CHAPTER ONE

Recent Advances in Nuclear Shielding Calculations

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Abstract

Nuclear magnetic shielding calculations have reached a great deal of sophistication, as these now incorporate both relativistic and correlation effects. Approaches now include molecular dynamics as well as effects of the medium in condensed phases. With these computational tools, calculated shielding values are now obtained under conditions as close as possible to those of a sample inside a nuclear magnetic resonance spectrometer. Indeed, computations are approaching the limits of experimental uncertainty. A brief description of new methodologies of shielding calculations is presented followed by a review of the various factors that may influence shielding. The usefulness of being able to reproduce experimental data is highlighted by citing how shielding calculations in many instances have enabled avenues for extracting information on various systems.

Key Words: Absolute shielding, Chemical shifts, Chirality, Cluster models, Conformational dependence, Density functional theory, Disorder in crystals, Electron correlation, Four-component calculations, Gas phase NMR, Hydrogen bonds, Intra- and intermolecular effects, Isotope shifts, Medium effects, Molecular dynamics, NMR crystallography, Non-bonded interactions, Periodic boundary calculations, Polarizable continuum model, Polymorphs, Pseudopotentials, Relativistic calculations, Rovibrational averaging, Shielding surfaces, Structure determination, Temperature dependence, Tensor, Torsion angles, Two-component calculations

ABBREVIATIONS

AE all-electron
BO Born–Oppenheimer
BPPT Breit Pauli perturbation theory
CCSD coupled cluster singles and doubles
CFP charge field perturbation
CI configuration interaction
COSMO conductor-like screening model
CPMD Car-Parinello molecular dynamics
CSGT continuous set of gauge transformation
DFT density functional theory
DHF Dirac–Hartree–Fock
ECP effective core potential
EIM embedded ion method
EPR electron paramagnetic resonance
GAPW Gaussian and augmented plane-wave method
GGA generalized gradient approximation
GIAO gauge-including atomic orbitals
GIPAW gauge-including projector augmented wave
HAHA heavy atom heavy atom
HALA heavy atom light atom
HF Hartree–Fock
HOMO highest occupied molecular orbital
IGAIM individual gauge for atoms in molecules

KS Kohn–Sham
LAPW linear-augmented plane waves
LDA local density approximation
LHF-CEDA localized Hartree-Fock-common energy denominator Green's function approximation
LLH localized local hybrid
LMF local mixing function
LR-ESC linear response elimination of small component
LUMO lowest occupied molecular orbital
MAS magic angle spinning
MB-GIAO magnetically balanced gauge-including atomic orbitals
MC Monte Carlo
MD molecular dynamics
MM molecular mechanics
NAO numeric atomic orbital
NBO natural bond orbital
NICS nucleus independent chemical shift
NMR nuclear magnetic resonance
OEP optimized effective potential
OOD occupied-orbital dependent
PAW projector augmented wave
PBC periodic boundary conditions
PCM polarizable continuum model
PES potential energy surface
PW plane wave
QM quantum mechanics
RMB restricted magnetic balance
RPA random phase approximation
RSC relativistic small core
SCF self-consistent field
SCREEP surface charge representation of the electrostatic embedding potential
SO spin–orbit
SPARTA shift prediction from analogy in residue type and torsion angle
SPC simple point charge
SSNMR solid-state nuclear magnetic resonance
STO Slater-type orbitals
SWNT single-walled nanotube
USPP ultrasoft pseudopotential
XC exchange correlation
XRD X-ray diffraction
ZORA zeroth-order regular approximation

1. OVERVIEW OF THIS REVIEW

Monographs on shielding calculations have traced the advances in this field over the years: Nuclear Magnetic Shieldings and Molecular Structure (1993),[1] Modeling NMR Chemical Shifts: Gaining Insights into Structure and Environment (1999),[2] Calculation of NMR and EPR (electron paramagnetic resonance) Parameters: Theory and Applications (2004).[3] Reviews on shielding calculations have been published in various venues.[4–8] In addition, a review of *ab initio* shielding calculations as an emerging tool for protein structure determination[9] and of the PAW/GIPAW approach for the study of solids[10,11] have been published. The physical and theoretical aspects of nuclear shielding are reported on an annual basis in Specialist Periodical Reports on NMR.[12]

Early reviews of shielding calculations include the two reviews in this particular series of volumes (vol. 29, 1994).[13,14] Excellent recent reviews in this series have detailed the theoretical basis for the relativistic and density functional theory (DFT) methods for nuclear shielding computations.[15,16] We do not repeat a development of these theoretical foundations here. Rather we update with recent developments in exchange-correlation functionals (since the Wilson review in vol. 49, 2003) and in relativistic computations (since the Autschbach review in vol.67, 2009). To minimize duplication, we have limited this review primarily to papers published in 2004 and later.

A crucial role of theoretical calculations is for understanding physical systems, thus we stay connected to the concepts and motivations of experimentalists but use a limited number of examples which illustrate the quality and reliability of the information that calculations provide. For example, in part 2 of this review, we discuss how important are relativistic effects on shielding and which parts of the corrections are largest for what systems. We consider here the current thinking about which of the exchange and correlation functionals works best for which types of systems. In reviewing theoretical calculations in parts 3–6, we have grouped examples, such as to serve as a guide to approaches that have worked well for various types of systems. Thus, in part 3, we consider cases where single molecule calculations may be used, and cases where model fragments are the best systems for understanding the dependence on conformation separately from other factors, and cases where using supramolecular clusters including interacting neighbours is the most logical approach, especially when hydrogen bonding is involved. We review

various approaches in including subtle quantum effects such as electrostatic field effects from distant neighbours that influence the electron distribution of the local neighbour atoms and therefore affect the shielding of the nucleus in question. Local effects are paramount in understanding shielding in a majority of cases; thus, approaches that focus on local effects, using clusters and fragments and embedding them in a charge field may often be the most logical theoretical approach. On the other hand, some aspects of shielding in extended networks cannot be properly treated by using local approaches such as cluster and fragment models, and we have to consider the long-range effects of the entire network by doing calculations in periodic systems; this is especially true for covalent solids. Thus, in part 4, we discuss calculations which use methods which have been developed for these systems, theoretical methods that have become an important tool for experimentalists making measurements in the solid state. In part 5, we consider dynamic effects. For some systems, dynamic averaging is such a significant part of the observed chemical shift that calculations using a static geometry (atomic coordinates) do not provide the whole shielding story and may even lead to incorrect assignments of chemical structure. We consider both rovibrational averaging, which leads to isotope shifts and temperature dependence of shielding even in the gas phase, and dynamic averaging in condensed systems, notably in liquids. There are different approaches which have been used, and we consider which of the approaches is most logical for the type of system at hand. In the earlier parts, we discuss how the physical aspects of the system (bond length, bond angles, torsion angles, presence of neighbours, dynamics of bonded and non-bonded atoms, relativistic neighbours bonded and otherwise) have to be introduced into the model so as to carry out a proper calculation that can be compared with experimental measurements. In part 6, we discuss how to turn the information arrow the other way around: in favourable circumstances, what can the observed differential shieldings tell us about the nature of the physical system? Here, we provide some examples where theoretical calculations have been used to verify hypothetical information about the physical system under study.

2. ADVANCES IN METHODS OF CALCULATION

2.1. Relativistic calculations

In the calculations of nuclear magnetic shielding, the vector potential produced by the nuclear magnetic moment is very local and therefore affords a weighted sampling of the electronic wavefunction in the close vicinity of the

nucleus. Thus, the nuclear magnetic shielding in a molecular system is intrinsically an all-electron relativistic property. Methods and application of relativistic approaches to the calculation of nuclear shielding have been reviewed by Autschbach in this series of volumes in 2009. Therefore, in this review, we consider developments from 2009 on.

Conceptual and computational difficulties have conspired to delay the availability of fully four-component all-electron treatments at correlated levels using distributed gauge origins. However, the situation is largely clearing up. A difficulty particular to relativistic calculations of magnetic properties originates from the fact that the inclusion of a vector potential affects the balance between the large and the small components of the four-component spinors. This magnetic balance must be taken into account, explicitly or implicitly, in order to obtain accurate results for magnetic properties. An important difference between relativistic and nonrelativistic theory is the lack of an explicit diamagnetic term in the Hamiltonian in relativistic theory. However, the diamagnetic term enters through the contribution of negative energy states. The negative energy states are important for nuclear shielding because magnetic fields are introduced through operators which couple the large and small components, so the negative energy states cannot be neglected in relativistic treatment of magnetic properties, but it has been suggested that they may be treated in a simplified manner.[17] Extremely compact negative energy states require additional steep *s* and *p* functions in the basis set when highly accurate absolute NMR shieldings are sought. Effects of highly compact negative energy states essentially cancel out for relative shieldings (chemical shifts).[18] Kutzelnigg proposed a field-dependent unitary transformation of the four-component relativistic Hamiltonian in order to introduce an explicit diamagnetic term.[19] When magnetic balance between the small and large components is explicitly built in, the otherwise missing diamagnetism arises naturally[20] and the heavy demand on the basis sets of high angular momenta is also greatly alleviated.

Several groups considered a unified approach to four-component relativistic treatment of nuclear shielding nearly simultaneously. Kutzelnigg and Liu presented the formulation of a logical and systematic classification of existing methods of calculations of NMR parameters within relativistic quantum chemistry, together with new variants and presented new methods as well.[21] Various methods have been reported separately in this series over several years; the Kutzelnigg and Liu analysis puts all systematically in the proper context. They consider transformations at operator level versus matrix level, the possible formulations of the Dirac equation in a magnetic field,

traditional relativistic theory, field-dependent unitary transformation, bispinor decomposition, equivalence of the methods at operator level. They then consider relativistic theory in a matrix representation, expansion in unperturbed eigenstates, expansion in a kinetically balanced basis, and expansion in an extended balanced basis. The authors explore decomposition of the lower component, decomposition of the full bispinor, unitary transformation at the matrix level. They pay careful attention to singularities. First they discuss methods which are exact in the sense that their accuracy is only dependent on the quality of the chosen basis. In the limit of a complete basis, all these methods yield the same results, but the rate of convergence to the limit can be different.[21] Among these methods, they consider the ones best suited for each of the magnetic properties. For the case of nuclear magnetic shielding where one vector potential is due to an external field and one is due to a nuclear magnetic dipole, they suggest to discard the method based on the untransformed Dirac operator because it does not give the correct nonrelativistic limit. They also suggest to discard the method based on a unitary transformation of the full magnetic field because it is plagued by singularities. They offer the good choice as the method based on a unitary transformation of the external field only and formalisms equivalent to it because these lead to the correct nonrelativistic limit and are not plagued by singularities. They also recommend as a further possibility the method called FFUTm (full-field unitary transformation "at matrix level") by Xiao *et al.*,[22] where one starts formally from a unitary transformation at matrix level but evaluates the diamagnetic term exactly. They suggest that the restricted magnetic balance (RMB)[17] should be used. The performance of the various methods with respect to the basis set requirement has recently been investigated by Cheng *et al.*[18] The results differ very little, even for a small basis. Finally, Kutzelnigg and Liu[21] consider various approximations previously proposed which do not give the exact results in the limit of a complete basis, for example, see Xiao *et al.*[22] All of these approximations are based on methods which give the correct nonrelativistic limit and use a pseudo sum-over-states formulation with the restriction of the intermediate eigenstates to those with positive energy. Along the way, various commonly used approximations such as the Douglass-Kroll-Hess approximation[23] and the zeroth-order regular approximation (ZORA)[24] are discussed in context.

Cheng *et al.* showed that these variants of approaches using magnetic balance can all be recast into one unified form.[18] The various schemes previously proposed for incorporating the magnetic balance dependence are then shown to be equivalent to this new approach and therefore can be combined

with any level of theory for electron correlation. As mentioned in the analysis of Kutzelnigg and Liu, it has been recognized recently that the incorporation of the magnetic balance condition between the small and large components of the Dirac spinors is absolutely essential for four-component relativistic theories of magnetic properties. Cheng *et al.*[25] showed that the magnetic balance can be adapted to distributed gauge origins, leading to, for example, magnetically balanced gauge-including atomic orbitals (MB-GIAOs) in which each magnetically balanced atomic orbital has its own local gauge origin placed on its centre.[25] This MB-GIAO scheme can be combined with any level of theory for electron correlation.[26] Close inspection reveals that zeroth-order negative energy states are only important for the expansion of first-order electronic core orbitals. Their contributions to the paramagnetism are therefore transferable from atoms to molecule and are essentially cancelled out when taking shielding differences for chemical shifts.[25] As did Kutzelnigg and Liu, Cheng *et al.* also provided, in their introduction, critical remarks on the various schemes for relativistic calculations of NMR properties, classifying and comparing, noting where singularities occur and where numerical instabilities could occur, comparing various schemes to recover the relativistic diamagnetic contributions to the nuclear shielding, such as to guarantee the correct nonrelativistic limit.

Komorovsky *et al.* have also incorporated the gauge-including atomic orbitals (GIAO) approach in relativistic four-component DFT method for calculation of NMR shielding tensors using restricted magnetically balanced basis sets.[27] The authors carried out relativistic calculations for xenon dimer and the HX series (X = F, Cl, Br, I), where spin–orbit (SO) effects are known to be very pronounced for hydrogen shielding. It is not surprising that, when compared to shielding calculated at the four-component level with a common gauge origin, the results clearly demonstrate that the GIAO approach solves the gauge-origin problem in fully relativistic calculations as it does in the nonrelativistic case. Finally, what had been routine (use of GIAOs) for nonrelativistic calculations of shielding is becoming an integral part of four-component calculations of nuclear shielding. The formulation by Olejniczak *et al.*[28] is in many aspects similar to the one proposed by Komorovský *et al.*[17] except for a fully analytical approach and a possibility to use hybrid exchange-correlation (XC) functionals. To test their formalism, they carried out calculations of NMR shielding tensors for the HX series (X = F, Cl, Br, I, At), the Xe atom, and the Xe dimer.

In addition to the formulation of four-component relativistic theory of NMR parameters,[18] Cheng and co-workers[29] also presented an exact

two-component relativistic theory for nuclear magnetic shielding (and magnetizability and J coupling). This is obtained by first a single block-diagonalization of the matrix representation of the Dirac operator in a magnetic-field-dependent basis and then a magnetic perturbation expansion of the resultant two-component Hamiltonian and transformation matrices. They showed that all the problems (singularities, numerical instabilities) associated with the earlier attempts at an exact two-component treatment of NMR parameters can be avoided by going to a matrix formulation. That is, the matrix representation of the full Dirac operator in a magnetic-field-dependent basis can be block-diagonalized in a single step, just like the previous matrix formulation of the exact two-component algebraic Hamiltonians in the absence of magnetic fields. The resulting Hamiltonian and transformation matrices can then be expanded to obtain the expressions for NMR parameters. Such a matrix formulation is not only simple but also general in the sense that the various ways of incorporating the field dependence can be treated in a unified manner. The diamagnetic and paramagnetic terms agree individually with the corresponding four-component ones up to machine accuracy for any basis. The authors suggest that this formulation be adopted in lieu of quasi-relativistic theories that had been used previously.[29]

Polarization propagators have been successfully applied since the 1970s to calculate NMR parameters. They are special theoretical devices from which one can do a deep analysis of the electronic mechanisms that underlie any molecular response property from basic theoretical elements, such as molecular orbitals, electronic excitation energies, coupling pathways, entanglement, contributions within different levels of theory, etc. All this is obtained in a natural way in both regimes: relativistic and nonrelativistic. In a review article, Aucar *et al.*[30] discuss the new insights on magnetic shielding from relativistic polarization propagators, using model compounds CH_3X molecules (X = F, Cl, Br, I) and XH_n (X = Xe, I, Te, Sb, Sn; $n = 0$–4) as examples.

