground state zero-field splitting manifold makes significant contribution, and the higher order zero field splitting and the higher order Zeeman terms can be neglected, then a non-relativistic calculation such as proposed by Pennanen and Vaara (Pennanen and Vaara, 2008) could be used, provided that corrections to their original formulation are made, a flaw originally pointed out by Soncini *et al.*, leading to an incorrect temperature dependence limiting behavior at low temperatures (Soncini and Van den Heuvel, 2013). Vaara *et al.* recently provide the corrected formulation, which now includes the magnetic couplings arising from the Zeeman and hyperfine coupling interactions between the states belonging to different degenerate manifolds (Rouf et al., 2015). They then apply the corrected theory to calculations of  $^1\text{H}$  shifts in three paramagnetic systems of high spin Co(II) pyrazolylborate complexes. They find that using DFT calculations for geometry

optimization and calculations of all tensors:  $\mathbf{g}$ , zero field splitting ( $\mathbf{D}$ ), and hyperfine  $\mathbf{A}$ , for the paramagnetic contributions, in addition to the usual (orbital) nuclear magnetic shielding with various functionals gave poor results, making it impossible to assign the protons correctly. Using *ab initio* CASSCF for calculating the tensors  $\mathbf{g}$  and  $\mathbf{D}$ , even with locally dense basis sets gave accurate results. The choice of basis functions is very important for accurate calculation of the  $\mathbf{A}$  tensor and choice of functional does matter. A 25% admixture of exact exchange in these systems gives better results than other recipes.

As increased MAS spinning speeds became technically practical, it became possible to develop solid state NMR analogs of many solution state paramagnetic NMR experiments. The pseudocontact shift and paramagnetic relaxation enhancement are taken as dependent on the distances to and the orientations of the molecular paramagnetic susceptibility tensor arising from neighboring unpaired electrons. In the solid state, additional information is afforded by the anisotropy of the paramagnetic shift of each NMR active nucleus. These anisotropic paramagnetic shifts can be calculated via the general formalisms described above (Gendron et al., 2015), and the anisotropic tensor components provide more stringent tests of theory than isotropic shifts obtained from gases or solutions. At this point it is important to remember the caveats raised by Autschbach *et al.*, that only under specific conditions is the pseudocontact shift dominantly from the dipolar mechanism and only under those conditions (spin-orbit coupling is weak, orbitally non-degenerate ground state, absence of low-energy excited states) may it be related to structure as commonly used. From the observed anisotropic shift tensors structural information is deduced, or starting structures are refined. Furthermore, the correlation of the paramagnetic shift tensor with other tensor quantities such as the quadrupolar coupling tensor can provide additional constraints. A recently developed method for correlating quadrupolar and paramagnetic shift interactions has been proposed by

Grandinetti *et al.* that also enhances sensitivity and eliminates artifacts (Walder *et al.*, 2015). They demonstrate the utility of these pulse sequences in obtaining accurate parameters for the  $^2\text{H}$  paramagnetic shift and quadrupolar coupling tensors for the model compound  $\text{CuCl}_2 \cdot 2\text{D}_2\text{O}$ . In a typical Grandinetti approach, they then closely examine point dipole models for predicting the full paramagnetic shift tensor and propose a modified approach, guided by the shape of the singly occupied molecular orbital (SOMO), that yields excellent agreement with their measured results. While only a general theory, such as given above (Gendron *et al.*, 2015), can include all possible relative magnitudes of contributions, thereby providing a systematic approach to accurate calculations for reproducing experimental quantities, a simple model is often useful to help us focus on the fundamental understanding that is possible in simple model systems. In this model system, their analysis of the full deuterium paramagnetic shift tensor reveals that a nuclei-centered point dipole model, which delocalizes the unpaired spin density from the copper onto the two closest chlorides, yields poor agreement with their measured values, incorrectly predicting not only the sign of the paramagnetic shift anisotropy but also the tensor orientation. Agreement with the nuclei-centered point dipole model is improved when the unpaired spin density is additionally delocalized onto the two oxygen ligands, yielding the correct sign of the paramagnetic shift anisotropy and closer agreement with the measured tensor orientation. Nearly perfect agreement within the uncertainty of their measurement, however, is found with a model with point dipoles displaced away from the nuclei and at positions *consistent with the maximum electron density of the lobes of the singly occupied anti-bonding molecular orbital* (Walder *et al.*, 2015). Not only does this model yield excellent agreement, but it results in fractional delocalization of 13.3% onto the two closest chlorides and 1.6% onto the two closest oxygen ligands, a finding that is more consistent with results obtained from electron paramagnetic resonance and magnetic neutron scattering experiments on this system.

***Ab initio and DFT calculations.*** The *ab initio* coupled-cluster CCSD(T) is the gold standard method for accurate quantum mechanical electronic structure and properties calculations, when full configuration interaction is not feasible. On the other hand, density functional method (DFT) is in widespread use for relativistic and non-relativistic calculations, especially for large systems, despite the fact that there is no universal exchange-correlation functional that works uniformly well for all systems, even for a particular property such as nuclear magnetic shielding. A large number of functionals are in current use for this purpose, but for non-relativistic calculations, most functionals do not perform well relative to the benchmark calculations using CCSD(T) for the identical molecular system. A comprehensive assessment of nuclear shielding calculations using DFT has been carried out by Gauss and co-workers against CCSD(T) calculations for relatively small molecular systems where gas phase absolute shielding data are also available for comparison (Teale *et al.*, 2013). Four-component relativistic calculations are not yet fully developed to include electron correlation at the CCSD(T) level. Thus, DFT (with some electron correlation) and Hartree-Fock (without electron correlation, but with exact exchange) calculations are used.

Accurate non-relativistic calculations of absolute shielding and spin-rotation tensors for fluorine-containing diatomic molecules XF (where X = B, Al, Ga, In, Tl) using CCSD(T) for BF, AlF, and GaF and CCSD for InF and TlF, and relativistic corrections from four-component relativistic density-functional theory (using the PBE functional) added together with rovibrational averaging, are seen to provide good agreement with experimental values, where available (Jaszunski *et al.*, 2014). The restricted magnetic balance scheme was used for the nuclear magnetic shielding tensor calculations, whereas the restricted kinetic balance scheme was used for spin-rotation. The common gauge-origin approach was used in the four-component calculations of both spin-rotation and absolute shielding. As expected, the relativistic effects play an

increasingly important role as one proceeds to the heavier elements in the Periodic Table. The calculated values for the spans,  $\Omega$  ( $^{115}\text{In}$ ) and  $\Omega$  ( $^{205}\text{Tl}$ ) are 1805 and 7136 ppm, respectively, showing the importance of the relativistic effects in determining the shielding anisotropy. For example, the previously reported  $\Omega$  ( $^{205}\text{Tl}$ ) based on the experimental spin-rotation constant and the Ramsey non-relativistic identity relation (Ramsey, 1950) <sup>11</sup> is smaller by 26% than the relativistically corrected value. This example affirms the need for the relativistic mapping of spin-rotation and nuclear magnetic shielding, as derived by Liu *et al.* (Xiao *et al.*, 2012). Overall, for the light nuclei there is good agreement between the calculated values and experimental data, which is not the case for the heavier nuclei;  $\Omega$  ( $^{115}\text{In}$ ) is off by 145 ppm and  $\Omega$  ( $^{205}\text{Tl}$ ) by 1840 ppm. Even for  $\Omega$  ( $^{19}\text{F}$ ) the difference between experimental and calculated values increases from 4 ppm to 43 ppm with increasing atomic number of the other atom.

Relativistic 4-component calculations using polarization propagators at the RPA level (uncorrelated) are compared against 4-component DFT (using 6 different functionals) for  $^{207}\text{Pb}$  and  $^{119}\text{Sn}$  in the Sn and Pb halides (Sn or Pb) $\text{Y}_{4-n}\text{Z}_n$  (Y, Z = H, F, Cl, Br, I) (Maldonado and Aucar, 2014). Using 2-component LRESC (a relativistic linear response theory with elimination the two small components) approach, calculations of Sn, Ge, and Si shielding in molecules with halogen ligands (halo = F, Cl, Br, I) are compared against 4-component relativistic polarization propagator formalism at the RPA level. Both the calculation of non-relativistic and the leading LRESC contributions to the shielding were carried out at RPA level, the gauge origin placed at the nucleus of interest for all LRESC calculations (Maldonado *et al.*, 2014).