2.1.1 Four-component relativistic calculations

Maldonado *et al.* investigated the application of different magnetic kinetic balance prescriptions using the four-component polarization propagator approach in the calculation of nuclear magnetic shielding.[31] They find that, while working with relativistic polarization propagators, there is no formal requirement to enforce the application of magnetic kinetic balance prescription. The performance of various prescriptions was studied for molecules containing more than one heavy atom in order to examine the electronic

effects on the shielding of a heavy atom due to the presence of vicinal heavy atoms. The shieldings of X, Y, and H nuclei in XYH_3 molecular systems with X = C, Si, Ge, Sn and Y = Br, I were calculated thereby reproducing the HALA effect (vicinal heavy atom effect on the shielding of the light atom). The total shielding for ^{13}C in CH_3I is 235.57 ppm compared to ^{13}C in CH_4 where the total shielding is 195.55 ppm. Relativistic effects on the shielding of X due to heavy halogen atoms are larger for heavier X nuclei, which authors refer to as HAVHA + HAHA effects (heavy atom effects on the shielding of the vicinal heavy atom + heavy atom effects on its own shielding). The hydrogen shieldings exhibited an effect from the two-bond distant heavy atom Br or I; this effect is found to be more pronounced when the central atom is X = Si. All of these results are at the random phase approximation (RPA) level and so did not include electron correlation.[31]

Arcisauskaite *et al.*[32] investigated the importance of relativistic effects on NMR shielding tensors and chemical shifts of linear HgX_2 (X = Cl, Br, I, CH_3) compounds using three different relativistic methods: the fully relativistic four-component approach and the two-component approximations, linear response elimination of small component (LR-ESC), and ZORA. LR-ESC reproduces successfully the four-component results for the ^{13}C isotropic shielding value in $Hg(CH_3)_2$ within 6 ppm but fails to reproduce the ^{199}Hg shielding tensors and chemical shifts. The latter is mainly due to an underestimation of the change in SO contribution. Even though ZORA underestimates the absolute (relative to the bare nucleus) Hg NMR shielding values by ~2100 ppm, the differences between ^{199}Hg chemical shift values obtained using ZORA and the four-component approach without spin–density contribution to the exchange-correlation (XC) kernel are less than 60 ppm for all compounds using three different functionals, BP86, B3LYP, and PBE0. However, larger deviations (up to 366 ppm) occur for ^{199}Hg chemical shifts in $HgBr_2$ and HgI_2 when ZORA results are compared with four-component calculations.[32]

Relativistic calculations of NMR properties of RgH^+ ion (where Rg = Ne, Ar, Kr, Xe), ^{195}Pt shielding in platinum complexes, and ^{207}Pb shielding in solid ionic lead(II) halides have been reported.[33] For the Rg nucleus in the RgH^+ ions, four-component Dirac–Hartree–Fock (DHF), two-component (ZORA), nonrelativistic correlated, and nonrelativistic uncorrelated methods were used and results compared with each other. The difference between the DHF and HF (Hartree–Fock) calculations shows that for the Rg nucleus the relativistic effect on shielding scales with atomic number as $Z^{3.4}$. There are small effects on the shielding of the proton

in RgH^+ ion, 18.1, 5.2, 1.0, and 0.0 ppm in going from Xe to Ne, a trend similar to the one observed in the isoelectronic HX halides.[33] Seino and Hada likewise employed a four-component scheme to calculate the NMR shielding of the Hg atom.[34]

Relativistic four-component DFT-GIAO based calculations of ^{1}H NMR chemical shifts of a series of 3d, 4d, and 5d transition metal hydrides have revealed significant SO-induced heavy atom effects on the hydride shifts, in particular for several 4d and 5d complexes.[35] The SO effects provide substantial, in some cases even the dominant, contributions to the well-known characteristic high-field hydride shifts of complexes with a partially filled d-shell, thereby augmenting the Buckingham–Stephens model[36] of off-centre paramagnetic ring currents. In contrast, complexes with a $4d^{10}$ and $5d^{10}$ configuration exhibit large deshielding SO effects on their hydride ^{1}H NMR shifts.

2.1.2 Two-component calculations

Despite the new developments in four-component relativistic calculations of shielding described above, most relativistic shielding calculations are carried out with various two-component methods, DFT ZORA being the most commonly used method. Nuclear magnetic shieldings on the heavy atom for the systems $SnXH_3$ (X = H, F, Cl, Br, I), $SnXYH_2$ (X, Y = F, Cl, Br, I), and $PbXH_3$ (X = H, F, Br, I) were calculated using LR-ESC and compared to benchmark RPA calculations and then analyzed in order to determine the main trends and discuss the electronic origin of the shielding of two kinds of atoms involved in such systems: central and substituent atoms.[37] DFT ZORA calculations have been carried out with or without SO in a large number of systems, for example. ^{195}Pt shieldings in complexes,[38,39] ^{187}Os in osmium phosphines,[39] ^{207}Pb in cluster models of lead(II) halides,[40] ^{183}W in the polyoxometalates of W and Au,[41] ^{77}Se shielding in 40 molecules,[42] and for ^{195}Pt and ^{207}Pb in the $[Pt@Pb_{12}]^{2-}$ "superatom".[43]

Heavy atom effects on light atoms have also been demonstrated theoretically for ^{17}O in $[UO_2(OH)_4]^{2-}$,[44] ^{13}C in monohalo(F, Cl, Br, I) organic compounds,[45] ^{13}C and ^{14}N shielding in 6-halo(Cl, Br, I) purines,[46] ^{29}Si with Pd and Pt,[47] ^{13}C in methyl hydride complexes of Rh and Ir,[48] and ^{19}F in uranium chlorofluorides.[49]

2.2. Density functional calculations

The number of single point (one structure, usually the equilibrium structure) calculations of shielding reported annually[12] continues to grow. For single molecules, more important than the choice of functional is the use of an

energy-optimized geometry, preferably in the appropriate environment. The extreme sensitivity of shielding to bond lengths, angles, and torsions means that even X-ray diffraction (XRD) derived geometries need to be optimized. The widely accepted benchmarks for shielding calculations are the full-configuration interaction (CI) or coupled cluster singles, doubles, and triples calculations by Gauss *et al.*,[6,50,51] and they remain test systems against which any shielding calculation method should be checked. However, most systems of practical interest have larger numbers of electrons, therefore, for these systems, the method of choice has been DFT. There are many flavours of functionals in wide use, with or without admixture of exact exchange. When the perfect universal functional is found, no doubt the reliability of the results will be the same regardless of which part of the NMR Periodic Table is being investigated in organic, inorganic, or biomolecular systems. However, currently, some functionals perform better than others, depending on the nucleus of interest. Gauss's benchmarks only include molecules from which some reasonable absolute shielding scale has been developed, that is, where gas phase measurements have been done towards the isolated molecule limit. It is well known that cancellation of systematic errors can occur in calculating differences in shielding rather than absolute shielding (shielding in the system of interest relative to the bare nucleus). Therefore, the true test of a theoretical method is to be able to reproduce the full absolute shielding tensor as Gauss has done for light systems. Unfortunately, for many heavy nuclei this is not a possibility. Precisely for heavy atom nuclei, the identity that connects the spin rotation tensor and the shielding tensor,[52,53] in nonrelativistic theory does *not* hold in the relativistic domain. This has been proven experimentally by Wasylishen and co-workers by measuring the shielding tensors for XeF_2 in the solid state.[54] Here, there are well-defined shielding reference systems, the isolated Xe atom and the well-established ^{19}F absolute shielding scale (see a review of this proof in Ref. 55). Aucar et al. have carried out an analysis of the relativistic spin-rotation tensor and the nuclear magnetic shielding tensor by deriving in parallel the expressions for these tensors, considering relativistic electrons and non-relativistic nuclei for a molecule with a singlet ground state.[56] The coupling of the electronic distribution to the magnetic field is described by the vector product of the position and velocity operator, while the coupling of the electronic state and the rotational state is described by the total angular momentum operator. These quantities are simply related at the non-relativistic limit, but in relativistic quantum mechanics, the two operators couple the upper and lower components of the 4-component wavefunction very differently.

A combination of lack of gas phase absolute shieldings and the prevalent condensed phase environments, with attendant complexities of structural dependence on solution conditions, makes it difficult to judge which of the used functionals works best for calculations of transition metal shieldings, for example. At best, it is possible to observe whether the slope of calculated chemical shifts (usually using one of the compounds in the set as the reference) versus experimental chemical shifts is close to 1.0 for a wide range of compounds. Bühl has carried out many such comparisons for several transition metal nuclei, comparing the performance of different functionals. Hybrid functionals perform somewhat better for Ru chemical shifts, for example. This is in contrast to the situation for light, main-group nuclei where generalized gradient approximation (GGA) functionals (such as KT1 and KT2) can be more accurate than hybrid functionals.[57] For the present, the slope of the chemical shift plot for the whole range of compounds may be the best test, but it suffers from an inability to detect cancellation of systematic errors (in the treatment of core electrons, for example), and it could be misleading when the solution environment imposes differing amounts of environmental contributions for different compounds, as when a mix of neutral and charged complexes are included. Transition metal complexes that have net charge cannot be compared directly with uncharged carbonyl complexes, for example.

Since the Wilson review of this topic in this series (vol. 49, 2003), research on improvements on the currently available exchange-correlation functionals remains an important and active area of theoretical research. Despite the great success of global hybrid functionals, for example, B3LYP and PBE0, in predicting various molecular properties, they turned out not to be sufficiently flexible: It is usually not possible to find a unique constant for the amount of exact-exchange admixture that provides consistently high accuracy for different properties as well as for different classes of systems.

The Tozer group has been developing methods of devising corrections that improve the structure of the exchange-correlation potential, in particular, using the challenging diatomic molecules CO, N_2, and PN as the systems for testing.[58] They developed the KT1 and KT2 GGA functionals designed specifically to provide high-quality NMR shielding tensors. For shieldings in molecules of light main group elements, the results using KT1 and KT2 are encouraging; errors approach those of correlated wavefunction methods.[59] They also developed a new functional KT3 by an introduction of additional gradient-corrected exchange and correlation terms which preserve the high-quality shielding calculations of KT1 and KT2 and compared the performance with other GGAs.[60] For Se

compounds, they find that KT3 can simultaneously provide good quality geometries and ^{77}Se shielding tensors, without the inclusion of exact exchange, whereas the widely used B3LYP functional gave relatively poor results.[57] Tozer *et al*. have been studying the influence of optimized effective potential (OEP) and Coulomb-attenuation in DFT calculations of shielding and chemical shifts.[61]

Kaupp has been very active in constructing improved functionals that are still computationally efficient yet more accurate than existing ones. As he also has an active program in calculating NMR properties, the functionals he develops are tested for performance not only in thermochemistry and reaction barriers but also for NMR properties such as shielding and spin–spin coupling, in particular. Local hybrid functionals are a promising new generation of exchange-correlation functionals. In contrast to the constant exact-exchange admixture of global hybrids, local hybrids include exact exchange in a position-dependent way, governed by a "local mixing function" (LMF). Therefore, considerable effort has been spent recently in developing a hybrid function which determines the position-dependence of the exact-exchange admixture.[62] Recently, Arbuznikov and Kaupp reviewed the advances in hybrid functionals and discussed different strategies to construct LMFs (semiempirical vs. *ab initio*), different levels of the implementation of local hybrids (self-consistent vs. non-self-consistent), and some methodological aspects associated with the calculation of second-order magnetic properties (a coupled-perturbed scheme for general hyper-GGA functionals).[63] They provided some examples for the performance of local hybrids in the description of NMR properties. Localized local hybrid (LLH) potentials derived from corresponding local hybrid functionals with position-dependent exact-exchange admixture governed by appropriate LMFs were tested in calculations of nuclear shielding in molecules containing main-group nuclei and found to yield results that were comparable to those from global hybrid functionals, but this was achieved without generalized gradient corrections.[64] A more detailed examination of the performance of local hybrid functionals for NMR properties is given in Ref. 65 where recent work in the field of occupied-orbital dependent (OOD) exchange-correlation functionals in DFT is reviewed, with emphasis on the development of local hybrid functionals, and on the nontrivial self-consistent implementation of complex OOD functionals. Recently proposed LMFs have provided local hybrids of high accuracy in the computation of thermochemical data and with good performance for some magnetic resonance parameters. These local hybrids require very few semiempirical parameters. Two levels of the self-consistent implementation of

OOD functional are discussed: one may stop after the derivation of the functional derivatives with respect to the orbitals, leading to nonlocal potentials. This is discussed for local hybrids and for general OOD functionals up to and including the complicated B05 real-space model of nondynamical correlation. Alternatively, one may append an additional transformation to local and multiplicative potentials based on the OEP approach or of approximations to the OEP.[66] The localized Hartree–Fock-common energy denominator Green's function approximation (LHF-CEDA) to the OEP has been used to compute nuclear shielding tensors within an uncoupled Kohn–Sham (KS) framework.[67] The OEP approach has been tested with conventional hybrid functionals B3LYP and PBE0 for calculations of transition metal shieldings (Ti, Cr, Mn, V) in selected complexes and the results are an improvement over conventional hybrid values.[68] Numerical results for performance of local hybrid functionals for various properties including nuclear magnetic shielding have been reviewed.[65]

3. LOCAL EFFECTS ON SHIELDING: SINGLE MOLECULES, CLUSTERS, AND FRAGMENTS

That which makes the observed NMR chemical shift an extremely useful tool is the exquisite sensitivity of shielding to small differences in electronic environment. Of course, in turn, this means that theoretical calculation methods have to meet the challenge of explicitly including these factors. Our increasing ability to do quantum calculations for larger collections of atoms means that larger parts of the chemical environment can *a priori* be included in the theoretical system under study. Complete success would mean that we could reproduce measured values to experimental accuracy. Towards this goal, we have noted above that shielding calculations using four-component wavefunctions are beginning to be accessible and exchange–correlation functionals are being devised which are suitable for the demanding description that shielding calculations require more than does calculation of thermochemical data. Meanwhile, NMR practitioners still value the insight that can be gained by including various parts of the chemical environment of the nucleus, focusing on one or more factors at a time, thereby discovering what knowledge is largely transferable from one physicochemical system to another. In this section, we consider the current approaches to include various intra- and intermolecular effects on shielding. Even with increased computational capabilities, the use of small molecular fragment models or clusters to reproduce local effects, either via conformation or non-bonded interactions, continues to be a method

of choice. The information derived from these model calculations permits in most cases a decomposition of the NMR chemical shifts into its various contributing factors, and at times, fortunately provides one dominant element that determines the experimentally observed differences in NMR chemical shifts.

3.1. Conformational effects

With a firm basis supported by *ab initio* calculations that show convincingly that protein NMR shieldings are intimately dependent on backbone torsion angles, NMR chemical shifts are now widely recognized as important determinants of protein secondary structure. SPARTA (shift prediction from analogy in residue type and torsion angle) from Shen and Bax[69] is one example that utilizes a database of assigned protein chemical shifts and known X-ray structures. On the theoretical front, theoretical shielding surfaces that describe the dependence of NMR shielding on backbone torsion angles using *N*-formyl-$(Ala)_3$-NH_2 have been shown to be adequate in qualitatively describing backbone chemical shifts of all amino acid residues except Cys.[70] Taking into account motional averaging of $^{13}C^{\alpha}$ chemical shifts, thousands of computations can now be performed on model fragments, resembling hundreds of possible conformations, thereby allowing for the evaluation or validation of NMR-derived protein structures.[71] And as expected, one consequence of averaging is a reduction in the chemical shift anisotropy, as noted by Tang and Case[72] in their study of ^{15}N sites in peptides.

The success in understanding conformational effects on protein chemical shifts originates from the success in predicting these changes in small molecules. Confidence in this approach, as achieved in smaller systems, has led to its application to other larger systems, some of biochemical interest. With a fragment model consisting of a dimethyl phosphate and water molecules in the first solvation shell, a description of how ^{31}P shieldings in DNA are affected by the phosphate backbone torsion angle has been accomplished.[73] Other examples along this line of research involve studies on polymorphs,[74–81] confined molecules,[82] substituted calixarene systems,[83] sugars,[84,85] α, β-unsaturated carbonyl compounds,[86] and phase transitions.[87]

3.2. Neighbouring non-bonded atom effects

We consider (a) van der Waals contribution to the shielding which arise from the shielding response of the electrons of the neighbour atoms in interactions with the electrons of the atom in question and (b) the shielding contributions from the electrons of the neighbour atoms that would be

present even for a nuclear magnetic dipole at that position without its own electrons. The latter is independent of the nucleus under study, commonly referred to as NICS (nucleus independent chemical shift). The latter (NICS) is usually small compared to the former contribution to intermolecular shielding and is the same for all nuclei, so it is a relatively significant intermolecular effect only in the case of proton shielding. Also, NICS can be significant when aromatic rings are present, so it is often discussed in terms of "ring current" contributions.

In the field of intermolecular effects on NMR shielding, ^{129}Xe remains a nucleus of choice. The unsurpassed versatility of ^{129}Xe shielding is dramatically demonstrated in diastereomeric ^{129}Xe chemical shieldings, when Xe is placed inside a chiral cage, such as cryptophane-A, with a chiral compound attached to the cage. Calculations permit the assignment of the individual peaks in the diastereomeric sets.[88] Using O_2 as a model paramagnetic compound, even the changes in ^{129}Xe line shapes for Xe gas inside nanochannels containing paramagnetic impurities have been theoretically predicted.[89] Constitutive (CH_3, CH_2 contributions) solvent effects on ^{129}Xe shieldings of Xe dissolved in normal and cyclic alkanes have been theoretically determined,[90,91] again, with the use of model fragments.