A careful analysis of neighbor effects in relativistic systems is reported for  $^{199}\text{Hg}$  shielding tensors in 11 solids, from  $\text{HgF}_2$  to  $\text{Hg}_2(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$ , using various molecular cluster systems for the structures used in shielding calculations (Alkan and Dybowski,

2014). Careful design of a cluster to represent the solid-state structure, inclusion of relativistic components in the Hamiltonian at least at the spin-orbit level (in this case using DFT-ZORA, a popular method using zeroth-order regular approximation), and judicious use of approximations are essential to obtain good agreement with experimental results. It is of course essential to have the correct site symmetry at the nucleus, especially when calculating individual tensor components rather than isotropic averages. The largest neutral cluster that is feasible and has the correct site symmetry at the nucleus of interest is arrived at starting from the first coordination shell and growing outward to include the next coordination shell. The frozen core approximation may be used for the remotest atoms, with their inner core of electrons treated relativistically. Total neglect of relativistic terms is the poorest approximation; inclusion of scalar relativistic terms improves the calculation slightly, but for the highest accuracy, one must include spin-orbit components in the Hamiltonian. This molecular cluster approach was further applied to solid state NMR of  $^{207}\text{Pb}$  and  $^{119}\text{Sn}$  in the pigment leadtin yellow type I that had been used until the first half of the 18<sup>th</sup> century (Catalano *et al.*, 2014). The calculations were used to identify the individual chemical species in the pigment.

Spin orbit contributions to  $^{13}\text{C}$  and  $^{15}\text{N}$  shielding in Pt and Au complexes were calculated using sum-over-states finite-field third-order perturbation theory with scalar relativistic effective core potentials for Pt and Au and are compared with ZORA-SO calculations (Vicha *et al.*, 2015). Analysis in terms of the atoms-in-molecules approach is offered for understanding the effect of heavy atoms on light atom shielding. Calculations of  $^{13}\text{C}$  shielding in dihaloethenes (halo = F, Cl, Br, I) using DFT-ZORA including SO (and using the KT2 functional) are analyzed in NBO/MO terms to understand the differences between *cis* and *trans* isomers (Viesser *et al.*, 2015). Using natural bond orbitals (NBO) analysis permits an intuitive view using the familiar MOs that chemists are most

comfortable with. In a separate study of dihaloethenes, the principal factor responsible for the difference (17 ppm) in the  $^{13}\text{C}$  NMR chemical shift between the *cis*- and *trans*-diiodoethene isomers was the steric interaction observed between the two iodine atoms in the *cis* isomer. DFT-ZORA calculations with SO of  $^{19}\text{F}$  shielding in 20 fluorinated organic molecules used the BLYP functional. Even with the Cl- and Br-substituted organic groups, the relativistic contributions are found to be modest (Saielli et al., Computational, 2014).

MP2 and DFT calculations have been reported for  $^{31}\text{P}$  shielding in 51 different organophosphorus compounds (Fedorov et al., 2014) using various functionals, with the best results arrived at using the functionals of Keal and Tozer, KT2 and KT3 (Keal and Tozer, 2003; Keal and Tozer, 2004). MP2 (up to second order in the Møller-Plesset perturbation theory) occupies a unique role in quantum chemistry due to its unusually cheap *ab initio* treatment of electron correlation. The locally dense basis set approach results in a further dramatic decrease in computational cost without loss of accuracy. Solvation effects are modeled by polarizable continuum model (PCM). Relativistic corrections, calculated using 4-component DFT are 20-30 ppm.

DFT non-relativistic, relativistic scalar ZORA, and spin-orbit ZORA calculations of  $^{15}\text{N}$  shielding in complexes of rhodium(II) tetraformate with 11 organic ligands used PCM for solvent effects (Leniak and Jazwinski, 2015). Correlation coefficients for shielding versus experimental chemical shifts had slopes equal to  $\sim 0.87$  (ideally should be 1.0) for various functionals used when all 11 ligands are included in the plot. The  $^{77}\text{Se}$  shielding in 28 selenium-containing molecules, for which the  $^{77}\text{Se}$  chemical shifts are unambiguously known, were calculated to help in assignment of  $^{77}\text{Se}$  in cyclic selenium imides 1,3,5,7- $\text{Se}_4(\text{NMe})_4$  puckered crown-shaped molecules and in other cyclic imides  $\text{Se}_6(\text{NMe})_2$  and disordered cyclo  $\text{Se}_8$  molecules (Karhu et al., 2015). First of all, solvent effects were not modeled in any way (DFT

calculations of single molecule in vacuum); furthermore, some relativistic corrections for this moderately heavy atom should have been included.

Non-relativistic DFT calculations of shielding for light atoms, usually with PCM standing in for the solvent, provide quick resolution of spectral assignments and answers to structural questions for experimentalists. Some recent examples are the following: DFT calculation of  $^{15}\text{N}$  NMR chemical shifts of the nitrogen-containing heterocycles (best results with KT3 functional) (Samultsev et al., 2014), using the KT3 functional and PCM for  $^{15}\text{N}$  NMR chemical shifts of 27 azoles and azines in 10 different solvents (Semenov et al., 2014), using mPW1PW91 functional for calculations of  $^1\text{H}$  chemical shifts in lactones (Aimola et al., 2015), using B3LYP for  $^1\text{H}$  and  $^{13}\text{C}$  in tautomeric 1-[(pyridin-2-yl amino) methyl] pyrrolidine-2,5-dione (Boobalan et al., 2014), using mPW1PW91 and PCM for  $^1\text{H}$  and  $^{13}\text{C}$  in lignin amino acid adducts (Diehl et al., 2014), using 16 different functionals for  $^1\text{H}$  and  $^{13}\text{C}$  in (R)-ispinesib, a drug molecule (Hill et al., 2015), using B3LYP in COSMO solvent model for for  $^1\text{H}$  and  $^{13}\text{C}$  shielding in bis(4-trimethylammoniumbenzoate) hydroiodide hydrate in DMSO (Komasa et al., 2015), using B3LYP for  $^{13}\text{C}$  shielding in tautomers of vitamin B-13 in PCM solvent model (Kubica and Gryff-Keller, 2015), using 7 different functionals for  $^{13}\text{C}$  shielding in 2-hydroxylamino-4,6-dinitrotoluene (Liu et al., 2015), using BP86 functional for  $^{13}\text{C}$  shielding tensors in  $\text{C}_{60}$  and  $\text{C}_{60}^{10+}$  (Munoz-Castro, 2015), using BHandH functional for  $^{13}\text{C}$  and  $^{17}\text{O}$  in 1,3-dioxolane and  $^{19}\text{F}$  in perfluoro-1,3-dioxolane (Nozirov et al., 2014), using B3LYP for  $^1\text{H}$  and  $^{13}\text{C}$  in in 2-bromo-1H-benzimidazol (Sas et al., 2015), using B3LYP for  $^1\text{H}$  and  $^{13}\text{C}$  shielding in 1:2 complex of dimethylphenyl betaine with 2,6-dichloro-4-nitro-phenol in DMSO (Szafran et al., 2015), and using the MPW1K (Lynch et al., 2000) hybrid functional with PCM solvent model for  $^{29}\text{Si}$  in 24 organosilanes (Zhang et al., 2014). A review article on addressing the stereochemistry of complex organic molecules by density functional theory calculations of NMR

parameters, nuclear shielding in particular, has appeared (Bagno and Saielli, 2015).

DFT/B3LYP calculations of  $^{13}\text{C}$  and  $^{17}\text{O}$  shielding in vitamin E models in chloroform and in water suggest that a proper description of the solvent shift for  $^{17}\text{O}$  nuclear magnetic shielding of the hydroxyl group in water requires the use of explicit solute-solvent hydrogen bonds (Oliveira et al., 2015). The association of two small molecules is studied by DFT calculations using IGLO-II basis set for the  $^{11}\text{B}$  and  $^{15}\text{N}$  shielding in  $\text{NH}_3\text{BH}_3$  (Kobayashi et al., 2014). This provided insights into the dehydrogenation mechanism of  $\text{NH}_3\text{BH}_3$ , insights that have not been available through  $^{11}\text{B}$  NMR alone.

In a study of  $^{17}\text{O}$  in solid N-acyl imidazoles, quantum chemical computations show that the dependence of  $^{17}\text{O}$  NMR parameters on the Ar-C(O) bond rotation is very similar to that previously observed for the C(O)-N bond rotation in twisted amides. The authors conclude that one should be cautious in linking the observed NMR chemical shifts only to the twist of the C(O)-N amide bond (Kong et al., 2015).

In a study of disilene-doped (6,0) zigzag single-walled boron nitride nanotubes, the shielding values of  $^{11}\text{B}$  and  $^{15}\text{N}$  nuclei were calculated using three different ways of taking care of the gauge problem that arises when using incomplete basis sets: by Gauge-Including Atomic Orbital (GIAO), Continuous Set of Gauge Transformations (CSGT) and Individual Gauges for Atoms in Molecules (IGAIm) methods. The authors used the B3LYP functional and a hydrogen-terminated section of nanotube model ( $\text{B}_{14}\text{N}_{14}\text{H}_8$ ) (Arshadi et al., 2014). The disilene doping is modeled by  $\text{C}_4\text{Si}_2$  replacing the three B and three N atoms in a ring in the model. The results reveal a significant effect of disilene doping on the nuclear shielding tensors at the sites of those  $^{11}\text{B}$  and  $^{15}\text{N}$  nuclei located in the nearest neighborhood of the disilene-doped ring. In another study, DFT-B3LYP calculations on covalent addition of homo- and hetero-diatomic molecules (AB) including  $\text{H}_2$ ,  $\text{O}_2$ ,  $\text{N}_2$ ,  $\text{NO}$  and  $\text{CO}$  at the external

surface of H-capped pristine armchair (5, 5) single-walled carbon nanotube (SWCNT) were conducted (Jankowska et al., 2015). The SWNT is modeled by an H-terminated section ( $\text{C}_{70}\text{H}_{10}$ ) and the corresponding  $\text{C}_{70}\text{H}_{10}$ -AB covalent adducts were fully optimized at the B3LYP/6-311G\* level of theory. Significant changes of carbon NMR atom chemical shifts (up to -100 ppm) and shielding anisotropies (up to -180 ppm) at sites of addition (chosen as C3 and C4 positions from the hydrogen terminated end) were calculated. This is not at all the “adsorption” of gases that it is erroneously called in the abstract.

## PHYSICAL ASPECTS OF NUCLEAR SHIELDING

**Anisotropy of the Shielding Tensor.** The study of nuclear shielding includes advances in our understanding of what and how various factors affect this electronic property as well as practical improvements in measurements and theoretical predictions. The various papers recently published in this area are now either tackling deeper details by introducing better experimental and theoretical techniques, or finding new applications by unraveling new correlations for this ubiquitous NMR parameter.

Proton shielding tensors are inherently difficult to determine accurately. The inhomogeneity of the radiofrequency field sometimes impairs recoupling sequences in solid state NMR measurements. This difficulty often manifests in experiments geared toward the determination of proton chemical shift tensors. Through the incorporation of a series of phase-alternating  $270_0$ - $90_{180}$ -composite-180 pulses, inhomogeneity effects can be significantly reduced, as demonstrated in the measurements of proton shielding tensors in citric acid and malonic acid (Pandey et al., 2015). The proton shielding tensor for water in barium chlorate monohydrate has been determined via solid state NMR under both static and magic-angle spinning conditions. A two-dimensional technique has likewise been employed to separate the shielding tensor from the dipolar interaction. Both techniques yield similar anisotropy and asymmetry.

Calculated values from plane wave calculations are made to agree with experiment only upon incorporation of motional averaging caused by the fast rotation of the water molecule about its  $C_2$  axis (Carnevale et al., 2014). With a magnetic field of 19.9 T and MAS frequency of 62 kHz, three dimensional heteronucleus-detected dipolar based solid state NMR experiments have been used to observe and assign backbone resonances for the 89-residue dynein light chain 8, LC8 protein (Guo et al., 2014). In this scheme, the fast spinning allows for  $^1\text{H}$  resonances to be included, which aids greatly in making assignments, while direct observation of  $^{13}\text{C}$  provides greater resolution.

The type of secondary helix structure poly( $\beta$ -benzyl L-aspartate) assumes in the solid state depends on its molecular weight and removal rate of the solvent thereby paving the way to examine both right-handed and left-handed helices. Employing the Switching-Angle Sample-Spinning (SASS) method, the carbonyl  $^{13}\text{C}$  shielding tensors have been recently measured. It is found that the intermediate component of the carbonyl shielding tensor is very sensitive to the handedness of the helix. This is only expected as the  $\text{C}=\text{O}$  group begins to interact with the sidechain when a peptide assumes a left-handed helical conformation. The experimental  $\delta_{22}$  values in the right-handed  $\alpha_{\text{R}}$ , and left-handed  $\alpha_{\text{L}}$  and  $\omega_{\text{L}}$  samples are 184, 174, and 164 ppm, respectively (Kamihara et al., 2015). Restraints derived from  $^{15}\text{N}$  chemical shift anisotropy have been shown to improve the structure of the bacterial mercury transporter protein MerF (Tian et al., 2014). Lastly, measurements of cross-correlation effects between dipolar ( $^1\text{H}^{\text{N}}-^1\text{H}^{\alpha}$ ) and amide-proton chemical shift anisotropy ( $^1\text{HN}$  CSA) on longitudinal relaxation times of the amide proton in a model tripeptide  $\text{Piv}-^1\text{Pro}-^1\text{Pro}-^1\text{Phe}-\text{OMe}$  have shown that hydrogen bonding increases the anisotropy of the amide proton shielding tensor (Pichumani et al., 2015).

To obtain both magnitude and orientation of the shielding tensor components, a single crystal is required. Kusumi and coworkers

have demonstrated that this can be equally achieved in the case of the  $^{31}\text{P}$  chemical shift tensor in phenyl-phosphonic acid (PPA) by making use of a sample of PPA microcrystals aligned three-dimensionally in a polymer matrix (Kusumi et al., 2015). With new  $^{43}\text{Ca}$  double-rotation (DOR) and multiple-quantum magic-angle spinning (MQMAS) spectra and powder diffraction data, combined with computer-generated structural models and chemical shift tensor and electric field gradient calculations, possible structures for the vaterite polymorph of  $\text{CaCO}_3$  have been narrowed down to two candidates, hexagonal  $P3_221$  and monoclinic  $C2$  (Burgess and Bryce, 2015). NMR parameters for  $^{13}\text{C}$ ,  $^{15}\text{N}$ , and  $^{51}\text{V}$  have been successfully tapped in combination with model calculations to determine in greater detail the structure in the solid state of  $[\text{VO}(^{15}\text{NGlySal})(\text{OCH}_3)(\text{CH}_3\text{OH})]$ , a compound that is now known to have a methanol molecule coordinated to vanadium (Li et al., 2015).  $^{35}\text{Cl}$  electric field gradient (EFG) and chemical shift tensors have been measured in a series of chlorine-containing transition metal complexes (O'Keefe et al., 2014). It is observed that the observed EFG tensor is quite sensitive to whether the chlorine ligand is bridging, terminal-axial or terminal-equatorial. An experimental and theoretical NMR study of  $^{185/187}\text{Re}$  has been carried out on several perrhenates ( $\text{KReO}_4$ ,  $\text{AgReO}_4$ ,  $\text{Ca}(\text{ReO}_4)_{22}\text{H}_2\text{O}$ ),  $\text{ReO}_3$ , and  $\text{Re}_2(\text{CO})_{10}$  (Widdifield et al., 2015). The  $^{77}\text{Se}$  chemical shift tensor for L-selenocystine has also been measured in the solid state (Struppe et al., 2015). The observed isotropic value in the solid state is about 50 ppm more shielded compared to what is seen in solution. Model calculations reveal that this difference is likely a consequence of the dramatic sensitivity of the  $^{77}\text{Se}$  shielding on the  $\text{C}-\text{Se}-\text{Se}-\text{C}$  dihedral angle. This dihedral angle can change the  $^{77}\text{Se}$  shielding by as much as 600 ppm.