Calculations of molecular shielding surfaces, the nuclear magnetic shielding at points in space around a molecule that would be experienced by a probe magnetic moment such as that of a neutron probe (sometimes referred to as NICS) provide visualization and quantification of the magnetic anisotropy effects arising from aromatic rings, C=C double bonds, or other groups. Ring currents can be an important factor in understanding and utilizing intermolecular NMR chemical shifts. For calculations of these contributions to shielding, there is likewise a need to take the appropriate cluster unit for the quantum calculations, for example, a trimer.[92] On account of the marked dependence of the ^{1}H chemical shift to ring currents arising from nearby aromatic rings, the calculated ^{1}H chemical shifts are found to be very sensitive to the stacking arrangement of the hexabenzocoronene molecules. Moreover, the ring current effect is found to be particularly long range, with a considerable influence of the second neighbour, at a distance of 700 pm, being observed. Modelled by a trimer structure, the shielding values for the molecule in the middle are then compared against experiment.

The visualization and interpretation of ring currents remains an active field of research. Ring currents have been shown, for example, to be dominated by contributions from the HOMO–LUMO virtual excitations,[93] as suggested by ipsocentric calculations on benzene, cyclooctatetraene,

borazine, coronene, and corrannulene. This approach has been extended to relatively large polycyclic aromatic compounds containing up to 438 carbon atoms.[94] Stagnation graphs displaying both vortices and saddle lines of the current density have also been drawn to explain general features in diatropic molecules.[95,96] Plots of magnetic shielding density combined with a visualization of the current density allow for a detailed interpretation of aromaticity and sigma ring currents, as exemplified in the simple model of a cyclopropane molecule.[97] Spatial models have been constructed likewise to display current densities around small molecules such as LiH, BeH_2, CO_2, C_2H_2, and C_2H_4.[98,99] Lastly, computations of magnetic shielding at points in space in the vicinity of small model molecules (NICS) are still widely used in quantifying anisotropy effects from aromatic rings and other groups containing a double bond. Examples include rigid cyclophanes and their derived carbocations,[100] inorganic clusters of boron,[101] highly congested hydrocarbons that contain alkene groups,[102] nitrate ion in complexes,[103] trisannelated benzenes,[104] fullerenes,[105] cyclobutadiene dianion derivatives,[106] calicene,[107] tetraazanapthalenes,[108] metallabenzenes,[109] and 9-arylfluorenes.[110]

3.3. Hydrogen-bonding effects

Hydrogen bonding, with its prevalence in nature, is an important factor for medium effects on NMR shielding. The most important effects are on the shielding of the donor atom, the acceptor atom, and the bridging H itself, but there are effects on neighbouring atoms of the donor and acceptor as well, especially when those atoms are themselves involved in hydrogen bonds. Duma *et al.* have recently summarized ways by which solid-state NMR can be used to characterize hydrogen bonding. These include not only a study of the shielding tensors of the non-hydrogen atoms (e.g. ^{13}C and ^{15}N) but also ^{1}H chemical shifts and relaxation times, which provide important clues with regard to not only the strength but also the dynamics of hydrogen bonding.[111] The least shielded and intermediate components of the ^{15}N shielding tensors are significantly affected by hydrogen-bond formation. By closely deciphering the observed ^{1}H and ^{13}C chemical shifts in anomeric maltose, Yates *et al.*[112] have found a quantitative correlation between the NMR chemical shifts and the geometry (distance and angle) of weak CH···O hydrogen bonds.

Cluster calculations are oftentimes seen necessary for reproducing hydrogen-bond effects on shielding. For example, explicit water molecules in the first solvation shell for *N*-formyl-alanyl-X amides (where X is one of the naturally occurring amino acids) appear to be consequential in

reproducing correctly the amide ^{15}N chemical shifts.[113] Likewise, taking hydrogen bonding into account in calculations of shielding for H, N, and O nuclei in amino acids, peptides, proteins, nucleic acids, DNA, sugars requires including each hydrogen-bonding partner or its surrogate donor or acceptor in the cluster. Using an approach previously used for interpreting ^{13}C chemical shifts in proteins by varying the torsion angles in a model cluster, the variation in the ^{31}P shielding tensor components as a function of DNA and RNA backbone conformations has been predicted from calculations on a solvated model cluster dimethyl phosphate.[114] The ^{31}P nucleus also serves as a probe for hydrogen bonding and ionization states in phosphorylated serine residues.[115] More accurate calculations necessitate including the next shell of hydrogen-bonding partners beyond those partners of the molecule in question. Some examples are ^{17}O shielding calculations in crystalline urea by Wu and co-workers.[116] It took six neighbouring urea molecules at the crystallographic positions to provide a suitable cluster for calculations that could reproduce the experimental ^{17}O shielding tensor in urea.[116]

The number of hydrogen bonds is particularly important in interpreting the shielding tensors for Cl^- ions in various amino acid—HCl salts.[117] As the chloride ion is usually present as a counter ion in amino acid salts, ^{35}Cl NMR measurements and shielding calculations have likewise been performed on these systems.[118] The ^{35}Cl shielding in these compounds is sensitive to the type of hydrogen-bonding present, which, in turn, depends on the type or identity of amino acid.

Calculations of the ^{1}H and ^{17}O shielding tensor components in liquid water itself are challenging. For this system, a hybrid approach, one that uses a small core of water molecules (about 10) treated quantum mechanically while adding a self-consistent reaction field that models the environment, has been applied.[119] This model makes it possible to incorporate dynamics and the following elements of *ab initio* computations; effects of electron correlation, gauge-origin independence, and type of semiempirical potentials, on the quality of the calculations can then be properly evaluated. Further discussion of shielding calculations for liquid water, a challenging system, is found in Section 5.3.4.2.

3.4. Electrostatic field effects

Approximations for including solvent effects on NMR shieldings are available. These approximations basically describe the environment provided by solvent molecules with an electrostatic potential. The simplest approach is an

implicit solvent model, that is, to use a reaction field approximation for the medium. No specific interactions of the cluster with the solvent molecules are included, a dielectric continuum is assumed. Methods in wide use for geometry optimization and shielding calculations incorporating solvent effects using continuum models are the conductor-like screening model (COSMO)[120] and polarizable continuum model (PCM).[121] Another approach is by embedding of the cluster in a point charge field. The representation of the crystal lattice with point charge arrays in quantum mechanical nuclear magnetic shielding calculations was pioneered by de Dios *et al.*[122–124] in the charge field perturbation (CFP) method which they applied to proteins. In these calculations, the shielding for the nuclei of interest in a given subject molecule are computed at a high *ab initio* quantum mechanical level, whereas the long-range contributions from beyond the subject molecule are simulated using AMBER point charges. Including charge distributions in the quantum chemical calculations does not significantly increase the computational costs, as the use of point charges does not require basis functions. A more formal approach is a self-consistent embedded ion method, EIM.[125] The method simulates the electrostatic crystal potential that is experienced by each atom in a given molecule or ion inside an infinite crystal lattice, the Madelung potential, with a large but finite array of point charges. A finite point charge array that reproduces the Madelung potential in a defined, central region of the array with the desired accuracy is obtained in an iterative procedure, that is, the embedding charges are determined by an SCF (self-consistent field) procedure. Subsequently, the nuclear magnetic shielding tensors of interest are calculated for a given ion or molecule embedded inside the point charge array, located inside its central region. Another method that gives comparable results to EIM is SCREEP (surface charge representation of the electrostatic embedding potential).[126] This method simulates the Madelung potential at a given subject molecule by a point charge distribution on a van der Waals surface surrounding the subject molecule. A direct comparison between using EIM and SCREEP for representing the electrostatic equivalent of the long-range intermolecular effects on ^{13}C and ^{15}N shielding tensors in Gly-Gly hydrochloride monohydrate, acetic acid, calcium formate, naphthalene, ammonium hydrogen oxalate hemihydrate, sucrose, and L-histidine monohydrate gives comparable results for the two methods.[127] An improvement over EIM is the extended embedded ion method (EEIM) of Weber *et al.*[128] It is similar to the EIM of Stueber *et al.*[125] in the manner of embedding the quantum chemically

treated part in an exact, self-consistent Madelung potential, and requires no empirical parameters. The comparison between EIM and EEIM is discussed by Weber *et al.*[128] A different way of choosing the embedding charges and a closer attention to the boundary between the cluster and the charge field gives the EEIM better agreement with experiment for ionic solids.[128] In the past, the EIM was mainly applied to organic compounds with relatively low ion charges. Deficiencies which gain importance when typical inorganic compounds with highly charged ions are involved are attended to in EEIM.

These approximations using point charge arrays and other similar approaches influence chemical shift computations in two ways, a direct and an indirect contribution. Calculating NMR shieldings with the perturbation of an electrostatic potential provides a direct contribution; this is a small effect and is determined by the values of the shielding derivatives with respect to electric fields, the so-called shielding polarizabilities and hyperpolarizabilities.[129] Calculations of shielding polarizabilities have been carried out at various levels of theory; they are notoriously dependent on basis set size and the level at which electron correlation is included.[130–132] The most accurate calculations at the highest coupled cluster levels indicate that the direct contribution of an electrostatic potential is usually small.[133] The Xe shielding in the presence of an electrostatic field from point charges representing the H and O atoms of crystalline clathrate hydrate cages is only 0.5 ppm lower shielding than in an isolated Xe atom.[134] As NMR shielding is extremely sensitive to local geometry, particularly bond length, geometry optimizations in the presence of the electrostatic field lead to a potentially significant indirect contribution to the calculated shielding. Using water to illustrate these two contributions, it has been shown that approximations have a greater effect on calculated shieldings via the structures that these charge field embedding approaches generate in the geometry optimization step, that is, the structure of the model system for the shielding calculation, rather than the level of electronic quantum calculations used in the shielding calculation itself.[135]

Some recent examples using continuum models are ^{195}Pt nuclear shielding in *cis* platin derivatives,[136] ^{183}W shielding in polyoxotungstates of different shapes and charges,[137] ^{31}P shielding in the phosphate head group of sphingomyelin,[138] ^{15}N and ^{13}C nuclear shieldings in halopurine nucleosides.[139] Examples of embedded clusters using EIM include the calculation of the ^{13}C chemical shift tensors in potassium carbonate, bicarbonate and related monomethyl derivatives,[140] the ^{13}C and ^{15}N chemical shift tensors in

adenosine, guanosine dihydrate, 2-deoxythymidine, and cytidine,[141] the ^{13}C chemical shift tensors in *p*-aminosalicylic acid, isaniazid, and pyrazinamide,[142] and also the ^{129}Xe shielding hypersurface for a xenon atom inside a cage of clathrate hydrate structures I and II.[134,143] EIM and EEIM results for ^{19}F and ^{31}P shielding tensors in NaF and in four different magnesium phosphates have been compared with experimental values from solid-state MAS (magic angle spinning) NMR. The improved agreement of EEIM results in comparison with experiments allows new signal assignments for the different P-sites in $Mg_2P_4O_{12}$, a-$Mg_2P_2O_7$, and MgP_4O_{11}.[128]

3.5. Intermolecular relativistic effects

Relativistic effects are significant for the absolute shielding of ^{129}Xe in an isolated atom,[144] but how important are relativistic contributions to intermolecular effects on ^{129}Xe shielding, that is, do the relativistic contributions remain largely unchanged as Xe atom comes close to another atom? In an attempt to answer this question,^{129}Xe shielding calculations have been performed at the BPPT (Breit Pauli perturbation theory) level with an uncontracted [29s25p24d2f] basis.[145,146] The relativistic calculations show that the BPPT contributions to the intermolecular shielding of ^{129}Xe in the Xe_2 dimer are about 10% at an internuclear distance of 3 Å, and 7% at the equilibrium separation of 4.36 Å. These differences are quite comparable in magnitude and opposite in sign to the contributions arising from electron correlation, as provided by the differences between calculations at the Hartree–Fock and CCSD(T) levels of theory.

A possible example of intermolecular relativistic effect is the large gas-to-solution shift of solutes in CH_nI_{4-n} solvent, becoming larger with the number of iodine atoms (Karol Jackowski, private communication). This phenomenon had been puzzling for some time, but no relativistic calculations have yet been carried out to determine how large the relativistic contributions are.

Both the intermolecular effects on shielding and those arising from non-bonded neighbour atoms in the secondary or tertiary structure of the same molecule can be reasonably reproduced via Hartree–Fock or density functional calculations for ^1H, ^{13}C, and other light nuclei, provided that heavy atoms are not present. Otherwise, relativistic corrections are necessary. For instance, in polyamine H_2O and alcohol complexes of transition metals Rh, Co, and Ir, SO contributions to ^1H shielding are found to be significant.[147]

Deprotonation of the H_2O or alcohol ligands in these systems depicts interesting trends such as SO-induced spin polarization, transmitted across at least three bonds from the central transition metal atom. In addition, the effects across increasing atomic numbers are unusual as these do not increase with the square of the atomic number in the series Rh, Co, and Ir. Also, a Karplus-like behaviour is observed in how the SO effects behave with changes in dihedral angle. This marked dependence holds promise in utilizing SO effects to probe the stereochemistry of these complexes.

3.6. Shielding and chirality

NMR shieldings are, in general, identical for a given set of enantiomers L and R in a magnetic field. Only the presence of chiral influences such as other chiral molecules, chiral potentials,[148] and/or parity violations[149] can give rise to a pseudoscalar addition to the shielding and thereby generate differences in the shielding between enantiomers in a magnetic field. Particular aspects of chirality and diastereomerism have been investigated, namely, chirality induced in an achiral system, that is, induction of a chiral response in an achiral molecule by a chiral environment, which may be called induced chirality.[148,150–152] This was done by studying the full nuclear magnetic shielding tensor of the Xe atom in a chiral environment and also in the chiral field of other asymmetric groups. Helices of neon atoms were used to model the chiral environment and a helical arrangement of point charges to model a chiral field. The findings were as follows: (1) The Xe shielding tensor components for the R and L systems are related by a rotation that changes the signs of the off-diagonal elements, but the eigenvalues of the symmetric matrix which provide the principal components of the Xe shielding tensor are identical. (2) The non-zero antisymmetric part of the shielding tensor is one measure of the induced chirality. Three principal components of the tensor and the directions of the principal axes system relative to the laboratory axes are a maximum of six quantities that can be determined from a single-crystal NMR experiment. At most three principal components can be obtained from a powder NMR spectrum. Only the isotropic shielding can be obtained from a solution NMR spectrum. The antisymmetric part is not observed in the usual NMR spectrum. Therefore, we can see that the R and the L systems produce the same Xe NMR spectrum in this model system. With the exception of the chiral point groups, D_n, T, and O, which forbid the existence of antisymmetric shielding,[153] chirality is a sufficient

condition for the existence of antisymmetry in the shielding but not a necessary condition.

The standard method of generating different magnetic responses for a given enantiomer is to create the diastereomer, where in a racemic mixture there would now be two resonances in the NMR spectrum, one corresponding to Ll+Rr, the other to Lr+Rl, as opposed to a single resonance for L and R. This is to be expected, as diastereomers are not mirror images of each other; hence, the magnetic responses from components of a diastereomeric set are not identical. On the other hand, the mirror images Ll and Rr are not distinguishable from each other by NMR, nor is Lr distinguishable from Rl. The shielding difference between the two components (say Ll vs. Lr) of a diastereomer is not necessarily small, as the structure and shape of the two can be significantly different; they are two different molecules after all. Thus, observed NMR chemical shifts have been used traditionally to distinguish diastereomers. An experimental example of induced chirality is Xe trapped in chiral cages such as cryptophanes.[154] The Xe atom acquires induced chirality, but the only way to observe it is to create diastereomers, for example, by placing the cage in a chiral medium or in the presence of a chiral group bound to one of the external faces of the cage. The ^{129}Xe shielding of an Xe atom in chiral cages such as those of cryptophanes has led to observation of diastereomeric signals.[154,155] Calculations have provided good estimates for the splittings of the signals and the assignments of one peak to Ll+Rr, the other to Lr+Rl.[154] Experimentally, the use of left-handed amino acids in the group chemically attached to a racemic mixture of cages, led to having only Ll and Rl systems in the sample, where the cage chirality is in upper case. Furthermore, for the chemical systems where the attached group had two asymmetric centres, the four peaks could be individually assigned to each one of (Ll_1l_2+Rr_1r_2), (Ll_1r_2+Rr_1l_2), (Lr_1r_2+Rl_1l_2), (Lr_1l_2+Rl_1r_2), where the cage chirality is in upper case and the chiral centres on the attached group are designated by lower case letters.[154] Again, in this case, the use of only left-handed amino acids in the synthesis led to having only Ll_1l_2, Ll_1r_2, Rl_1l_2, and Rl_1r_2 being present in the sample.