***Shielding Surfaces and Rovibrational Averaging.*** Even in the solid state, atoms are still in thermal motion. An accurate comparison between calculated and experimental chemical shifts must therefore go beyond a static lattice approximation. Due

to the large number of vibrational modes, incorporation of dynamics in shielding calculations in the solid phase imposes high demands on computational resources and time. For instance, Monte Carlo simulations often require hundreds of sampling points at any given temperature. On the other hand, shielding surfaces constructed by a finite displacement method require much less sampling points. With this scheme, Monserrat and coworkers have been able to compute vibrational corrections to shieldings in magnesium oxide and the molecular crystals L-alanine and  $\beta$ -aspartyl-L-alanine (Monserrat et al., 2014). Results obtained from the constructed shielding surfaces are as accurate as those obtained via Monte Carlo simulations. Since quadratic and anharmonic contributions are obtained separately when the shielding surfaces are used, it is likewise straightforward to see that thermal corrections to shielding in solids are dominated by the quadratic terms.

The conformational flexibility of saccharides is an absolute requirement for the molecular recognition by biological targets, such as enzymes and antibodies. Therefore, structural determination is crucial for understanding these recognition processes. The application of DFT calculations for the NMR determination of the conformation of  $\beta$ -cellobiose in water has been carried out (Yan and Yao, 2015). The cellobiose flexibility mainly arises from two dihedral angles,  $\phi$ (H1'-C1'-O'-C4) and  $\psi$  (C1'-O'-C4-H4), which in principle vary from  $-180^\circ$  to  $+180^\circ$ . The authors employed several different functionals and used PCM for solvent model. The PW1PW91 functional is found to be the best with a correlation slope of 1.026 and 1.008 for  $^{13}\text{C}$  and  $^1\text{H}$  chemical shifts, respectively. They report  $^{13}\text{C}$  NMR chemical shifts for C4 and C' at three energy-minimum conformations: *syn- $\phi$ /*syn- $\psi$*  ( $\phi = 32.2^\circ$ ,  $\psi = \sim 23.9^\circ$ ), *anti- $\phi$ /*syn- $\psi$*  ( $\phi = 178.2^\circ$ ,  $\psi = \sim 0.4^\circ$ ), and *syn- $\phi$ /*anti- $\psi$*  ( $\phi = 10.5^\circ$ ,  $\psi \sim 180^\circ$ ). The calculations suggest that the C1' chemical shifts are sensitive to the conformational changes, with the values of 103.3 ppm at *syn- $\phi$ /*syn- $\psi$* , 98.9 ppm at *anti-*****

*syn- $\psi$* , and 95.3 ppm at *syn- $\phi$ /*anti- $\psi$* . Likewise, the C4 chemical shifts are sensitive to the conformational changes, with the values of 80.4 ppm at *syn- $\phi$ /*syn- $\psi$* , 70.0 ppm at *anti- $\phi$ /*syn- $\psi$* , and 75.6 ppm at *syn- $\phi$ /*anti- $\psi$* . The  $^{13}\text{C}$  chemical shifts' ability to distinguish between characteristic positions is helpful for the determination of conformations, especially for those with equivalent energies. The shielding tensor analysis shows that for C1', the directions and amplitudes of two shielding components ( $\sigma_{22}$  and  $\sigma_{33}$ ) vary distinctly with  $\phi$  and  $\psi$ , whereas for C4,  $\sigma_{33}$  remains unchanged, but  $\sigma_{22}$  varies by 13 ppm from *syn- $\phi$ /*syn- $\psi$*  to *anti- $\phi$ /*syn- $\psi$*  (*syn- $\phi$ /*anti- $\psi$* ). (For the C1' the corresponding value is 26 ppm). The distinctive C4 and C1' chemical shifts at different conformations suggest that they can be useful in ( $\phi$ ,  $\psi$ ) dihedral angle determinations (Yan and Yao, 2015). The dependence of  $^{13}\text{C}$  shieldings on the glycosidic torsional angles ( $\phi$ ,  $\psi$ ) has also been calculated using a disaccharide model (Garay et al., 2014). As expected, shieldings at the carbon sites participating in the glycosidic linkage are most sensitive to this conformational angle, exhibiting a range of about 20 ppm. This  $^{13}\text{C}$  shielding surface is found to depend on several factors such as the identity of the disaccharide, the anomeric state, and the conformation of a nearby hydroxyl group. It is then estimated that before  $^{13}\text{C}$  shieldings can be accurately used for validation, determination, and refinement of glycan structures, more than the 20,000 shielding computations are necessary.*******

Model clusters containing up to 20  $[\text{P}(\text{OAl}(\text{OH})_3)_4]^{3-}$  units have been employed to extract computationally the dependence of  $^{31}\text{P}$  shielding on P-O-Al bond angles and P-O bond lengths. With these constructed shielding surfaces, successful predictions of  $^{31}\text{P}$  chemical shifts in calcined aluminophosphates have been attained (Dawson and Ashbrook, 2014). The  $^{23}\text{Na}$  shielding is presumed to be a function of Na-O distances in silicate glasses. A linear relationship between  $^{23}\text{Na}$  chemical shifts and Na-O distances, however, becomes evident only

when coordination number is carefully taken into account (Gambuzzi et al., 2014). A Boltzmann weighing of  $^{17}\text{O}$  shielding from four low-energy structures of brownmillerite-type phase  $\text{Ba}_2\text{In}_2\text{O}_5$ ,  $\text{Ba}_2\text{In}_2\text{O}_4(\text{OH})_2$ , is shown to reproduce the observed solid state  $^{17}\text{O}$  NMR spectra obtained from these perovskites (Dervisoglu et al., 2015). In this hydrated form of brownmillerite, the oxygen nuclei of hydrogen bond donors are shown to be shielded while both nonhydroxyl and hydrogen bond acceptor oxygen sites are found to be deshielded.

$^{29}\text{Si}$  shielding traces with respect to the Si-O-Si bond angle have been constructed for three different tetrahedral environments  $\{\text{Si}\}\text{O}_4$ ,  $\{\text{Si}\}\text{O}_3\text{C}$ , and  $\{\text{Si}\}\text{O}_2\text{C}_2$  (Nimmo II and Kroll, 2014). With these traces, Si-O-Si angle distributions can be extracted from the  $^{29}\text{Si}$  NMR spectra of amorphous silicon oxycarbide ceramics. Results derived from this approach are in agreement with those obtained from x-ray and neutron diffraction data. The dependence of  $^{29}\text{Si}$  NMR chemical shifts on the  $^{10}\text{B}/^{11}\text{B}$  ratio in borosilicate glass has been utilized to characterize the structural effects of europium on these materials (Bouty et al., 2014). Similarly,  $^{29}\text{Si}$  chemical shifts, being dependent on local structure and less sensitive to long-range order, have been demonstrated to be useful in the determination of the layered framework structure of the new silicate material CLS-1 of composition  $[\text{Si}_5\text{O}_{11}\text{H}][\text{C}_9\text{N}_2\text{H}_{15}] \cdot 1.9(\text{H}_2\text{O})$  (Cadars et al., 2014).

$^{31}\text{P}$  solid state NMR spectra combined with two-dimensional experiments have been employed in characterizing a series of  $(\text{NaPO}_3)_{1-x}(\text{Ga}_2\text{O}_3)_x$  glasses ( $0 \leq x \leq 0.35$ ) (Ren and Eckert, 2014). Here,  $^{31}\text{P}$  spectra are deconvoluted to provide phosphorus speciations.  $^{31}\text{P}$  chemical shifts are known to be sensitive to the identity of the next neighbor atom in phosphates as illustrated in the case of  $\text{Mg}^{2+}$  and  $\text{Zn}^{2+}$ -substituted aluminophosphates (Seymour et al., 2015). In this particular case, the  $^{31}\text{P}$  chemical shift is found to be significantly influenced by the P-O-M bond angle.