Under certain conditions, the application of a static or an AC electric field could remove the chiral blindness of conventional NMR.[156,157] Although demonstrated in principle, experimental realization is yet to be designed.

An example of a small diastereomeric shift is found for ^{3}H in the diastereomeric set (L-CHDT)-(α)-isosparteinium and (R-CHDT)-(α)-isosparteinium.

The L-CHDT group has a ^{3}H chemical shift that is 49 ppb downfield from the R-CHDT resonance.[158] The observed sign and magnitude of this diastereomeric shift is found to be in agreement with the values calculated from Hartree–Fock, DFT-B3LYP, and DFT-B3PW91 using the 6-311+G(2d,p) basis set. The shieldings of the three limiting positions (rotamers) were calculated and the mole fractions of each rotamer were also theoretically calculated. The three rotamers have distinct conformational energies. Weighting these limiting values with the populations yields the expected shielding difference between the diastereotopic methylene protons of the CHDT group. That such a small difference in chemical environment between the two diastereotopic sites could be observed is another confirmation of the extreme sensitivity of the shielding to the electron distribution at the nuclear site.

NMR shielding calculations have been carried out to help assign the stereochemistry in newly synthesized organic and natural products. Computations are made on several candidate structures in the gas phase with geometries previously optimized either by *ab initio* methods or MMs force field dynamics. Conformational distribution for each stereoisomer can be incorporated in these calculations by Boltzmann averaging over all low-energy conformers. This approach has been elegantly illustrated in the analysis of 16 diastereomeric stereopentads,[159] and the assignment of stereochemistry of 21 natural products, some of which had been previously incorrectly assigned.[160] It is in this pursuit that theoretical calculations may be able to aid in interpreting spectra, having in theory what shielding each specific diastereomer has and taking into account its distribution in the population.

4. SHIELDING IN EXTENDED NETWORKS

4.1. Approaches to extended networks

As we have described above, to apply the first-principles quantum mechanical calculation techniques to solid-state NMR, it had been necessary to devise finite clusters of atoms which model the local environment around a site of interest and embed the cluster in a charge field or other representation of the true extended structure, point charge embedding to model the long-range Coulomb interactions (e.g. EIM, Refs. 125,128). While this has led to unprecedented understanding of structure and neighbour influences on shielding, and successful predictions of NMR chemical shifts in systems such as molecular crystals,[161–165] ionic crystals[128,166,167] and supramolecular assemblies,[92] there are attendant difficulties particularly for covalent solids,

where capping of truncated covalent bonds may bring edge effects into play. Therefore, approaches are needed that inherently take account of the long-range effects in extended systems and also preserve the nuclear site symmetry by properly describing the periodic nature of the solid. For large systems, highly accurate quantum chemical calculations are prohibitively expensive and thus, only the computationally more affordable DFT can be used.

Several alternative DFT methods for periodic systems have been developed. These methods can be applied to crystalline and amorphous insulators under periodic boundary conditions (PBC), as well as to isolated molecules using a supercell technique. We refer to these methods collectively as PBC methods. (a) The most extensively used method originates from the first developed approach to shielding calculations in periodic solids by Mauri *et al.*[168] who overcame the inherent difficulty that the position operator which explicitly enters the perturbed Hamiltonian for NMR is not well defined for periodic systems. This original approach was adapted later via implementation of GIPAW,[169] gauge-including PAWs, which is a modification of PAW (projector augmented wave) for systems in an external magnetic field. GIPAW plays a role similar to GIAO in quantum chemistry techniques. The GIPAW algorithm reconstructs the all-electron wavefunction in the presence of a magnetic field. The code for this method is implemented in the CASTEP software suite,[170] in PARATEC,[171] and also in Quantum ESPRESSO.[172] All these software suites are based on density–functional theory, plane-wave (PW) representations, and pseudopotentials. (b) The method developed by Sebastiani[173] transforms Bloch states to localized Wannier orbitals to overcome the position operator problem. This is implemented in the CPMD (Car-Parinello molecular dynamics) suite of programs.[174] This approach has been extended by Weber *et al.*[175] to an all-electron description of the system with mixed Gaussian and augmented plane waves (GAPW), implemented in QUICKSTEP,[176] which is part of the CP2K suite.[177] (c) The converse approach of Thonhauser *et al.*[178,179] calculates shielding as the finite difference of orbital magnetization with respect to nuclear moment, thus without having to resort to linear response theory, and a later development uses GIPAW for pseudopotential augmentation.[180] The converse method is implemented in Quantum ESPRESSO.[172] (d) Ziegler *et al.* have developed a method of calculating shielding in periodic systems using atom-centred basis functions,[181,182] implemented in the BAND program suite.[183] In BAND the Bloch basis set is

constructed from Slater-type orbitals (STOs) and/or numeric atomic orbitals (NAOs). The electronic density matrix near the nuclei is very important for NMR shielding and both STOs and NAOs afford a potentially accurate description of the KS orbitals in this region; in particular some users prefer STOs because they satisfy the cusp at the origin. Atomic-centred basis functions allow for use of gauge-included atomic orbitals (GIAOs) to ensure gauge-invariant shielding results. (e) The linear-augmented plane waves (LAPW)[184] all-electron approach (implemented in the WIEN2k software package for electronic structure of solids)[185] has been extended to shielding calculations by Laskowski and Blaha.[186] We consider these methods in turn.

(a) Mauri *et al.* (1996, 2001, 2007)

In solids, the task of computing the induced current is complicated by the fact that the magnetic field breaks translational symmetry. Moreover, the position operator, which explicitly enters the perturbed Hamiltonian, is not well defined for periodic systems. The first method that overcame this difficulty was proposed by Mauri *et al.*, where the external magnetic field was modulated with a finite wave vector.[168] The response was then calculated taking the limit at infinite length of the modulation vector. Although this method was developed within an all-electron formalism, it has been applied using pseudopotentials. It can be shown that for finite systems PAW and GIPAW use special pseudopotentials which, by reconstructing all-electron density close to atomic nuclei, correctly account for electrons in this region. The response is calculated taking the limit at infinite length of the modulation vector. It has been shown that for finite systems the Mauri *et al.* method is equivalent to a variant of the continuous set of gauge transformations (CSGT) method.[187] The method of Mauri *et al.* has been derived and implemented for plane-wave (PW)-based pseudopotential codes; however, it neglects the effects of the wave functions that have been modified by the pseudopotentials on the induced current, which should be considerable in the core region of heavier atoms. It has been used for light elements and with the use of hard pseudopotentials in several applications, particularly for covalent solids,[188–191] and in ice and liquid water.[192] This drawback has been removed by Pickard and Mauri.[169] Their approach operates within the projector augmented-wave method (PAW)[193] and has defined the PAW transformations such that they ensure correct gauge (translational) symmetry of the pseudo-wavefunction in the presence of the external magnetic field. The method is referred to in literature as the GIPAW method. Within the framework of the pseudopotential approximation,

the GIPAW method is able to converge towards all-electron magnetic response calculations. One contributing factor to this success is the assumption of a rigid contribution to the shielding NMR parameters of core electrons, that is, the assumption of the validity of the frozen core approximation. Therefore, the all-electron atomic potential can be replaced by a pseudopotential which mimics the potential created by the nucleus surrounded by its inner electrons. The orthogonality condition between the valence and the core states being relaxed, the valence wave functions become smoother and easier to calculate using PW basis sets. For second and third row elements, the core-valence states separation is quite obvious and usual selections of core states are employed by the community for first-principle pseudopotential calculations. A large number of GIPAW shielding calculations in this form have been carried out on covalent solids such as boron carbide,[194] carbon nanotubes,[195] SiO_2,[196] silicate crystals and glasses,[197–199] aluminosilicates,[200,201] molecular crystals,[112,202–204] including polymorphs.[205,206] Difficulties appear for the fourth row elements, for example, for the 3d transition metals. First row elements, transition, and rare-earth metals require very large numbers of PWs to accurately describe the valence wave functions. As both the calculation time and the memory requirement scale as roughly the 3/2 power of the maximum plane-wave cutoff energy, it is desirable to use softer and hence more efficient pseudopotentials. Thus, the GIPAW approach has been reformulated such that it can be based on ultrasoft pseudopotential (USPP) calculations.[207] Vanderbilt's "ultrasoft" pseudopotentials are designed to be as soft as possible in the core region and require a minimum number of PWs for full convergence.[208] This softness is achieved at the cost of relaxing the property of norm conservation and so the pseudo-wavefunctions obey a generalized orthonormality condition. GIPAW with ultrasoft pseudopotentials has been applied to elements in various parts of the Periodic Table: in minerals such as kaolinite,[209] perovskites,[210] molecular crystals,[211–214] organic single crystals,[215] inorganic solids, for example, ^{95}Mo shielding in solid-state molybdenum compounds,[216] Br in alkaline earth bromides,[217] glasses, for example, ^{73}Ge correlation with Ge–O–Ge bond angle in vitreous GeO_2,[218] ^{19}F, ^{29}Si, ^{31}P, and ^{23}Na in bioactive glasses,[219] biomolecules in the solid state, for example, peptides.[220] Truflandier *et al.*[221] have designed ultrasoft pseudopotentials for 3d transition elements in GIPAW. In a further development, relativistic GIPAW operators have been included for shielding calculations in the ZORA,

and applied to ^{77}Se and ^{125}Te shieldings in a range of compounds.[222] Availability of reliable pseudopotentials has certainly greatly contributed to the quick widespread usage of the GIPAW method. There is a growing list of publications involving various applications.[223]

(b) Sebastiani *et al.* (2001, 2009)

An alternative method to calculate nuclear shieldings in extended systems under PBC was proposed by Sebastiani and Parinello.[173] The formalism relies on the exponential decay of KS-wavefunctions which are maximally localized in space, also called Wannier orbitals,[224] treat these localized orbitals as virtually isolated, combined with a saw-shaped "periodized" position operator,[173] such that the discontinuity due to the periodization appears in a region where the Wannier functions vanish. The main advantage of this method is that for large systems which in any event require large unit cells, such as *ab initio* molecular dynamics (MD) simulations of biological systems,[225] or extended disordered systems, it demands considerably lower computational efforts than GIPAW. For the gauge problem, a particular variant of the CSGT method[226] is adapted and applied to these localized orbitals. The original implementation by Sebastiani and Parinello used a pseudopotential plane-wave representation of the electronic structure in the frozen core approximation. The method is implemented in CPMD, a DFT pseudopotential suite of programs based on a PW representation.[174] The results by this approach has been compared directly to the Mauri *et al.*[168] results for the same systems and are found to agree within about 0.3 ppm[173] when using the same cutoff and the same level of theory (LDA) as Mauri *et al.* For systems that can be described by a small primitive cell, Sebastiani's method would have to use a supercell technique to obtain sufficiently localized Wannier functions, whereas the method of Mauri *et al.* works with the primitive cell only and is therefore more efficient for such cases. The improvement of the Sebastiani method by Weber *et al.* called GAPW[175] avoids the use of the pseudopotential approximation. The underlying idea in GAPW is that the electron density varies smoothly in the interstitial region and is therefore easily representable in a plane-wave basis, whereas the quickly varying electron density near the nuclei is more efficiently manipulated in terms of localized functions, in particular Gaussian-type functions, allowing for reduced complexity algorithms. Weber *et al.* use either of Keith and Bader's methods to circumvent gauge-origin problems, IGAIM (individual gauge for atoms in molecules)[227] or CSGT[226] methods. A direct comparison of IGAIM-GAPW with the original Sebastiani and Parinello implementation for isolated adenine

molecule shows that the calculated shieldings differ by tens of ppm for C and N nuclei. The differences can be attributed to the incomplete description of the core electron contributions. On the other hand, IGAIM-GAPW and GIPAW results are in good agreement.[175] It appears that this new implementation of the Sebastiani-Parinello method is a competitive alternative for Pickard and Mauri's GIPAW method. Recent applications of the Sebastiani method in hydrogen-bonded systems have been reported.[228–231]

(c) Thonhauser *et al.* (2009)

In most theoretical treatments, the external magnetic field is introduced as the initial perturbation, inducing a current density with which the second perturbation in the form of the nuclear magnetic dipole interacts. Nearly, all NMR software codes treat the two perturbations in this order. The converse approach by Thonhauser *et al.*[178] is fundamentally different from the other solid-state methods that calculate the induced magnetic fields at the nuclear positions in response to an applied, uniform magnetic field within a linear response framework.[168173] In the converse approach, the NMR shielding tensor of a particular nucleus is obtained from the total orbital magnetization induced by a magnetic dipole placed at the position of that particular nucleus.[232] In the converse approach, a linear response treatment of the electronic states is circumvented. The ground state Bloch functions of the perturbed Hamiltonian, that is, including the vector potential of the magnetic dipole, are calculated and their k-gradients are used to obtain the induced orbital magnetization[233] which is a ground state quantity. This method can be applied in the framework of the GIPAW, where it is used to calculate a pseudopotential contribution to the shielding tensor. As is done for the linear response methods, a PAW[193] reconstruction in the core region is needed to obtain accurate shieldings. The complete derivation of this converse approach in the GIPAW framework was recently presented by Ceresoli *et al.*[180] Converse calculations of σ could be implemented in other standard band structure codes, including all-electron methods. The disadvantage of the converse method is that it requires a supercell approach to ensure a proper separation of the localized dipoles. An example of its application is illustrated in polycyclic aromatic hydrocarbons.[179]

(d) Ziegler *et al.* (2010, 2011)

The method of Ziegler and co-workers[181,182] differs from the other solid-state methods in using the Bloch basis set constructed from atom-centred functions, STO or NAO. The atom-centred functions permit the use of GIAO to ensure gauge-invariant results. This method also treats the two perturbations in the converse order. Their method first evaluates the

current density induced by the three components of the nuclear magnetic moment, followed by the response of this induced current density to the three components of the external magnetic field. Initially, they determined the induced current density from a zero-order field-free calculation on a supercell large enough so that the induced current density vanishes at the supercell border.[181] This requirement was necessary to determine the interaction with the non-periodic constant magnetic field. Thus, the calculations considered an array of periodic supercells, each containing a magnetic dipole. They later found a more efficient scheme, which they call the single dipole method, as it considers the perturbation from the single magnetic dipole in a large crystal.[182] Use is still made of a supercell that is now extended to the entire crystal, but the determination of the induced current density over the entire crystal is based on zero-order KS orbitals from SCF calculations involving only a primitive unit cell. This is made possible by a combination of first-order analytic perturbation theory and the relationships for Bloch functions and their derivatives. In addition, use was made of the transformation relationships between the local representations of KS orbitals obtained with the whole crystal as the periodic unit and those of the crystal momentum. This transformation is specific to atom-centred basis sets. Relativistic effects within the scalar ZORA have been included in the new scheme. Only a few results are available as yet for this new method. Results for ^{15}N shielding calculations in boron nitride crystal (a diamond-like structure) give a chemical shift relative to the standard ^{15}N reference substance (nitromethane) equal to -359.8 ppm,[182] which is in very good agreement with the experimental value of -358.6 ppm and with an earlier calculation using the cluster method (an H-saturated cluster containing 71 atoms) which gave a value of -359.0 ppm. The calculated ^{67}Zn chemical shift in ZnS (zincblende) crystal was 1199 ppm relative to a free Zn atom, to be compared with the experimental chemical shift of 1068 ppm.

(e) Laskowski and Blaha (2012)

The NMR shielding calculations for the full-potential all-electron LAPW method has been implemented in the Wien2K code.[186] The implementation follows the GIPAW method, except that the integration of the current cannot be performed in reciprocal space only (as in GIPAW), so has inherently different integration of the induced all-electron current density in the presence of a uniform external magnetic field. In the LAPW method, the unit cell is partitioned into non-overlapping atomic spheres centred on

the nuclei and the interstitial region. The basis functions are PWs in the interstitial region that are augmented by a linear combination of functions inside each atomic sphere. The standard LAPW basis set is accurate for valence and lowest conduction bands. In order to cover a larger energy region, additional basis functions have to be supplied in the form of local orbitals (called NMR-LO functions) which vanish at the sphere boundary and at the interstitial region, so they are not coupled to the PWs. Most of the shielding is generated in the atomic sphere, but integration of the current density in the interstitial region and also in neighbour atomic spheres is of course necessary for accurate calculations of shielding. The disadvantage of the LAPW method for calculating shielding is that a large number of local orbitals have to be used to increase the flexibility of the basis. So far, only a comparison with Pickard and Mauri's GIPAW for isotropic ^{1}H, ^{13}C, ^{17}O, ^{19}F, ^{29}Si shieldings in small molecules, oxides, and fluorides from the literature has been carried out, finding reasonably good agreement between the two methods for small molecules; for ^{13}C in diamond, the difference is nearly 9 ppm and for oxides and fluorides it is as large as 20 ppm.