A combination of molecular dynamics simulation and plane wave shielding calculation has been applied to reproduce  $^{77}\text{Se}$  NMR spectra of selenium-rich  $\text{Ge}_x\text{Se}_{(1-x)}$  glasses (Sykina et al., 2014). Agreement with experimental spectra in this particular case is taken as a validation of the molecular dynamics simulation.  $^{207}\text{Pb}$  chemical shifts, especially their tensor span, are sensitive to the coordination number around Pb. In a series of lead(II) carboxylates, it is found that with short chain carboxylates (octanoate or smaller),  $^{207}\text{Pb}$  tensor spans are more than 2500 ppm. With nonanoate or longer carboxylates, the span is reduced to 740 ppm, suggesting a closer to being spherical local structure at the lead atom site (Catalano et al., 2015).

$^1\text{H}$  chemical shifts have been used with powder diffraction and theoretical calculations to arrive at possible structures for a substituted zeolitic imidazolate metal-organic framework (Baías et al., 2015). In these systems,  $^1\text{H}$  chemical shifts are predicted to be sensitive to the relative orientation of aldehyde and aromatic groups. Computed  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{31}\text{P}$  chemical shifts using optimized crystal structures are found to be helpful in a further refinement of the solid state structure of phospho-tyrosine (Paluch et al., 2015), and plane wave shielding calculations are found to be of value in assigning the  $^{13}\text{C}$  and  $^{15}\text{N}$  resonances observed in polycrystalline materials containing co-crystals of theophylline with malonic, maleic and glutaric acids (Pindelska et al., 2014). The  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts have been successfully predicted for the four crystal forms ( $1\alpha$ ,  $1 \cdot \text{H}_2\text{O}$ ,  $1\beta$ , and  $1\gamma$ ) of the solid wheel-and-axle metal-organic compound  $[(p\text{-cymene})\text{-Ru}(\kappa\text{N-INA})\text{Cl}_2]$  (Presti et al., 2014), and plane wave calculations of  $^{13}\text{C}$  chemical shifts can likewise be employed to validate an x-ray structure of a polymorph as demonstrated in the case of clopidogrel hydrogensulfate (Pindelska et al., 2015). The  $^{43}\text{Ca}$ ,  $^{13}\text{C}$ , and  $^{17}\text{O}$  NMR chemical shifts have been calculated for bulk and surface atoms in calcite. In addition, the  $^{43}\text{Ca}$  chemical shifts have been determined to be sensitive to hydrocarbon adsorption (Bevilaqua et al., 2014). Lastly, by including

proton jumps and discriminating phosphate group rotations,  $^{17}\text{O}$  NMR spectra at various temperatures can be used to characterize in greater detail the dynamics in the protonic conductor  $\text{CsH}_2\text{PO}_4$  (Kim et al., 2015).

NMR crystallography is defined as the combined use of experimental NMR and computation to provide new insight, with atomic resolution, into structure, disorder and dynamics in the solid state. In this context, calculations of NMR parameters using the GIPAW (gauge-including projector augmented wave) method have been performed for a wide variety of organic solids. GIPAW calculations for the hemihydrate of 2', 3'-O-isopropylidineguanosine, whose crystal structure has been solved by single crystal x-ray diffraction, were performed with the CASTEP code using the PBE functional with a dispersion correction scheme (Reddy et al., 2015). A plane-wave basis set with ultra-soft pseudopotentials was used. Comparing the experimental and GIPAW calculated  $^1\text{H}$  chemical shift, it is evident that there are greater discrepancies for the protons bonded to nitrogen than for protons bonded to carbon, notably the calculated  $\text{NH}_{2b}$   $^1\text{H}$  chemical shifts are significantly less than the experimental values. The authors suggest a possible explanation is the known temperature dependence of hydrogen-bonded protons, while the GIPAW calculation is performed for a static structure at a temperature of absolute zero. Another explanation is that H shielding in bonds to C is in general more permissive of the basis sets and electron correlation description than is H shielding in bonds to O or N.

GIPAW calculations and a detailed analysis using complementary 1D and 2D SSNMR methods using  $^1\text{H}$ ,  $^{19}\text{F}$ ,  $^{15}\text{N}$ ,  $^{13}\text{C}$  and  $^{35}\text{Cl}$  nuclei have been conducted on a novel crystalline form of ronacaleret hydrochloride, a calcium-sensing receptor antagonist under development for the treatment of osteoporosis. The paper serves as a paradigm for the comprehensive application of experimental and computational methods to a complex but typical drug in the solid phase (Vogt et al., 2014). CASTEP code with PBE

was used for structure refinement and shielding calculations for all nuclei, in addition to quadrupole coupling tensor for  $^{35}\text{Cl}$ . The GIPAW calculation performed on the room temperature structure was found to lead to slightly more accurate reproduction of many NMR properties of interest in the present case than the low temperature structure obtained from x-ray diffraction.

A correspondingly comprehensive combined experimental-computational effort to characterize the Al surface sites of  $\gamma$ -alumina was undertaken (Wischert et al., 2014). The authors calculated  $^{27}\text{Al}$  NMR parameters from first principles in periodic boundary conditions using the VASP code for structural optimization with a PW91 functional and CASTEP code using PBE functional for the NMR shielding and nuclear quadrupole coupling tensors. They did these calculations for a large number of Al sites with different coordination schemes, potentially present on the alumina surface. They calculated NMR parameters for all terminations, surface sites, and hydration levels. The nature and accordingly the NMR parameters of these sites change with the level of hydroxylation and thereby change with the pretreatment temperature of  $\gamma\text{-Al}_2\text{O}_3$ . Hydration leads to addition of O atom(s) to the first coordination sphere of Al, resulting in stronger shielding and accordingly a lower chemical shift. To see only surface Al nuclei they used a surface sensitive  $\{^1\text{H}\}$   $^{27}\text{Al}$  cross-polarization technique. Surface Al sites show a large variety of symmetry (tetrahedral, octahedral, trigonal bipyramid, square pyramid, trigonal), associated with very different EFG tensors. OH groups have a direct effect on the Al on which they are bound, changing not only the EFG but also the shielding (Wischert et al., 2014). The same computational approach would have been a good one to use for the exploration of isomorphously substituted effects on the hydrogen electric field gradient and nuclear shielding tensors in the Bronsted acid site of H-ZSM-5 zeolite. Instead the authors used an inadequate cluster model  $(\text{H}_3\text{SiO})_3\text{Si} - \text{O}(\text{H}) - \text{X}(\text{H}_3\text{SiO})_3$  where X = B, Al, Ga (Soltanali et al., 2014).

A combined DNP surface enhanced NMR-computational approach to the study of the active sites in Sn- $\beta$  zeolite as a function of Sn loading has been reported (Wolf et al., 2014). This approach unambiguously shows the presence of framework Sn(IV)-active sites in an octahedral environment, which probably correspond to so-called open and closed sites, respectively (i.e., Sn bound to 3 or 4 siloxy ( $R_3SiO$ ) groups of the zeolite framework). The authors used cluster models of increasing groups of atoms. For the most realistic cluster model, that includes the zeolite framework, the tetrahedral site has a calculated Sn isotropic chemical shift  $\delta_{iso} = -396$  ppm, in good agreement with experimental values and the chemical shift decreases by approximately 100 ppm with the addition of each (1 or 2) coordinated water molecule. The calculated NMR parameters for the hexacoordinated Sn sites, resulting from the coordination/reaction of at least two water molecules, are consistent with the experimental values. When Sn-sites have two water molecules in the first coordination sphere and one additional water molecule hydrogen-bonded to the coordinated  $H_2O$ , the calculated NMR parameters are in very good agreement with the experimental chemical shift parameters:  $\delta_{iso}$ ,  $\Omega$  and  $\kappa$  values -654 ppm, 228 ppm, and 0.31 respectively for open sites and -684 ppm, 248 ppm, and 0.02 respectively for closed sites, allowing the assignment of the observed signals at  $\delta = -654$  ppm to an open site and  $\delta = -685$  ppm to a closed site, coordinated by two  $H_2O$  molecules (Wolf et al., 2014). DFT GIPAW calculations using the CASTEP code predicted  $^{47/49}Ti$  NMR parameters that may assist in spectral assignments and help correlate  $^{23}Na$  and  $^{29}Si$  NMR resonances to crystallographic sites in 6 different titanosilicates (Xu et al., 2014). In these systems, the  $^{23}Na$  and  $^{39}K$  calculations probe the local environment of the counter cations.

**Isotope Shifts.** When protons from hydroxyl (OH), sulfhydryl (SH), and amino ( $NH_2$ ) groups in a protein do not exchange readily with a deuterated solvent, resolved peaks are easily observed for  $^{13}C$  nuclei that are one bond away from any one of these groups.

When the exchange rate is not too fast yet not slow enough to afford well separated peaks, a line shape analysis of the  $^{13}C$  NMR signals of carbon nuclei near these polar groups, which are affected by deuterium-proton isotope shifts in a mixture of  $H_2O$  and  $D_2O$ , can help identify such cases (Takeda et al., 2014). Deuterium induced isotope effects on  $^6Li$  chemical shifts have been recently used to elucidate the structure of aggregates formed by butyllithium in diethyl ether in the presence of bromide ions (Böhler and Günther, 2015). In this particular case, the measured isotope shifts caused by deuterated butyllithium, the observed intensity pattern and multiplicity, and the shielding effect of a bromide ion are all taken into account to arrive at the identity of the nearest neighbors to lithium in the aggregate. Isotope effects through more than three bonds are expected to be sensitive to conformation. Böhm and coworkers have shown in the case of fluoroethane that a single D-substitution on C-2 can lead to isotope effects on  $^{19}F$  that vary depending on the conformation: 0.411 ppm (*anti*) and 0.158 ppm (*gauche*). These numbers are obtained with CCSD(T)/qz2p calculations, but the results from a lower level of theory, HF/tz2p, are not significantly different. Similar calculations performed on endo-2-fluoronorbornanes suggest that the experimental assignments of conformers made previously are mistaken (Böhm et al., 2014). For the study of the tautomeric equilibria of pyridoyl benzoyl b-diketones, deuterium-induced isotope effects on  $^{13}C$  chemical shifts are found to corroborate conclusions derived from coupling constants regarding the equilibrium positions in these asymmetric diketones (Hansen et al., 2015). Two-bond deuterium isotope effects on  $^1H$  NMR chemical shifts in  $W(PMe_3)_3H_{6-x}D_x$  are of normal sign (the lighter isotopomer is deshielded) and are of similar magnitude to those observed in  $CH_{4-x}D_x$ , suggesting that these are indeed classical hydride compounds and not dihydrogen complexes (Sattler et al., 2014). The  $^{35/37}Cl$  isotope effects on  $^{195}Pt$  chemical shifts appear to be simpler in chlorohydroxidoplatinum(IV) complexes than in the corresponding aquachloro complexes.

Engelbrecht and coworkers (Engelbrecht et al., 2015) have shown that for each  $^{195}\text{Pt}$  NMR resonance of the  $[\text{Pt}^{35/37}\text{Cl}_{6-n}(\text{}^{16/18}\text{OH})_n]^{2-}$ , where ( $n = 1-5$ ), anions is resolved only into  $[(6 - n) + 1$  for  $n = 1-5]$  peaks. Since calculations have not reached the desired accuracy for these systems, it is tentatively suggested that the greater *trans* influence of the hydroxido ligand is responsible for this difference. Lastly, one-bond oxygen isotope effects on  $^{99}\text{Tc}$  chemical shifts in  $\text{TcO}_4^-$  have been recently reported,  $^{16/18}\Delta = -0.616$  ppm  $^{16/17}\Delta = -0.302$  ppm (Tarasov et al., 2015).

### ***Intermolecular Effects on Nuclear Shielding.***

An absolute shielding scale for the purpose of evaluating *ab initio* methods is usually composed of resonance measurements in the gas phase extrapolated to zero density. In this manner, the experimental values correspond to those of an isolated molecule. There is no doubt that liquid to gas shifts are often significant. In order to incorporate medium effects on chemical shifts molecular dynamics simulations can be applied. Snapshots can be taken during the simulation and chemical shifts are then calculated from the clusters of molecules obtained during these snapshots. This approach has been performed on nitromethane. The calculated  $^{15}\text{N}$  chemical shift difference between liquid and gas phases is about 15 ppm. Compared to a dilute solution in cyclohexane, the  $^{15}\text{N}$  shielding in nitromethane in the gas phase is about 5 ppm more shielded (Gerber and Jolibois, 2015). Computational time and resources are not limitless so the size of the cluster employed in the calculation needs to be judiciously chosen. For instance, a number of acetonitrile solvent molecules in a 3.5 Å thick shell, sampled from molecular dynamics simulation trajectories has been incorporated in the  $^{13}\text{C}$  shielding computations of perylenic antenna molecules (Ozcan et al., 2014). Results show that for nuclei residing on the molecular perimeter acetonitrile causes deshielding while those near the center become shielded. Various approximations are also available where the solvent is modeled by a continuum. Albeit cheap, continuum models are generally not accurate enough to

reproduce accurately solvent effects on shielding. It is therefore not surprising to see calculations that make use of such approximate methods not performing well in predicting chemical shifts due to chiral solute-chiral solvent interactions (Kessler et al., 2015). For the solid phase, Holmes and coworkers have discovered what is necessary to perform shielding calculations using clusters of molecules that aim to reproduce shielding tensors (Holmes et al., 2014). The cluster must preserve the symmetry properties of the crystalline space group. Failing to observe symmetry leads to errors in the calculated principal shielding components.

Since intermolecular interactions affect what is observed in an NMR spectrum, NMR spectroscopy in the gas phase continues to be of great utility in host-guest systems. For instance,  $^{13}\text{C}$  in  $\text{CO}_2$  has been exploited in probing cavities inside macrocyclic coordination supramolecules (Bassanetti et al., 2014). The residual anisotropy of the  $^{13}\text{C}$  shielding tensor combined with pulse-field gradient experiments have been examined to study the diffusion of carbon dioxide along the channels of a metal-organic framework DMOF-1 ( $\text{Zn}_2(\text{benzene-(1,4)-dicarboxylate})_2$  (1,4-diazabicyclo [2.2.2]octane)) (Peksa et al., 2015).  $^1\text{H}$  and  $^{13}\text{C}$  NMR experiments have been applied to study the kinetics of methane replacement with carbon dioxide and nitrogen gas in methane gas hydrate prepared in porous silica gel matrices (Cha et al., 2015). Changes in  $^3\text{He}$  shielding have been observed as a result of He gas interacting with sodium and calcium ions in the micropores of 5 Å molecular sieve (Garbacz and Jackowski, 2015).

The position of protons in flexible hydroxyl groups is difficult to pinpoint by x-ray diffraction.  $^1\text{H}$  chemical shifts of the hydroxyl proton, of course, can tell whether a site is participating in hydrogen bonding or not. Oftentimes,  $^1\text{H}$  chemical shifts are unable to provide specific conformational information not to mention that resolving these signals in the solid state are often very challenging. Filip and Filip (Filip and Filip, 2015) have

suggested using  $^{13}\text{C}$  chemical shifts instead since these are usually resolved and are quite sensitive to conformation. This approach has been demonstrated to be feasible in the case of quercetin dehydrate. Clusters containing an increasing number of pyrazole molecules have been utilized to determine the hydrogen bond effects on  $^1\text{H}$  and  $^{15}\text{N}$  shieldings in crystalline pyrazole (Amini, 2014). By plotting the calculated shielding values against the reciprocal of the cluster size, values that correspond to the crystal limit can then be extrapolated.