These PBC methods of calculating shielding are the methods of choice for covalent solids, ionic solids, strongly hydrogen-bonded solids, proton-conducting molecular crystals, and systems where slight differences in crystal packing forces create subtle differences in shielding and other properties for the same chemical compound composition, that is, polymorphs. In addition to the early success cases already mentioned above, we consider some examples below.

4.2. Crystalline materials

PBC methods for shielding calculations in solids are a natural choice in covalent solids like quartz, diamond, chalcogenides, or extended networks constituted with covalent bonds, not necessarily in three dimensions, such as carbon nanotubes. The prediction of NMR properties for these and many more systems may be found in the GIPAW list of references[223] because the methods developed by Mauri *et al.* came first and were accessible. Undoubtedly the other more recent methods discussed in Section 4.1 will catch up in terms of numbers of applications, as soon as solid-state NMR spectroscopists become more aware of them. Particularly useful is the ability to calculate both the shielding and the electric field gradient tensor, which becomes indispensable when dealing with the quadrupolar nuclei that inhabit most of the NMR Periodic Table.[234] Some interesting recent results include the

finding that the ^{13}C shielding in single-walled carbon nanotubes correlate with the tube diameter.[235] The linear relation found tends to asymptotically approach the line position expected in graphene. Those doing work in NMR crystallography are beginning to find the PBC methods to be very useful.[236] Interesting trends are found especially when both the shielding and quadrupolar tensors are interpreted together, for example, ^{35}Cl shielding and electric field gradient tensors in a series of alkali and alkaline earth chloride hydrates.[237] By doing calculations for ^{35}Cl, ^{81}Br, and ^{127}I, Bryce and coworkers have found that when an isostructural series of related compounds pack in the same space group, it has been possible to interpret trends in the NMR data in terms of the strength of the halogen bond.[238] For example, in the case of a series of haloanilinium bromides, they find the ^{81}Br shielding tensor span and isotropic value both decrease as the bond is weakened. Studies of Br^- ion in triphenylphosphonium bromides[239] provides trends of the chemical shift tensor components with the Br–P distance in the crystal structure, a clear neighbour effect that could just as well have been found by a cluster calculation. On the other hand, GIPAW calculations could distinguish between the two chemically similar bromine sites, which helped in the analysis. An example which clearly demonstrates the success of a periodic approach is the ^{17}O shielding tensor in three crystalline sodium phosphates[240]: sodium trimetaphosphate, $Na_3P_3O_9$, tripolyphosphate, $Na_5P_3O_{10}$, and pyrophosphate, $Na_4P_2O_7$. A cluster-based calculation, including either the anion or the first coordination sphere demonstrates that the first coordination sphere does not determine the ^{17}O shielding tensor; GIPAW calculations clearly show that the long-range structural organization influences the shielding. Only a PBC approach could reproduce the observed NMR spectra.

Some of the success stories are in studies of polymorphs, where the small differences in environment can lead to significant differences in physical properties in the solid state for the same compound that becomes one entity in solution. With the same chemical formula and chemical structure, polymorphs differ only in subtle bond length and bond angle differences, differences possibly imposed by packing forces in the solid state, yet they can have different physical properties such as solubility. Solid-state NMR is particularly suited to the discovery of the nature of these subtle differences. SSNMR can distinguish between polymorphs, and the PBC methods of calculating NMR properties help in understanding the slight differences in environment. Examples of such applications are ^{1}H, ^{13}C, and ^{19}F shieldings in a molecular crystal flurbiprofen,[202] ^{15}N shielding

tensors in *N*-benzoyl-L-phenyalanine,[241] ^{13}C in *N*,*N*″-diacetybiuret,[242] ^{13}C in prednisolone,[74] ^{13}C in the anticancer drug paclitaxel,[75] ^{17}O and ^{29}Si shielding tensors for six polymorphs of $MgSiO_3$,[76] α and β polymorphs of poly(*p*-xylylenes),[77] ^{17}O and ^{29}Si in Mg_2SiO_4 polymorphs,[243] polydiacetylenes,[244] vaterite $CaCO_3$ polymorph,[245] ^{17}O in glutamic acid polymorphs,[205] carbamazepine and its dihydrate,[206] oxybuprocaine hydrochloride,[211] and polymorphs of alumina,[246] ^{1}H and ^{13}C in thymol,[78] and ^{13}C in piroxicam.[81]

On the other hand, for the polymorphs of glycine, cluster calculations appear to have better agreement with experiment.[247] With the availability of ultrasoft potentials, shielding of nuclei such as ^{77}Se in inorganic and organoselenium systems[248] and Sn in organotin compounds[249] have also been studied, as well as ^{19}F in alkali, alkaline earth, and rare-earth fluorides,[250] and even transition metal shielding.[251]

Despite these successes, there are some issues which have been raised. We need to do better than the commonly used PBE for solids. For a given geometry, both LDA and common GGA functionals (PBE, Wu-Cohen, PBEsol) give a very similar description of NMR parameters. Usually, the agreement with experiment is reasonably good—a rough rule of thumb is that errors in the chemical shift are within 2–3% of the typical shift range for that element. There are, however, some notable exceptions: Several groups have shown[252] that while present functionals can predict the trends in ^{19}F chemical shifts, a graph of experimental against calculated shifts has slope significantly less than 1.0. Another example is the calculation of ^{17}O chemical shifts[201] in calcium oxide and calcium aluminosilicates. There are significant errors in the ^{17}O shifts which arise due to the failure of PBE to treat the unoccupied Ca 3d states correctly. In Ref. 201, it was found that a simple empirical adjustment of the Ca 3d levels via the pseudopotential was sufficient to bring the ^{17}O chemical shifts into good agreement with experiment. However, in both cases, it is clear that current GGAs do not describe all of the relevant physics of shielding in solids.

4.3. Non-crystalline materials, glasses

GIPAW represented a major step forward for the investigation of glass structure when combined with MD simulations (the MD-GIPAW approach).[198,201] The combination of MD simulations with GIPAW calculations has made it possible to study the dependence on distributions of structural parameters, such as those found in glasses. Mauri and

co-workers have shown that the combination of the CP simulations with NMR GIPAW calculations can be helpful to gain insight into the structural interpretation of the NMR parameters. For lithium and sodium tetrasilicate glasses, configurations were extracted from the CP simulations, and then relaxed to 0 K using the CPMD code. For one model, this relaxation of the atomic positions was done on a last configuration of the CP run, and the relaxed model presented a perfect SiO_4 network. For the other model, the starting configuration from the CP simulation presented a defective network and was extracted quite shortly after an observed topology change. Through the relaxation to 0 K, it became a non-defective model. Investigation of the strong sensitivity of ^{17}O and ^{29}Si NMR to the bond angles, in addition to the influence of the modifier cation environment, reveal that for T = Q(4), Q(3), Q(2), the dependence of $\sigma_{iso}(^{29}Si)$ on Si–O–T angle could be well described by means of a single (i.e. the same for both glasses) simple linear dependence.[253] The subsequent example of the analysis of how ^{29}Si, ^{17}O, and ^{23}Na shieldings depend on the environment in sodium silicate glasses is another good one.[254] The mean values and also the distributions of structural parameters can be obtained by the GIPAW-MD approach to glasses. The independent variation of the MD-GIPAW ^{29}Si isotropic shielding with the Si–O–Si angles of the *n*Si tetrahedral linkages in Q(1), Q(2), Q(3), Q(4) coordination types is convincing. The MD-GIPAW ^{17}O shielding variation with Si–O bond length for the bridging and non-bridging oxygens is less so.

Conventional diffraction studies do not provide sufficient information to determine the short-range order in chalcogenide Ge_x–Se_{1-x} glasses, which can include corner- and edge-sharing tetrahedral arrangements, under-coordinated and over-coordinated atoms, and homopolar bonds. ^{77}Se NMR studies obtained using MAS showed two large, but rather broad peaks. Two conflicting interpretations had been suggested: the first consists of a model of two weakly linked phases, one characterized by Se–Se–Se sites, the other Se–Ge–Se. The second model assumes a fully bonded structure with the contributions from Ge–Se–Se and Ge–Se–Ge linkages overlapping. To answer this question, Kibalchenko *et al.*[255] carried out first-principles calculations on several crystalline precursors of germanium selenide glasses ($GeSe_2$, Ge_4Se_9, and GeSe) to establish the range of chemical shifts associated with each type of Se site. This connection between local structure and observed NMR parameters provides a reliable interpretation of the ^{77}Se spectra of Ge_x–Se_{1-x} glasses, ruling out the presence of a bimodal phase and

supporting a fully bonded structure. Recent work in glasses include analysis of the structure and changes in vitreous silica,[256] borosilicate glass,[257] phosphate glasses,[258] and fluoride-containing bioactive glasses.[259]

4.3.1 Disordered systems

First-principle calculations and solid-state NMR have recently been used to study disorder in the fluorine substituted hydrous magnesium silicate clinohumite ($4Mg_2SiO_4{\cdot}Mg(F,OH)_2$). This mineral is of considerable interest as model for the incorporation of water within the Earth's upper mantle. Diffraction provides the overall crystal structure but gives no information on the ordering of the F^-/OH^- ions. The ^{19}F NMR spectrum reveals four distinct fluorine environments. Griffin *et al.* performed GIPAW calculations[252] on a series of supercells of clinohumite using F and OH substitutions to generate all possible local fluorine environments. From these, it was found that the computed ^{19}F NMR parameters were clustered into four distinct ranges depending on their immediate neighbours. The ranges correspond well to the observed peaks providing an assignment of the spectrum. Shielding calculations have assisted the probing of disorder in ceramics using ^{89}Y[260] and ^{119}Sn nuclei.[261]

4.4. NICS in periodic systems

Sebastiani has presented a pseudopotential PW approach in which the electronic current density and the NICS map are obtained from an inverse Fourier transformation of the induced magnetic field represented in reciprocal space.[262] This NICS contributes the same amount to every nucleus, but for protons this contribution to the shielding is relatively important. The calculated NICS surfaces can be used to calculate the most substantial part of proton shielding (added to that in the isolated molecule) for a molecule trapped within the CNT or hydrogen-bonded calixhydroquinone nanotubes at low loading. In a subsequent paper, selected guest molecules are observed in these nanotube hosts, but no averaging of guest positions have been carried out.[263]

4.5. Relativistic calculations in solids

Mauri and co-workers have included relativistic calculations for heavy nuclei using pseudopotentials and ZORA.[222] Using this method for ^{95}Mo in solid $Mo(CO)_6$,[264] and other molybdenum compounds,[216] relativistic effects were included for all elements during the USPP generation by solving the scalar-relativistic equation of Koelling and Harmon,[265] which omits SO

but retains all other relativistic kinematic effects such as mass-velocity, Darwin, and higher order terms. Most of the scalar-relativistic effects acting on core electrons are included in the USPP and on valence electrons through the interaction with the USPP. Then, no additional calculation is needed. Spin–orbit coupling effects were not taken into account in this work. Nevertheless, the linear correlation plot between the ^{95}Mo shielding differences and observed chemical shifts has a slope of 0.95. Another method that includes ZORA is that of Ziegler *et al.*,[181,182] which is a very promising method for solids because atom-centred basis functions are used, but no calculations are yet published using this option.

4.6. The case for retaining cluster approaches in our toolbox

Now that we have seen the proper treatment of extended networks using PBC calculations, are there any justifications/advantages of using the old embedded cluster methods? It had been the case that only LDA and GGA DFT approximations were available for NMR calculations in periodic boundary condition methods, although this is no longer true with the development of other PBC approaches like GAPW.[175] On the other hand, standard all-electron quantum QM (quantum mechanics) chemistry methods, which are widely available in many QM chemistry computer programs are very mature and can calculate nuclear shielding tensors with a range of approximations, using well-tested Gaussian-type orbital basis sets. In increasing order of computational cost, these methods range from DFT, HF, and hybrid methods, to correlated approximations such as second- and higher order Møller–Plesset perturbation and singles, doubles, triples coupled cluster methods. The persistence of cluster based models is mainly due to the advantage that understanding the dependence of the shielding on structural parameters (bond length, bond angle, torsion angles, etc.) is very easy with embedded cluster methods. These dependencies can also be treated by periodic boundary calculations, but *implementation of a systematic variation of a structural parameter is more difficult, due to the geometrical constraints of the periodic crystal structure* and the often limited range or variety of experimental values available in reference crystalline compounds. Also, incomplete atomic coordinates in the crystal structure, for example, omission of hydrogens on waters in XRD data, do not permit periodic boundary condition methods to be used. Finally, cluster methods, including embedded cluster methods, make use of the locality of NMR properties. Thus, the cluster approaches described in part 3 are not completely superseded by

the periodic approaches. Sometimes cluster calculations can provide insight (e.g. about the hydrogen-bonding network) that PBC approaches cannot, and at the same time, get results closer to experiment than is possible with PBC approaches. For example, natural bond orbital (NBO)[266] analysis can be carried out to assess the strengths of intermolecular interactions present, allowing the significant non-covalent interactions to be identified. Such insights are important, as there are typically a large number of non-covalent interactions involving the site of a given nucleus in a crystal structure, such that it may be difficult to discriminate the important structural factors that influence the observed chemical shift.[247]

An excellent example is afforded by the use of calculations in catechin 4.5-hydrate to refine the atomic coordinate positions in the crystal.[267] Because neighbouring moieties often suggest more than one orientation for the hydrogens in the O–H groups to optimize hydrogen bonding, calculations using model clusters are required. Intermolecular-hydrogen-bond-dictated orientations can be energetically less favourable than conformations obtained from geometry optimization of a single molecule under vacuum. Here, calculations in model clusters with variable >C–O–H conformations were used to determine the O–H proton orientations with respect to the aromatic ring, using the sensitivity of the ^{13}C tensor components to the C–C–O–H dihedral angle. Then, the initial structure, solved using XRD heavy atom positions and SSNMR OH hydrogen orientations, had excellent agreement with diffraction data but gave a poor fit of computed ^{13}C tensor principal values (sp^2 and sp^3 carbons) with experimental data. This large error in SSNMR fit indicated that further atomic coordinate refinement was possible. A significant improvement in the fit was obtained in the final refinement by adjusting bond lengths and valence angles computationally, while holding dihedral angles constant at XRD values, that is, adjusting positions of heavy atoms, not only hydrogens. As hydrogens were also optimized during the iterative refinement process described, a separate analysis was performed to determine what portion of the improvement was due to hydrogen optimization. Optimal hydrogen positions were determined by holding heavy atoms rigid at the initially determined XRD-determined positions (i.e. before any bond length or valence angle refinement) and allowing only hydrogens to adjust via energy minimization. ^{13}C tensors were then computed using the coordinates of the modified structure. This hydrogen refinement altered the computed error by only 0.48 ppm relative to the structure before refinement. It may therefore be concluded that roughly 93% of the improvement in the SSNMR error comes from

refinement of non-hydrogen atoms. Note that accurate work such as described in this work requires that complete tensor information from SSNMR measurements have to be used, rather than isotropic shielding values which hide compensating errors in the components within the isotropic average. The complete tensor refers to the six observable symmetric tensor elements. It is more convenient, when comparing two complete tensors, to use the icosahedral representation of the shielding tensor. The Grant group converts all computed and experimental tensor data to the icosahedral representation[268] before using any least-squares fitting procedures, so as to make full use of the entire symmetric shielding tensor, thereby using not only the principal components but including also the principal axis orientation information.