Differences in the intermolecular packing of peptides are expected to manifest more in the chemical shifts of nuclei that are near the surface of the molecule. Using a model peptide (Ala-Gly)<sub>15</sub>, Asakura and coworkers have observed a distribution of  $^1\text{H}$  NMR chemical shifts, suggesting that silk II form, the silk structure after spinning, is not a simple antiparallel  $\beta$ -sheet, but is heterogeneous due to different packing arrangements (Asakura et al., 2015). This is further supported by the dissimilar  $^{13}\text{C}$  resonances observed for the side chain in alanine and the carbonyl carbons, as well as distinct amide  $^{15}\text{N}$  resonances, while seeing only small differences for  $\text{C}_\alpha$ .  $^1\text{H}$  and  $^{19}\text{F}$  NMR chemical shifts combined with infrared data have led to the conclusion that there is no significant hydrogen bond interaction in 2-fluoroethanol (Cormanich et al., Seeming, 2014). The observed trend of  $^{19}\text{F}$  resonances becoming more shielded when a F atom participates in an attractive interaction and deshielded when the interaction is repulsive has been used to characterize the  $\text{CF}\cdots\text{FC}$  interactions in selected organofluorine compounds (*all-syn*-1,2,3,4- and *all-syn*-1,2,4,5-tetrafluorocyclohexane, 1,8-difluoronaphthalene, 4,5-difluorophenanthrene, and 2,2',5,5'-tetrafluorobiphenyl). In all cases, the  $\text{CF}\cdots\text{FC}$  interactions are rendered repulsive (Cormanich et al., Analysis, 2014). Calculated  $^{13}\text{C}$  and  $^{17}\text{O}$  shielding tensors in carboxyl(-COOH) and amide (-CONH<sub>2</sub>) functionalized single-wall carbon nanotubes have been shown to correlate with hydrogen bond strength (Ghafouri et al., 2015). A range of

about 40 ppm has been observed experimentally and reproduced theoretically for the isotropic shielding of  $^{17}\text{O}$  in H<sub>2</sub>O bound in various hydrated crystalline amino acids (Michaelis et al., 2015). This variation in  $^{17}\text{O}$  chemical shifts has been attributed to changes in O-H bond distances and H-O-H bond angles. Hydrogen bond effects on  $^{13}\text{C}$  shieldings have been examined in detail in 1,4-bis(4-cyanobenzyl)piperazine and 1,4-bis(4-amidinobenzyl)piperazine tetrahydrochloride tetrahydrate (Rezler et al., 2014).

A relatively shielded resonance (-0.9 ppm from TMS) for methyl protons has been assigned to a methyl group lying closely to an aromatic group in a macrocyclic coordination supramolecule made from Ag<sup>+</sup>, thioether functionalized bis(pirazolyl)methane ligands, and CF<sub>3</sub>SO<sub>3</sub><sup>-</sup>/PF<sub>6</sub><sup>-</sup> as counter-anions (Bassanetti et al., 2014). Calculations involving dimers have been performed to deduce the structure of the dimer formed by a new shape-persistent macrocycle comprising two 2,3-triphenylene moieties bridged by *m*-phenylene ethynyls (Chu et al., 2014). The geometry that produces closest agreement with experiment is one where the arenes are stacked, about 3.6 Å apart, with a lateral displacement of about 3.5–4.0 Å along the molecular long axis. Computations of  $^{21}\text{Ne}$  and  $^{39}\text{Ar}$  shielding for rare gas atoms interacting with a furan suggest that these nuclei are more sensitive than  $^3\text{He}$  to intermolecular interactions (Nieradka and Kupka, 2014).

Nucleus independent chemical shifts (NICS) have been applied in the evaluation of aromaticity in equatorial BN-substituted nanocages (Anafcheh and Ghafouri, 2014). For fullerenes, BN substitution leads to less aromaticity while for nanocapsules, a greater aromaticity is suggested by calculated NICS. Current density calculations have shown that octaethylporphyrin zinc(II) dication, formally having 16  $\pi$  electrons, is anti-aromatic (Fliegl et al., 2015). Spatial maps of magnetic properties have also been calculated and drawn for a variety of porphyrins, hemiporphyrines and tetraoxo[8]circulenes

(Kleinpeter et al., 2014), cyclopropane, the heteroanalogous oxirane, thiirane, and aziridine and various substituted mono-, bis-, and tris-cyclic analogues (Kleinpeter et al., Anisotropy, 2015), and a number of substituted para-nitro-pyridine N-oxides (Kleinpeter et al., Interplay, 2015). These maps of NICS values around a functional group or aryl moiety are then employed to gauge the anisotropy and aromaticity effects arising from these moieties. Ring currents have been investigated using plane wave methods on semiconducting and carbon nanotubes (Ren et al., 2015). These calculations find that semiconducting nanotubes are more aromatic than metallic ones. Since deshielding of a proton is now considered as a defining evidence for hydrogen bonding, current density calculations have been recently performed to gain further insights on how hydrogen bonding affects chemical shifts. From these calculations, it is now evident that hydrogen bonding leads to a reduced electron density on the hydrogen causing a local reduction in the current density, which then manifests as a significant deshielding of the hydrogen nucleus (Monaco et al., 2015).

In a clever study modeling the NMR spectrum of ions diffusing in porous graphitic material, Grey *et al.* used NICS calculations to provide the shielding environment experienced by the ion at arbitrary positions in model slit pores of various widths to calculate the chemical shifts of the diffusing ion (Merlet et al., 2015). As diffusion inside pores is fast, the NMR spectrum of an ion trapped in a single mesopore will be a sharp peak with a pore-size-dependent chemical shift. To account for the experimentally observed NMR line shapes, the simulations must model the relatively slow exchange between different pores. For this purpose the authors used a lattice gas model. The simplest lattice-gas models to simulate diffusion describe the diffusing species as non-interacting particles performing kinetic Monte Carlo moves on a lattice that contains both accessible sites (the fluid) and excluded sites (the porous matrix). They show that averaging over all possible diffusive

trajectories of the ion can be achieved by a recursive numerical scheme called moment propagation, a very efficient method in which the computational effort scales as the number of lattice sites times the number of time steps.

The use of molecular clusters to take into account intermolecular effects is a relatively old method, many examples of which have been reviewed by us earlier (de Dios and Jameson, 2012). A recent example is the DFT calculation of  $^{13}\text{C}$  shielding in polymorphs of sulfanilamide (Hartman and Beran, 2014). The authors refer to the method as “fragment-based approach” and they treat the molecules beyond the one in the center as contributing higher order effects in a many-body expansion. In their present example, they report one-body and two-body calculations. Many methods of including long-range effects beyond the molecules of the cluster whose electrons are included in the quantum calculations had been employed. The simplest method is to use a continuum or reaction field model (e.g., PCM is very popular as an option in most electronic structure codes); others use electrostatic embedding such as partial charge field (de Dios et al., 1993), EIM (embedded ion method) (Stueber, 2006), the extended embedded ion method (EEIM) (Weber and Schmedt auf der Günne, 2010), or SCREEP (Surface Charge Representation of the Electrostatic Embedded Potential) (Stefanovich and Truong, 1998). For sulfanilamide the authors chose instead Stones’ distributed multipole analysis (Stone, 1981; Stone and Alderton, 1985), which they then truncate at the leading term, that is, point charges, for this work. For three sulfanilamide polymorphs, they consider one-body, one-body charge-embedded, 2-body, 2-body charge-embedded models and compare their results with GIPAW calculations. The assignment of peaks to the correct polymorph is somewhat questionable at the ‘one-body with charge embedding’ level. The ‘two-body with charge embedding’ captures the trends in the  $^{13}\text{C}$  chemical shifts much better and permits assigning the polymorphs.

Calculations of NMR chemical shifts in proteins using fragments surrounded by appropriate models for the rest of the protein (charge fields, or molecular mechanics, or both) has been used for some time, since the pioneering work of de Dios *et al.* (de Dios *et al.*, 1993). The fragment is typically treated at the highest correlated quantum mechanical level, the outer layers of the ONIOM (Morokuma's term) could be described using SCF and small basis set quantum calculations or else molecular mechanics, farther out, as needed, some electrostatic embedding may surround the first two layers, since carrying out self-consistent calculations in the presence of point charges is facile and cheap time-wise. Individual manual handling of the layers for preparing input to program suites still requires considerable attention, so an automated fragmentation QM/MM approach is potentially very powerful (He *et al.*, 2014). In this method, each amino acid and all the residues in its vicinity are automatically assigned as the QM region, using a distance cutoff for each residue-centric QM/MM calculation. They present a comparison of such calculations of  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{15}\text{N}$  isotropic shielding for gas phase protein, protein in implicit solvent (a reaction field), and protein in explicit water molecules (including only the waters in the first and second solvation shell), which they compare against experimental data for chemical shifts in proteins GB3 and ubiquitin. The use of explicit solvent greatly improves the correlation plot against experiment. The easiest set to get excellent agreement with experiment is  $^{13}\text{C}$  isotropic shifts. The effects of the electronic environment around the  $^{15}\text{N}$  nucleus is much more demanding to reproduce, as already shown in the early work (de Dios *et al.*, 1993).