In the case of catechin discussed above, the geometry *in situ* was made consistent with both the full ^{13}C tensors from SSNMR and the XRD data, using embedded cluster calculations to carry out the geometry variations. When the local structural distortions are largely intramolecular, it is logical to invoke a cluster or even a single molecule calculation to assist a GIPAW shielding calculation in the crystal, because exploring the intramolecular distortions within the full solid-state environment with PBC can be too challenging. Intramolecular distortions can occur where each molecule is found in a nonequilibrium (relative to an isolated molecule) geometry stabilized by its crystalline environment, principally through steric effects. In bisphosphinoamine, the ^{31}P isotropic shielding could be assigned to the various crystallographic sites with GIPAW calculations but the elongation of the ^{31}P–^{31}P cross peaks parallel to the diagonal in the 2D NMR spectrum, as well as the thermal ellipsoids associated with the uncertainties on the atomic positions of the XRD structure indicated some structural distortion.[269] Single molecule vibrational mode calculations revealed modes of structural distortions (variations of a couple of degrees in bond and dihedral angles) which are consistent with the observed slight disorder in the crystal. The authors suggest this approach should be applicable to a broad range of solids with small amplitude structural disorder and will ultimately allow us to link this type of disorder to their macroscopic physical and chemical properties.

Another good example of embedded cluster approach is the study of the ^{17}O shielding dependence on structural parameters, B–O bond length and B–O–B angle, in ABO_3 transition metal perovskite crystals.[166] The authors use a cluster embedded in point charges to model the long-range Coulomb interactions in the ABO_3 materials. The target oxygen atom is fully

coordinated with QM atoms located at its nn and nnn sites. Second, the target atom's nn QM atoms are themselves fully coordinated with nn QM atoms. Finally additional QM atoms are added, as required by ideal perovskite symmetry. This procedure results in a 21 QM-atom cluster: $(A_4B_2O_{15})^{14-}$, where A = Sr, Ba, or Pb; B = Ti or Zr. All-electron treatments were used for the O and Ti atoms, while the other QM atoms were represented using scalar-relativistic small core (scalar-RSC) pseudopotentials also called effective core potentials (ECP). The QM cluster is embedded in the crystal environment by surrounding it with a large array of point charges. The purpose of the point charges is to better simulate the crystal environment by generating the correct crystalline electrostatic Madelung potential in the QM region. The finite point charge distribution is determined using the EWALD program.[270] The method calculates an array of point charges that reproduces the electrostatic potential of the infinite crystal within an accuracy usually < 1 μV in the interior of the quantum cluster. In the first step, EWALD calculates the Madelung potential with the Ewald method for PBC, using nominal ionic values (e.g. $Q_i = -2$ and $Q_i = +2$ for O^{2-} and Pb^{2+}, respectively) for the atoms placed at crystallographic positions of the targeted system. In the second step, EWALD retains the nearest $O(10^4)$ Q_i centred on the target atom, adjusting the values of the outermost Q_i to reproduce the Madelung electrostatic potential on and in the vicinity of the QM atoms. In this second step, the nearest ca. 500–750 Q_i are fixed at their nominal values, and in addition, the net monopole and dipole moments of the point charge distribution are constrained to vanish. The large ^{17}O shielding anisotropy is analyzed in terms of the hybridization between the O(2p) and virtual B-site d-states. The calculations identify an incorrect experimental assignment of two of the five inequivalent ^{17}O sites in $PbZrO_3$.

The crystalline amino acids are another good example in which cluster calculations can provide insight. Using NBO analysis in the cluster calculations, the high-frequency chemical shift observed for H_4 in the α polymorph of glycine, compared to H_5 in the α polymorph and to H_4 and H_5 in the γ polymorph, can now be attributed to intermolecular C—H···O close contacts.[247] These results suggest that, in spite of the relatively narrow span of ^1H NMR chemical shifts (ca. 10 ppm), computation of ^1H NMR chemical shifts can successfully distinguish small differences in chemical shifts between polymorphs and, furthermore, can provide insights into the reasons underlying differences in chemical shifts induced by differences in molecular geometry and crystal packing. Shielding calculations for amino acids in the

crystal state have been carried out using supermolecular clusters,[271] using embedded cluster method (EIM),[272] and also by GIPAW.[273] The supermolecule calculations by Chen *et al.* considered all possible hydrogen bonds with the given amino acid, that is, including all possible hydrogen bonds with side chain atoms, in addition to the hydrogen bonds with the carbonyl oxygen and amino hydrogen atoms.[271] This means that the cluster includes the amino acid of interest with up to 8 complete amino acids as neighbours in the crystal configuration. The principal values of ^{13}C shielding *tensors* in nine crystalline amino acids were included in this cluster study, and an r.m.s. deviation of 10.6 ppm was found for the correlation with experimental values, using B3LYP. Agreement with experimental isotropic shieldings is much better, of course. For the embedded cluster study by Strohmeier *et al.*[272] the cluster calculations on α glycine, γ glycine, and L-alanine were performed on clusters of complete molecules where atomic positions were taken from the known single-crystal neutron diffraction studies. The γ glycine and L-alanine clusters included seven and the α glycine cluster six complete molecules; L-asparagine and L-histidine were provided with all their hydrogen bonds using smaller molecules (water, acetamide, and glycine). The clusters of complete molecules were placed inside the final point charge array obtained from the EIM calculations. As described in Section 3.4, the electrostatic crystal potential that is experienced by each atom in a molecule in the infinite crystal lattice is simulated with a finite, self-consistent array of point charges, which are generated using the Ewald summation method and quantum mechanical partial atomic charge calculations.[125] Subsequently, using standard quantum mechanical methods, the NMR shielding tensors are calculated for the cluster embedded inside the point charge array. Strohmeier found that the principal components of the ^{13}C shielding tensors for the 5 amino acids studied had an r.m.s. of 4.0 ppm in the correlation with experimental values.[272] Prior to doing a GIPAW study, Zhen *et al.* carried out an ONIOM study on the principal values of ^{13}C shielding tensors of the carboxyl carbon in three crystalline amino acids. The r.m.s. was 5.9 ppm when the geometry optimization was first carried out on the original XRD coordinates.[274] When the same lab did the GIPAW study, they reduced the r.m.s. for the carboxyl principal tensor components to 4.85 and 10.0 ppm for all carbons in 12 amino acids and one dipeptide.[273] This is comparable to the r.m.s. deviation of 10.6 ppm using supermolecule clusters.[271] If in addition the supermolecules had been embedded in point charge arrays as in the EIM method, the results would probably have been even better. It appears that EIM-embedded cluster calculations are capable of

producing shielding tensors of high accuracy. Given that XRD data are available for the system under study, the unquestioned advantage of all the periodic methods is that one needs absolutely no chemical knowledge to carry out the calculations whereas cluster methods make use of a general knowledge about hydrogen-bonding donors and acceptors, ring currents, van der Waals radii, to make good decisions about constructing suitable clusters.

5. DYNAMIC AVERAGING OF SHIELDING

5.1. Why is averaging so important for nuclear shielding calculations?

Fragment and single molecule and cluster calculations discussed in part 3 have demonstrated the exquisite sensitivity of nuclear shielding to local configuration, that is, bond structure (bond lengths, bond angles, torsion angles) and arrangements of non-bonded neighbours, which means that any motional changes in these configurations is accompanied by changes in the nuclear shielding. Atoms in the observed system are always in motion, even if only zero-point motion is available, thus, effects of dynamic averaging (e.g. vibrations, conformational averaging, molecular aggregation) can be more significant than differences arising from choices of exchange-correlation functional or basis set sizes. Explicit experimental manifestation of dynamic averaging effects on shielding are isotope shifts and the temperature dependence of shielding that has been observed in the gas phase at the limit of zero density, in the limit of no intermolecular interactions, or else in mixtures of gases where averages from intermolecular interactions can be carried out in closed form and verified against density and temperature dependence. In situations, as in liquids, where the configurations of the neighbours change dynamically, the intermolecular contributions to shielding also change with changing configurations. Therefore, dynamic averaging needs to be taken into account in the theoretical modelling, even when there are no significant strong interactions such as hydrogen bonding. The size of systems that can be studied using first-principles calculations has rapidly increased with the use of DFT. As the size increases so does the number of degrees of freedom, so also does the time scale of the dynamics that these systems exhibit. This is particularly relevant for biological systems where hydrogen bonding and van der Waals interactions are controlling factors for the secondary and tertiary structure, the greater dynamical freedom permits sweeping through large regions on the shielding hypersurface of every

nucleus in the structure. As NMR calculations are performed on ever larger systems, it is therefore going to be increasingly necessary to explicitly include dynamical effects in the theoretical treatment.

5.2. Rovibrational averaging

The effects of rovibrational averaging of shielding are observed as isotope shifts and temperature dependence of chemical shifts, even in the absence of intermolecular interactions (as in the extremely dilute gas phase).

5.2.1 Isotope shifts

As variations in the average geometry depend on the magnitude of the change in the reduced mass of the nuclei that are in motion, deuterium substitution leads to more easily observable isotope chemical shifts and are therefore most often noted. Nevertheless, halogen isotope shifts such as those induced by $^{35}Cl/^{37}Cl$ and $^{79}Br/^{81}Br$ have been measured for ^{19}F chemical shifts in a series of fluorinated cyclopropanes and cyclopropyl ethers.[275] These secondary isotope shifts are in the order of a few ppb. The $^{17}O/^{18}O$ isotope effects on ^{13}C chemical shifts have been employed to examine in more detail the structure of benzyloxycarbonyl-Ala-Pro-Phe-glyoxal as it binds to chymotrypsin.[276] The more common deuterium-induced isotope effects have been utilized in characterizing Schiff bases,[277] compounds containing nitro- and acetyl groups,[278] systems with strong hydrogen bonds,[279–281] and sugars.[282] Deuterium-induced isotope effects can be affected by conformation and solvent. In the case of proteins, a range of deuterium isotope effects have been observed on backbone ^{15}N chemical shifts.[283] This observation certainly adds to the increasing set of NMR parameters that can be used to elucidate protein secondary structure. This, of course, is in addition to the fact that deuterium-induced isotope shifts can be used to pinpoint exchangeable protons in a protein, as illustrated in the study of Cys residues in the protein EPPIb.[284] Similar studies have been employed using deuterium-induced shifts on ^{19}F chemical shifts in fluorine-labelled tyrosine residues in calmodulin.[285]

Isotope shifts arise mainly from the change in the rovibrationally averaged geometry of the molecule upon isotope substitution. Its calculation requires knowledge of the potential surface and its accurate experimental determination, to remove intermolecular effects, requires extrapolation to zero density. In this arena, deuterium-induced secondary isotope effects on ^{13}C and ^{17}O chemical shifts of methanol[286] and to ^{1}H shielding in water[287] (e.g. difference between HOD and H_2O) have been measured.

Extrapolation to the isolated molecule limit has been afforded by employing fluoromethanes as buffer gas to pressure-narrow the observed resonances. Benchmark calculations have been performed for deuterium-induced isotope shifts on ^{1}H in H_2, ^{35}Cl in HCl, and ^{23}Na in NaH using coupled cluster singles and doubles (CCSD) level of theory and employing aug-cc-pVTZ basis functions. Beyond the Born–Oppenheimer (BO) approximation, Gaussians that specifically contain kinetic energy terms that depend on nuclear mass have been used to estimate deuterium-induced isotope shifts on ^{15}N chemical shifts in lysine residues.[288]

5.2.2 Temperature dependence of shielding

The dependence of chemical shifts on local geometry is likewise revealed in variable temperature measurements. The earliest work was in diatomic and other small molecules in the gas phase.[289,290] The temperature dependence of NMR chemical shifts in small molecules can be treated in a rigorous fashion. Calculations can be carried out with large basis sets and with a high level of theory while experiments can be made in the gas phase which allows for extracting and removing intermolecular effects from the measured shifts. A systematic and comprehensive study of ^{1}H and ^{13}C NMR chemical shifts in halomethanes is a recent example.[291] As the heavy halogens (Br and I) are included in this work, these calculations require relativistic contributions. In particular, scalar and SO-induced relativistic effects have been incorporated. Large gauge-including basis sets are employed to guarantee basis set convergence and electron correlations at various levels are applied. To determine the chemical shift at any given temperature, it is important to have a good description of how the shielding changes with geometry. For this purpose, hypersurfaces involving a large number of points (about 100 geometries suitably chosen in the vicinity of the equilibrium geometry) have been constructed and from these surfaces, the derivatives of the shielding with respect to the symmetry coordinates of the molecule are extracted. By transforming these derivatives to terms based on the vibrational normal coordinates Q_k of the molecule, and applying the average values of $\langle Q_k Q_l \rangle^T$ and $\langle Q_k \rangle^T$, obtained from harmonic and anharmonic force fields as well as centrifugal distortion, calculated shielding values can be converted from their equilibrium values to those that should correspond for a molecule at 300 K, for example. A direct comparison with experiment can then be made using absolute shielding values, and in this case, the agreement is indeed excellent for the entire series of methyl halides.

In complex systems, this temperature dependence has been used to examine phase transitions, local and collective motions, and polymorphism, as illustrated in NMR measurements of potassium ferrocyanide trihydrate,[292] triethyleneglycol-substituted perylenetetracarboxdiimides,[293] branched polyolefins,[294] semifluorinated alkanes,[295] supercooled confined water,[296] and L-selenomethionine.[297] For condensed phases, the observed temperature dependence of the chemical shift depends not only on vibrations but intermolecular interactions, which theoretical approaches are discussed below

5.3. Dynamic averaging in condensed phases

5.3.1 Approaches to dynamic averaging of shielding in condensed phases

The dynamic averaging may be carried out in various ways, but in general one needs a means of generating configurations over which the averages are taken and a means of generating the shielding for a given configuration. The means of generating configurations may be via a Monte Carlo (MC) process for canonical or grand canonical ensembles or via a MD trajectory. Both methods of generating configurations have been used for dynamic averaging of shielding. In most early and many current uses, the interaction potentials between the particles are functions of the inter-particle coordinates and may include pairwise, three-body, and higher order terms, whose functional forms are related to the nature of interactions and bonding in the system under study. These potentials are commonly determined by choosing a parameterized functional form on the basis of physical and chemical considerations and fitting the parameters to a set of experimental or theoretically calculated data. Many widely used combinations of potentials (or force fields) specifically developed for biological systems (AMBER, CHARMM, GROMOS, etc.) or systems consisting of organic molecules (OPLS) have been used extensively in dynamic averaging of shielding in solutions. As the potential parameters are unchanging during the process of generating configurations either via classical MD or MC schemes, the applicability is limited in those circumstances where the system evolves into regions of configuration space not covered by the fitted data. Beyond classical MD are Born–Oppenheimer molecular dynamics (BOMD) methods in which the interatomic interactions underlying the evolution of the nuclear degrees of freedom are generated concurrently and consistently as the simulation evolves. That is, the determination of the potential is an integral part of the simulation, but the evolution of the system is restricted to a single electronic potential energy

surface (PES). The electronic energy on this PES and the forces on the nuclei are calculated "on the fly" which can then be used in the integration of the classical equations of motion of the nuclei, advancing them by a small time step to a new configuration. For MD on the ground state BO surface, this method can be realized with any *ab initio* method, including hybrid methods such as QM/MM. In the same spirit as standard BOMD, but using quite a different approach, in addition to the classical equations of motion for the nuclei, CPMD method, which is DFT based, solves in addition, a fictitious dynamics of the electronic system by describing the time evolution of the KS wavefunctions connected with the atomic motion.[298] For example, for ionic liquids, Bagno *et al.* used CPMD to generate the snapshots.[299] For periodic systems, CPMD uses pseudopotentials and plane-wave basis set expansion and is probably the most popular of BO type of MD methods which has been used for averaging shielding.[300] The use of a supercell or repeating images of the system is not an intrinsic feature of a BOMD and therefore may be used for clusters which may have multipole moments.[301,302]

There are various means of generating the shielding for a given configuration. Obviously, this is based ultimately on quantum mechanical calculations of shielding. For the purpose of dynamic averaging, shielding may be calculated using PBC methods for a completely QM description of the entire system as represented by a supercell,[135,192,220,303,304] or a quantum system that includes different layers of description nevertheless, as in an ONIOM approach where the few atoms closest to the nucleus in question may be treated at a higher level of theory than the next shell of atoms, or a quantum system in a QM/MM approach.[119,305–307] In a cluster approach, only a finite number of molecules are included, the molecule in question plus some number of neighbours. The cluster method has been used for a rare gas atom in a zeolite cage[308] or an organic cage,[309] or a pair of molecules at various distances and orientations.[89,310,311] The number of molecules in the cluster could be two or more; for example, calculations of the shielding for water have included 5–64 molecules in the cluster.[135,312–315] An improvement is afforded by an embedded cluster approach. The cluster may be placed in a reaction field,[315] or the cluster may be embedded in a collection of point charges, using EIM[125] or EEIM[128] methods to determine the charge field that describes the periodic lattice. A systematic variation of geometry in a fragment of the system embedded in a charge field of the remainder of the system has been used to generate a shielding surface, for example, a peptide residue in a protein.[122]

Finally, the methods of doing the averaging are (a) in general, to select a series of configurations from MD or MC simulations, do quantum calculations of shielding for those snapshots and take the equally weighted average or (b) to use pre-calculated shielding hypersurfaces and do the averaging during the process of generating the configurations in an MD or MC simulation. We cite some examples in the following sections.

5.3.2 Use of pre-calculated shielding hypersurfaces in MD or MC simulations

For the interpretation of Xe distributions and chemical shifts, PBC Grand canonical MC simulations were carried out in various crystalline zeolites,[316–318] aluminium phosphate,[319] dipeptides,[320] clathrate hydrates,[134,143] and in constructed idealized crystalline materials containing paramagnetic centres,[89] also canonical simulations of Xe in an organic cage (cryptophane A).[309] These studies are deficient in that the cages are not vibrating, although long-range effects are included by using PBC for zeolites, aluminium phosphate dipeptides, and clathrates in the MC simulations. Pre-calculated Xe shielding surfaces were constructed from *ab initio* calculations using a large number of positions for the Xe atom within the cage, distributing the points in a manner guided by the sharp dependence of Xe shielding on atom–atom distance. The calculated shielding tensors were all fitted to suitable pairwise additive functional forms and fitting parameters were determined so as to reproduce the *ab initio* Xe shielding at each location. When more than a single Xe atom is present in the same cage or channel in the crystal, then the shielding contributions from other adsorbed gases are added in. The Xe-molecule shielding surface is likewise carried out for a large number of configurations for the Xe+other supermolecule. Like the Xe-clathrate hydrate calculation, for example, this too can be expressed as a mathematical function with parameters fitted so as to regenerate the *ab initio* values. The quality of the Xe shielding hypersurface for the Xe+other supermolecule was tested against temperature and density dependent Xe chemical shift measurements in gas mixtures. As it has been found experimentally that at modest densities the latter are additive (i.e. as a sum of Xe–Xe shielding contribution plus Xe-other contributions and linear with density), it is a good approximation to assume additivity of the shielding contributions from zeolite and from other adsorbed molecules. The latter assumption is found to be reasonably good, as has been found for Xe shielding calculations involving 3 or more Xe atoms, or a Xe atom and some number of rare gas atoms.[146,150] For Xe

adsorbed in solids, the Xe-molecule shielding contributions were considered additive to the Xe shielding contributions from interactions with the cage or channel atoms. During the grand canonical or canonical MC simulations, Xe shielding tensors were calculated from the shielding hypersurfaces, along with energies. Average tensor components observed in these systems were reproduced by the MC simulations.[318–320,143] For Xe in clathrate hydrates, the *ab initio* shielding values for one type of hydrate structure were fitted to a pairwise additive functional form involving Xe–O and Xe–H. Therefore, MC averaging was easily done for several new structures of clathrate hydrates. Calculations of the isotropic shielding on the fly during the MD trajectories in simulations of Xe solution in liquid water[321] used the same pre-calculated Xe shielding hypersurface from clathrate hydrates, and similar MD simulations for Xe in solution with solvents such as normal and cycloalkanes used the pre-calculated Xe shielding hypersurface for Xe–CH_4.[90,91] Using a cutoff distance together with the shielding functions, in MC or MD simulations using PBC, permits simulations to be carried out for the entire crystal or solution. The biggest weakness in using classical MC or MD simulations to obtain average electronic properties such as nuclear shielding arise from the intermolecular potential functions used in the simulations. It is therefore important that these be tested independently by reproducing other physical quantities such as adsorption isotherms or solubility, or else use quantum MD such as CPMD, which calculates all interactions quantum mechanically.

5.3.3 Quantum calculations from MD or MC snapshots

This is a commonly applied method of averaging in condensed phase. In this method, the snapshots are first generated and then the shielding calculation is done for each snapshot. For Xe in benzene solution, the highly anisotropic nature of the interaction between Xe and the benzene molecule makes it difficult to precisely express the set of calculated shielding values for Xe at various positions relative to a benzene molecule into an analytic mathematical form of the Xe shielding hypersurface. Instead, Standara *et al.*[322] carried out classical MD simulations of one Xe atom in a periodic box of benzene molecules and selected snapshots from the classical MD trajectory. Then the ^{129}Xe shielding was calculated for each snapshot and a straight average is used. This is the most commonly used approach. Applications differ only in the many approaches described above (Section 5.3.1) for choosing the system for which the shielding is calculated. For example, a supercell was used for liquid water,[192,303] the periodic simulation box was used in its

entirety for Xe dissolved in benzene.[322] A cluster approach was used for ^{1}H shielding in an ionic liquid,[299] and for ^{1}H and ^{13}C shielding of α-D-glucose in water.[85] An embedded cluster approach (EIM) was used for Xe in crystalline clathrate hydrates.[134,143] An ONIOM approach with QM/MM shells was used for adenine in aqueous solution,[305] a hybrid QM/MM was used by Sebastiani *et al.* for liquid water.[307] Clusters containing various numbers of water molecules solvating anionic Pt complexes were used for ^{195}Pt shielding in tetrahaloplatinate(II) complex and hexahaloplatinate (IV) complexes.[323] For convergence, the number of configurations sampled from the *ab initio* MD trajectories was 128, and the number of solvating molecules needed in the cluster calculation (using ZORA DFT) for convergence of the average shielding was 12 for the smaller tetrachloroplatinate (II) complex, while 14 seem to be required for the larger corresponding bromo complex. Both octahedral hexachloroplatinate (IV) and hexabromoplatinate (IV) complexes required less (about 8 water molecules).

5.3.4 Dynamic averaging of long-range effects

We consider the dynamic averaging of shielding in crystals and in liquids.

5.3.4.1 Crystals

Two approaches accounting for motional effects in solids can be considered: (a) DFT MD method and (b) force field method.

(a) MD method

Here, *ab initio* MD simulations are carried out to sample the configuration space of the system, and snapshots taken at regular time intervals, for example, 50 fs. Shielding values are averaged over these snapshots. Dume and Pickard[324] carried this out for β-L-aspartyl-L-alanine crystal and observed that the usefulness of such simulations is limited by their short duration. In another study of shielding in L-alanine crystal, two strategies were used to avoid correlation between configurations generated using MD.[325] First they use a DFT-based MD method. In this case, Langevin dynamics implemented within the DFT code CASTEP is used to sample efficiently the configuration space. Once a trajectory has been generated, configurations are sampled from it at a regular time interval (e.g. every 15 fs). Once an ensemble of N uncorrelated configurations has been obtained, DFT calculations are carried out to calculate the shieldings. The shieldings for each configuration are then averaged to find the mean and standard deviation of

the mean. After around 16 configurations the standard deviations decrease smoothly with $1/\sqrt{N}$, indicating well-behaved convergence. After 256 configurations, the errors have become reasonably small: carbons are converged to better than 0.2 ppm and hydrogens to 0.02 ppm for the molecular crystal L-alanine. However, the computational expense of DFT means that this does not scale well to larger systems.

An alternative to DFT MD is to do classical MD using standard potential energy terms. For consistency, the force field parameters are fitted to DFT-calculated forces. For validation, the parameterized force field is then used with a classical MD suite to attempt to reproduce the DFT MD result. The problem with this approach is that standard force fields in wide use for classical MD (AMBER, GROMOS, CHARMM, OPLS, for example) are useful in that they are parameterized to be generally transferable from one system to another containing similar atom bonding situations. Having to fit the force field parameters to DFT-calculated forces for each system to be studied defeats this advantage.

(b) Force field method

This method focuses on vibrational motion and allows for an assessment of the zero-point correction to shielding, which is found to be significant. In this method, the contribution of the curvature of the property surface is explicitly calculated, and the anharmonic vibrational effects are taken into account. Using a DFT-based PBC code such as CASTEP, the crystal cell vibrations are obtained within the harmonic or anharmonic approximations. The shielding at equilibrium, the first and second shielding derivatives with respect to the dimensionless mode coordinates, and the cubic and semi-diagonal quartic force constants are calculated by numerical differentiation. Vibrational wave functions are obtained using a vibrational potential constructed with up to quartic terms in the force field. The average shielding is then obtained as a vibrational average. This procedure is analogous to the vibrational averaging procedure used for molecules in the gas phase at the low density limit.

Vibrational averaging of the ^{13}C shielding values for β-L-aspartyl-L-alanine crystal was carried out in this manner.[324] Later, the shieldings of ^{13}C, ^{15}N, and ^{1}H nuclei in crystalline α-glycine was carried out in this manner.[326] First, the authors calculated first and second shielding derivatives and force field parameters. The numerical differentiation required more attention than for static computations on isolated molecules, because of the limited accuracy of the PW method. The calculated harmonic vibrational frequencies used for the averaging provided excellent agreement with the experimental Raman and inelastic neutron scattering data. A suitable choice

of the differentiation parameters enabled the correction of the equilibrium shielding by using the vibrational averaging and also to simulate their temperature dependence. Both the first and the second shielding derivatives were found important for the temperature dependence. Both quantum dynamic averaging and classical dynamic averaging were carried out and the results compared. First, at the "quantum" approaches, crystal cell vibrations are obtained within the harmonic or anharmonic approximations, and an approximate vibrational wave function is used to average the NMR parameters. This is in principle the more advanced method but many approximations had to be adopted in practical computations, in particular for the treatment of the variation of the shielding with vibrational coordinates. Instead of doing *ab initio* dynamics, the second method relies on classical BOMD simulations to sample the configuration space of the system via classical Newtonian motion of nuclei. This may miss some quantum effects; however, the direct averaging of BOMD clusters is computationally more robust than the quantum approach and may be quite appropriate for low-frequency vibrations. Because of the large contribution of the lowest-frequency vibrational motions (e.g. lattice modes and NH_3 rotation) for which the BOMD averaging is appropriate, the classical dynamics approach produced the most important experimentally observable trends reasonably well. Although the accuracy of both the NMR experiment and the computations was limited, the computed results are reasonably consistent with the previously published experimental values.[326] Incidentally, these results were also in agreement with the classical BOMD model based on a direct cluster averaging. In analogy to the averaging method used for molecules in the gas phase,[327,328] the temperature dependence of the shielding in crystalline α-glycine was obtained from

$$\langle\sigma\rangle^{\mathrm{T}} \approx \sigma_e + \sum_i \sigma_i/4\omega_i \sum_k C_{ikk} \coth(\hbar\omega_k/2k_{\mathrm{B}}T) + \sum_i (\sigma_{ii}/4\omega_i) \coth(\hbar\omega_i/2k_{\mathrm{B}}T)$$

In another application of the approach by Mauri and co-workers to rovibrational effects in solids, ^{17}O and ^{25}Mg NMR shieldings in MgO were calculated as functions of temperature.[329]

5.3.4.2 Liquids

In a QM/MM approach the smallest part for which the highest level of quantum calculation is carried out consists of the solute molecule and potentially a selection of a few specific solvent molecules, for example, the first

and possibly also the second solvation shell. The remainder of the system is treated classical MM. There have been a large number of applications in solutions using this standard approach. A hybrid QM/MM method was introduced by Sebastiani *et al.*[307] and applied to the ^{1}H and ^{17}O shielding calculation in liquid water. An additional short-ranged repulsive potential (a simple Gaussian shape) pushes the electrons out of those regions that would be occupied by neighbouring electrons of the surrounding classical atoms, but no polarization effects are included. In an improvement over this method, a hybrid QM/MM method introduced by Ruud *et al.*,[119] the smaller subsystem is treated using DFT and the rest is treated at the level of MM including explicit polarization effects. The solvent is described by assigning to each atom a partial point charge. In addition, this DFT/MM approach includes explicitly a microscopic description of the solvent polarization, for example, to each solvent molecule an electric dipole polarizability is assigned, giving rise to instantaneous induced dipole moments in the solvent, thereby increasing the accuracy for the long-range part. The energy of the total system is given as $E_{tot} = E_{DFT} + E_{DFT/MM} + E_{MM}$, where E_{DFT} is given by the usual expression for the energy of a molecule in vacuum, $E_{DFT/MM}$ is the interaction energy between the DFT and MM systems and E_{MM} is the energy of the molecules described using MMs. In this model, the molecules treated using MM are described by assigning partial point charges to the atomic sites and a point polarizability at the centre of mass of each molecule. In addition, a set of Lennard–Jones potentials is introduced in order to describe dispersion and short-range effects. In the calculation of $E_{DFT/MM}$, the interaction energy between two induced dipole moments in the MM part of the system has an implicit dependence on the QM system and that E_{MM} therefore also contributes to the effective KS operator. In each self-consistent-field iteration, the latter operator, which has the contributions due to the introduction of a polarizable environment, has to be updated. Solute–solvent configurations dumped during the MD simulations are then used as inputs to the calculations of the shielding tensors in a DFT/MM approach, including the polarization effects in the environment. This is a distinct improvement over the PCM and goes beyond the Sebastiani method[307] in including polarization in the MM part of the system. For liquid water, for both σ^{H} and σ^{O} a very broad distribution of the shielding is observed, indicating the importance of a proper statistical sampling over a large number of solute–solvent configurations, for example, at least 300 configurations with 10 water molecules in the QM system. The oxygen absolute shielding and liquid to vacuum shift values are well

represented using polarized SPC water model with 10 water molecules in the supramolecular cluster. In sharp contrast, with only *one* water molecule treated quantum mechanically, immersed in the MM liquid, the calculated liquid to vacuum shift is opposite in sign to experiment! This is not surprising. Changes of local chemical structure accompanying thermal motion is significant in hydrogen-bonded liquids such as liquid water, so a single water molecule in the MM liquid completely misses the important local interactions.

Using empirical force fields for the solute, the solvent and solute–solvent interactions in a classical MD approach is sometimes the practical choice especially when slow (nanosecond time scale) conformational dynamics take place. The size of the cluster to be used for the shielding calculations would be an important factor in obtaining accurate results. Quantum mechanical calculations using DFT have been performed for a series of structures of liquid water generated by MC and MD simulations by Fileti *et al.*[330] The dependence of the resulting average chemical shifts on the empirical potential used in the simulations, on the cluster size and on the functional chosen for the quantum chemical calculations were investigated.

Liquid water has also been considered in a completely quantum approach, where the dynamically fluctuating hydrogen-bond network is taken into account explicitly in generating configurations. CPMD has been used by several groups.[173,192,303,315] In one approach by Vaara *et al.*,[315] the CPMD trajectory is sampled by cutting out nearly spherical clusters of molecules from the simulated liquid-state trajectory and used as an input for the QC calculations (DFT-B3LYP) using a reaction field model for the remaining waters. Each cluster contained a central molecule and a suitable neighbourhoods of molecules around it. A distance criterion was used to determine the neighbours of the central molecule. The molecules that were included had at least one of their atoms inside a sphere (of a chosen radius) centred at the oxygen nucleus of the central molecule. The cluster was placed in a spherical cavity cut into a dielectric continuum. The radius of the cavity equalled the distance between the centre of mass of the cluster and its most distant atom plus the van der Waals radius of this atom. The dielectric constant 78.5, appropriate for water, was chosen for the continuum. In a later study by Vaara *et al.*,[331] sampling instantaneous configurations from a CPMD simulation in water for calculations of nuclear shielding reveals how the tensors evolve as the environment changes gradually from gas to liquid upon increasing the number of hydrogen bonds (based on a distance criterion) to the molecule of interest. Liquid state distributions of the instantaneous values of shielding

show a wide range of values for each case of the classified hydrogen-bonding species, with significant overlap between the different cases.

In a different approach to the QC shielding calculation, Pfrommer *et al.*[192] modelled liquid water by nine snapshots from a CPMD simulation at 300 K and used this to build a supercell of 32 water molecules for an extended network shielding calculation for ^{1}H and ^{17}O. As an early test of the Sebastiani and Parinello approach for PBC systems, the shieldings in liquid water were compared directly with these results.[173] A later study considered water under normal and supercritical conditions.[303] In a recent CPMD in liquid water, a random set of about 30 snapshots from the MD trajectories was sampled, and all ^{1}H shieldings were computed.[135] The average thus consisted of typically 2000 individual proton shifts (for a system of 32 water molecules); unfortunately, only the ^{1}H shielding was calculated in this last example, and not ^{17}O.