The  $^{129}\text{Xe}$  nucleus has been used extensively in characterizing materials due to its great sensitivity to intermolecular interactions. Monte Carlo simulations have been incorporated in  $^{129}\text{Xe}$  shielding calculations aimed at reproducing observed trends in  $^{129}\text{Xe}$  chemical shifts as a liquid crystal undergoes a phase transition (Karjalainen *et al.*, 2015). A combination of molecular dynamics and

relativistic density functional calculations has likewise been carried out to reproduce the observed  $^{129}\text{Xe}$  NMR chemical shifts in room temperature ionic liquids (Saielli *et al.*, Understanding, 2014). The results qualitatively agree with experiment as the calculated values suggest the same experimental trend, a greater shielding is observed when  $\text{PF}_6^-$  is the counterion as opposed to  $\text{Cl}^-$ . The difference between these two ions leads to differences in both cage volume and the average charge surrounding the xenon nucleus, the two factors deemed important in these cases. This dependence of  $^{129}\text{Xe}$  shielding on cage volume and charge is also evident in  $^{129}\text{Xe}$  NMR spectra of Xe in clathrate hydrate lattices doped with  $\text{NH}_4\text{F}$  (Shin *et al.*, 2014).  $^{129}\text{Xe}$  NMR spectroscopy has proven to be useful as well in characterizing the anisotropic environment of the thermotropic nematic liquid crystal 4-cyano-4'-pentylbiphenyl (Vemulapalli *et al.*, 2015). On the other hand,  $^{131}\text{Xe}$ , a quadrupolar nucleus, via its EFG tensor, has been shown to report on the symmetry of phases in thermotropic nematic liquid crystals (Jokisaari and Zhu, 2014). Finally, Bryce and Viger-Gravel have recently authored an overview covering NMR experiments and interactions that are relevant to halogen bonding (Bryce and Viger-Gravel, 2015).

**Absolute Shielding Scales.** With new spin-rotation data combined with high quality calculations of relativistic effects, absolute shielding scales for the  $^{17}\text{O}$  and  $^{33}\text{S}$  nuclei have been recently refined (Komorovsky *et al.*, 2015). The new values for  $^{17}\text{O}$  are 328.4 ppm for  $\text{H}_2^{17}\text{O}$ , and  $-59.1$  ppm for  $\text{C}^{17}\text{O}$ . For  $^{33}\text{S}$  in  $\text{H}_2^{33}\text{S}$ , the new value is 742.9 ppm. The relativistic effects for both water and carbon monoxide are quite small, 3.0 and 1.8 ppm, respectively, but for the heavier nucleus,  $^{33}\text{S}$ , the corrections are quite substantial, 26 ppm. Spin-rotation data have also been obtained for various isotopomers of water yielding the following absolute shielding values for  $^{17}\text{O}$ : 332.0 ppm  $\text{D}_2^{17}\text{O}$  and 329.6 ppm for  $\text{HD}^{17}\text{O}$  (Puzzarini *et al.*, 2015). Both values contain relativistic corrections.

$^3\text{He}$ ,  $^{129}\text{Xe}$  and  $^{131}\text{Xe}$  NMR measurements of resonance frequencies in the gas phase have been repeated to extract nuclear magnetic moments. The frequencies for  $^{129}\text{Xe}$  and  $^{131}\text{Xe}$  of an isolated Xe atom given as a fraction of the frequency of an isolated  $^3\text{He}$  nucleus are 0.3630975 and 0.10763492, respectively (Makulski, 2015). A similar procedure has been applied to  $^{83}\text{Kr}$  which yields the following corresponding ratio,  $\nu^{83}\text{Kr}/\nu^3\text{He} = 0.05051616$  (Makulski, 2014). These frequencies have also been converted to nuclear magnetic moments using previously calculated absolute shieldings that incorporate both relativistic and electron correlation effects.

### PERSPECTIVE

Both plane wave and cluster calculations have extended shielding calculations to the condensed phase. Still, challenges remain in accurately incorporating dynamics into the computations. As one goes down the periodic table, relativistic effects as well as electron correlation and basis set size remain daunting. Nonetheless, there has been significant progress in this research field. Albeit accuracy in shielding computations still stands as a goal to be reached, how we understand the theoretical and physical aspects of nuclear magnetic shielding has greatly developed and matured. The study of nuclear shielding is definitely one area in which theoretical and experimental efforts have profoundly complemented each other. It is only expected that future experiments will continue to assist theoretical endeavors and computational work will remain indispensable as we explore ways to extract structural and dynamics information from NMR chemical shifts.

### ABBREVIATIONS

B3LYP      Becke 3-parameter Lee Yang Parr hybrid functional

CASSCF     Complete active space SCF

CCSD        Coupled-cluster singles and doubles

CCSD(T)    CCSD model augmented by perturbative corrections for triple excitations

COSMO      Conductor-like screening solvation model

CSGT        Continuous set of gauge transformations

DFT         Density functional theory

DHF         Dirac Hartree-Fock

DNP         Dynamic nuclear polarization

DOR         Double rotation

EFG         Electric field gradient

EEIM        Extended embedded ion method

EIM         Embedded ion method

EPR         Electron paramagnetic resonance

FC          Fermi contact

GIAO        Gauge-including atomic orbitals

GIPAW      Gauge-including projector augmented waves

HF          Hartree-Fock

IGAIM      Individual gauges for atoms in molecules

KB          Kinetically balanced basis

KT2, KT3   Keal and Tozer functionals

LRESC      Linear response elimination of small components

MAS        Magic angle spinning

MP2        Second order Møller-Plesset

MQMAS     Multiple quantum magic angle spinning

NBO	Natural bond orbital	X2C	Exact two-component relativistic theory
NICS	Nucleus-independent chemical shift	XC	Exchange correlation
NMR	Nuclear magnetic resonance	ZFS	Zero-field splitting
ONIOM	our own n-layered integrated molecular orbital and molecular mechanics method (Morokuma)	ZORA	Zeroth-order regular approximation

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PCM	Polarizable continuum solvent model	
RAS	Restricted active space	Alkan F, Dybowski C. Calculation of chemical-shift tensors of heavy nuclei: A DFT/ZORA investigation of <sup>199</sup> Hg chemical-shift tensors in solids, and the effects of cluster size and electronic-state approximations. <i>Phys. Chem. Chem. Phys.</i> 2014; 16:14298-14308.
RLO	Rotational London orbitals	
RPA	Random phase approximation (first order polarization propagator)	
SASS	Switching angle sample spinning	Amini SK. A systematic investigation of cooperativity between two types of hydrogen bonding in the nonlinear clusters of an aromatic molecule: pyrazole. <i>J. Mol. Struct.</i> 2014; 1068:112-123.
SCF	Self-consistent field	
SCREEP	Surface charge representation of the electrostatic embedded potential	Anafcheh M, Ghafouri R. BN belts: From small fullerenes to nanocapsules. <i>J. Cluster Sci.</i> 2014; 25:1173-1185.
sf	Spin-free	
SO	Spin–orbit	Arshadi S, Bekhradnia AR, Mohammadi E, Asghari A. Disilene-doped boron nitride nanotubes: A computational study. <i>J. Struct. Chem.</i> 2014; 55:629-635
SOMO	Singly occupied molecular orbital	
SSNMR	Solid state NMR	Asakura T, Ohata T, Kametani S, Okushita K, Yazawa K, Nishiyama Y, Nishimura K, Aoki A, Suzuki F, Kaji H, Ulrich AS, Williamson MP. Intermolecular packing in B. mori silk fibroin: Multinuclear NMR study of the model peptide (ala-gly)(15) defines a heterogeneous antiparallel antipolar mode of assembly in the silk II form. <i>Macromolecules</i> 2015; 48:28-36.
SWCNT	Single-walled carbon nanotube	
QED	Quantum electrodynamics	
QM/MM	Quantum mechanics molecular mechanics approach	
VASP	Vienna <i>ab initio</i> simulation package	Autschbach J. Perspective: Relativistic effects. <i>J. Chem. Phys.</i> 2012; 136:150902.

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