CPMD has also been used in the first-principles calculation of the ^{1}H NMR chemical shift distribution of an aqueous HCl solution as a function of concentration.[304] With the instantaneous shielding being very sensitively dependent on solute structure as well as hydrogen-bonding with the solvent, a quantum MD method such as CPMD is the method of choice, particularly when the solvation effects lead to changes in solute geometry and electronic structure. An example of this challenging case is the calculation of the ^{1}H and ^{13}C NMR spectra of α-D-glucose in water.[85] Here the relative stability of the various conformers in the isolated solute is significantly affected by solvation, and as the differences in energies of the conformers are small, quantum mechanical calculation of the equilibrium distribution of conformers is problematic. There are a large number of conformations of the glucose hydroxyl groups which in water form strong hydrogen bonds with water molecules. In a recent study, empirical potentials were used to generate a 10 ns MD trajectory which served as a source of configurations (one every 100 ps) for quantum mechanical calculations of ^{1}H and ^{13}C shieldings using a glucose and its first solvation shell of water molecules, and these were averaged over 100 snapshots.[85]

6. EXTRACTING INFORMATION FROM NMR CHEMICAL SHIFTS WITH THE HELP OF THEORETICAL CALCULATIONS

Twenty years ago, NMR shielding calculations faced the challenge of limited computer resources. Such limitation forced a piecewise analysis of shielding in the hope of arriving at an approach that would decompose

shielding into contributions that were more manageable. One benefit from this limitation was the required planning and resulting realization of how various factors might be influencing NMR chemical shifts. For diatomic molecules with only one internal coordinate, the observations of temperature dependence in the limit of zero density had a clear implication in terms of theoretical calculations.[289] Raynes and co-workers first evaluated how displacement coordinates of a polyatomic molecule affect shielding in small molecules like water[332] and methane.[333] These were followed by similar work on ammonia[334] and phosphine.[335] By working with these small molecules and coupled with gas phase NMR measurements, how the local geometry was affecting NMR chemical shifts became known to great detail. These small molecules contain only one heavy atom so the factors that may affect shielding are limited to bond lengths and bond angles. With the addition of a second heavy atom, a new internal coordinate, the dihedral angle, is introduced. It is in this area that proteins provided a good set of data to test shielding calculation methods. The use of model fragments in which only a specific dihedral angle is varied allowed for pinpointing exactly how shielding depends on the internal rotation about bonds. Through this, chemical shifts of the alpha carbon site in peptides and proteins have been shown to be strongly correlated with backbone dihedral angles.[122] How factors can be evaluated separately really went hand in hand with the computational limitations at that time.[123] The insights drawn from these studies not only demonstrated that theoretical reproduction of experimental results was possible, but, more importantly, origins of chemical shift differences were specifically identified. Now, both computational resources and methodology have allowed calculations for large systems, and in most cases, no longer requiring the design of model clusters or environment. Experimental chemical shifts in complex and condensed systems can be reproduced. However, the deeper understanding of the origins of chemical shift differences has unfortunately vanished inside a black box. Nevertheless, there are still excellent examples that have gone farther than just reproducing experimental NMR chemical shifts and selected examples are briefly mentioned in the following.

6.1. Shielding tensors as tools for NMR crystallography

The emerging field of NMR crystallography combines solid-state NMR together with computation with the aim of providing new insight, with atomic resolution, into structure, disorder and dynamics in the solid state. As theoretical methods have proven to be sufficient in reproducing not only

isotropic shielding values but also the entire shielding tensor for ^{13}C, calculated shielding tensors can now be used as filter for selecting computer-generated crystal structure candidates.[336] Applying this approach to methyl pyranosides of galactose, glucose, mannose, and xylose, calculated shielding tensors can eliminate as much as eighty percent of the structures suggested by energy calculations. And amazingly, the top-five structures that provide calculated shielding tensors that best agree with NMR data are the known structures of these sugar crystals. This is an example where the structural information provided by shielding calculations and chemical shift measurements is confirmed by pre-existing X-ray data. This is the case for many NMR crystallography publications on organic solids.[211,213,236,336–342] and for inorganic solids.[343,344] The ability of NMR chemical shifts to provide high-quality structural information is demonstrated in these instances where other approaches or methods are equally useful and agreement among the results provides corroboration. With the increased confidence in shielding interpretation, it is timely to show that NMR shielding tensors can indeed provide unique structural information. This is elegantly exemplified in the catechin example. In a case where only the positions of the heavy atoms can be determined by powder diffraction data, calculated ^{13}C chemical shift tensors compared to the experimental values can uniquely provide the unknown dihedral angles describing the orientation of the various —OH groups in catechin.[267] Catechin 4,5-hydrate forms powders unsuitable for high-resolution crystallography. Fortunately, NMR shielding tensors provide site-specific information, which enables the evaluation of the coordinates of each atom separately. Disagreement between experimental shielding values and those calculated from a given structure pinpoints errors within the vicinity of the nucleus concerned. As each nucleus presents six pieces of information in its shielding tensor, solid-state NMR spectroscopy really holds great promise in complementing diffraction studies. Shielding tensors have likewise been used to prove that the cyanides in the hydrazine adduct of CuCN are fully orientationally ordered.[344]

A decade and a half ago, the pioneering approach to protein structure via chemical shifts was pursued by mapping out the shielding surfaces in proteins through carrying out quantum mechanical calculations using fragments that include hydrogen-bonding partners and perturbing charge fields from the rest of the atoms in the protein.[122] Experiments such as those by Tjandra and Bax have nicely confirmed that large variations in $^{13}C^{\alpha}$ chemical shift indeed correlate with secondary structure.[345] In the previous decade,

theoretical calculations of nuclear shielding surfaces in amino acid residues indicated parts of the tensor that are much more sensitive to protein secondary structure.[346] These calculations also mapped how the principal axis system of shielding in these systems might be changing with the peptide backbone dihedral angles. It is expected that in the very near future these findings, with incorporation of motional averaging, will enable interpretation of protein NMR spectra with an emphasis on a much more dynamic rather than a static view of proteins in solution. More recently, the same approach is being applied to DNA. For example, using SOS-DFT-IGLO calculations on a solvated model of dimethyl phosphate, the changes in the ^{31}P shielding tensor components as a function of DNA and RNA backbone conformations have been predicted.[114] The dependence of ^{31}P shielding on the phosphate backbone torsion angle in DNA has been carried out using a model that consists of a dimethyl phosphate and water molecules found in the first solvation shell.[73] With MD simulations, the observed ^{31}P chemical shifts in B_I and B_{II} DNA can now be properly interpreted.[73]

Confidence in shielding tensor computations can also guide the design of novel NMR experiments. Knowing beforehand how the shielding tensor is affected by local geometry in a given system should provide inspiration for new experimental techniques that take advantage of trends that have been discovered from theoretical calculations. For example, with the knowledge gained from numerous shielding tensor calculations of carbonyl carbon sites, a solid-state NMR experiment that takes advantage of the interaction between anisotropy of the carbonyl carbon shielding and the dipolar vector C^{α}–H^{α} is now available, providing a direct measurement of the dihedral angle ψ in peptides and proteins.[339]

6.2. Details of local structure

The sensitivity of the shielding to local structure suggests that shielding tensors provide information about local structure. For example, refined structures for silica-ZSM-12, [343] and ITQ-4,[347] zeolites have been obtained by optimizing Si–O, O–O, and Si–Si distances to reach a closer agreement between calculated and experimental ^{29}Si chemical shift tensors. The ^{17}O and ^{29}Si shielding in $MgSiO_3$ and Mg_2SiO_4 have been studied by Ashbrook *et al.*, allowing for a full assignment of the ^{17}O sites and a deeper understanding of how the ^{17}O shielding depends on the Si–O bond length and coordination environment.[76,243] Isostructural analogs of zeolites, such as aluminium phosphate $AlPO_4$-15 are constituted of linked PO_4 tetrahedra

and AlO_6 octahedra which form channels. The channels are filled with ammonium cations and water molecules, both of which exhibit hydrogen bonds to the framework. There are two distinct P species, each coordinated by four O atoms. The two distinct Al species are coordinated by six O, four of which are bonded to P. Based on starting coordinates from a synchrotron X-ray single-crystal diffraction study carried out on the same sample as that used in solid-state NMR studies, the GIPAW calculations permitted the discrimination of the distinct Al and P environments and assignment of spectra to the distinct local structures.[348] With a combination of experimental and theoretical determinations of ^{109}Ag and ^{31}P chemical shift tensors, a dimer structure has been proposed for silver dialkylphosphite salts.[349]

The dependence of shielding on molecular conformation, as illustrated now by a wide array of calculations, paves the way for utilizing NMR chemical shifts in the determination of conformational distribution in the solid state, as well as to distinguish between polymorphs. Examples are studies on triphenylphosphite in two crystalline modifications,[350] polymorphs of the anti-rheumatic compound prednisolone,[74] the anticancer drug paclitaxel,[75] poly(*p*-xylylenes),[77] thiamin diphosphate,[351] ciprofloxacin-saccharinate,[79] piroxicam,[81] and the various perovskite phases of $NaNbO_3$. By making use of models, the physical basis behind the observed NMR chemical shift differences between polymorphs can be ascertained. For example, in piroxicam,[81] the difference is found to be not due to a conformational change, but to the formation of a zwitterion. The changes observed in the ^{13}C chemical shifts of hydrocarbons upon introduction to synthetic structure H gas hydrates have been shown to be mostly due to conformational changes.[82] And in the fast emerging field of self-assembly of inorganic compounds, ^{31}P solid-state NMR, *ab initio* calculations, and crystallography have afforded a detailed structural characterization of ligand complexes that serve as connecting moieties between metal cations.[352]

With the capability of predicting conformational effects on chemical shifts, shielding hypersurfaces can now be relied upon and applied to the study of local disorder in partially disordered solids. Calculated shielding tensors at various conformations combined with a set of possible local distortions yield spectra that can be compared against experimental 2D NMR lineshapes to determine which changes in local geometry are most likely present in the structural disorder in solids.[269] The ability to predict the dependence of shielding on local structure permits a more detailed interpretation of NMR results from variable temperature studies as well as

isotope-induced shifts. Combined with calculations, the temperature dependence of ^{207}Pb shielding tensors in Pb(II) compounds can now be explained by changes in bond lengths and deviation from octahedral symmetry.[353] On the other hand, ^{18}O/^{16}O isotope effects on ^{13}C chemical shifts in benzyloxycarbonyl-Ala-Phe-glyoxal have provided evidence that the glyoxal inhibitor binds to the active site serine hydroxyl group in chymotrypsin in a hemiketal fashion.[276]

6.3. Shielding as a probe for intermolecular interactions

Theoretical treatments that allow for a detailed examination of intermolecular interactions have likewise provided excellent opportunities for using chemical shifts to extract structural features that define these interactions. A difference in orientation between C═O and N—H bonds in the anti-parallel structure of the tripeptide Ala-Ala-Ala has been determined as the main reason for why this sample has two magnetically distinct ^{17}O sites in Ala-2 that differ by 32 ppm.[354] Calculations using a cluster of molecules have enabled the assignment of the observed proton resonances in hydroxylated MgO powders, in which the chemical shift dispersion is mainly due to differences in the number of hydrogen-bond partners.[355] GIPAW calculations can identify a specific intermolecular hydrogen-bonding arrangement for a pharmaceutical polymorph for which no crystal structure is available.[356] Proton irradiation on deuterated KH_2PO_4 results in an increase in its ferroelectric phase transition temperature, which is now explained by an increase in hydrogen-bond length, as suggested by both ^{2}H and ^{31}P NMR data.[357] These calculations can likewise rule out intermolecular interactions. For instance, while X-ray structures suggest that three of the six surfaced-exposed lysines of protein G form salt bridges, in solution, both the measured ^{15}N and ^{1}H chemical shifts and the deuterium-induced isotope effects are predicted by a simple hydrated amine model.[358] This leads to the conclusion that, in solution, unlike in the crystal, all lysine residues are not participating in salt-bridges. Taking advantage of intermolecular effects on chemical shifts, ^{1}H NMR data combined with *ab initio* calculations can now provide information regarding the location of guest molecules in host cavities.[340] *Ab initio* shielding calculations have made it possible to describe in detail how a Na^+ ion binds to a calix[4]arene–guanosine conjugate dimer.[359] In this system, the Na^+ ion lies above the G-quartet plane and is simultaneously coordinated to a water molecule in a square pyramidal geometry. Ring-current effects on ^{1}H and ^{13}C chemical shifts have been used to characterize two

crystallographically distinct host cavities within single crystals based on hexagonal frameworks comprising guanidinium ions and organomonosulfonates.[360] Likewise, effects of aromatic groups on chemical shifts have been used to assess how antimalarial drugs interact with a model porphyrin compound in which the paramagnetic Fe(III) centre has been replaced by diamagnetic Zn(II).[361]

The theoretical studies on ^{129}Xe started not even with a Xe atom, but with the use of a smaller noble gas atom, Ar, as a model.[362] With this model, in addition to reproducing successfully observed experimental intermolecular chemical shifts of ^{129}Xe in mixtures of gases where averaging is straightforward, important and useful insights were drawn on how and why ^{129}Xe NMR chemical shifts change with intermolecular interactions. The use of models that were designed not only to reproduce the experiment, but also, and perhaps, more importantly, to understand the origins and mechanism of intermolecular NMR chemical shifts, is one of the reasons why interpretation of ^{129}Xe chemical shifts has reached its current sophistication.

With the understanding of how ^{129}Xe NMR line shapes are influenced by intermolecular interactions,[363] ^{129}Xe NMR spectroscopy continues to be a powerful tool for characterizing porous materials and molecular cages. For example, knowing that systematic changes in ^{129}Xe chemical shifts with temperature are associated with the diameter of the channels leads to the conclusion that in the nanochannels formed by alanylisoleucine crystals, Xe atoms are unable to pass each other.[364] The absence of multiple peaks in ^{129}Xe NMR spectra of Xe inside nanochannels of aluminium napthalenedicarboxylate is deemed as an indication that the surface in these materials is homogeneous,[365] and phase transitions of van der Waals cages of *p-tert*-butylcalix[4]arene can now be easily monitored by ^{129}Xe NMR spectroscopy.[366]

6.4. Characterization of solids

The ability to calculate chemical shifts for infinite systems has definitely extended the usefulness of NMR data in characterizing systems in the solid state, as seen in the many examples mentioned in Section 4. ^{13}C NMR chemical shifts in single-walled carbon nanotubes (SWNTs) can now be used to study the diameter of these tubes,[367] the presence of functional groups such as –NH, $-NCH_3$, $-NCH_2OH$, $-CH_2NH_2$,[368] –F,[369] and the presence of Stone–Wales defects.[370] And in the case of $AlVO_4$, ^{51}V

shielding calculations that make use of the GIPAW method are accurate enough that errors in previous assignments of the three inequivalent ^{51}V sites can now be corrected.[251] The use of GIPAW has also introduced a new way of looking at shielding surfaces. In crystals, the shielding can be described as a function of lattice volume.[371] In this approach, the dependence of the shielding on both covalent and non-covalent distances can be examined. The application of any of the PBC methods which provide geometry optimization and calculate the shielding tensors (and the electric field gradient tensors for quadrupolar nuclei) provides the SSNMR spectroscopist with an indispensable tool for characterizing solids in terms of both local and long-range order, as we have seen in the many examples given here.

REFERENCES

1. Tossell JA, editor. *Nuclear magnetic shieldings and molecular structure*. Dordrecht: Kluwer Academic Publishers; 1993. 584 pp.
2. Facelli JC, de Dios AC, editors. *Modeling NMR chemical shifts: gaining insights into structure and environment*. *ACS symposium series*, vol. 732. Washington, DC: American Chemical Society; 1999. 384 pp.
3. Kaupp M, Bühl M, Malkin VG, editors. *Calculation of NMR and EPR parameters: theory and applications*. Weinheim: Wiley-VCH; 2004. 621 pp.
4. Jameson CJ. Understanding NMR chemical shifts. *Annu Rev Phys Chem* 1996;**47**:135–69.
5. Helgaker T, Jaszunski M, Ruud K. *Ab initio* methods for the calculation of NMR shielding and indirect spin–spin coupling constants. *Chem Rev* 1999;**99**:293–352.
6. Gauss J, Stanton JF. Electron-correlated approaches for the calculation of NMR chemical shifts. *Adv Chem Phys* 2002;**123**:355–422.
7. Vaara J. Theory and computation of nuclear magnetic resonance parameters. *Phys Chem Chem Phys* 2007;**9**:5399–418.
8. Casablanca LB, de Dios AC. *Ab initio* calculations of NMR chemical shifts. *J Chem Phys* 2008;**128**:052201.
9. Mulder FAA, Filatov M. NMR chemical shift data and *ab initio* shielding calculations: emerging tools for protein structure determination. *Chem Soc Rev* 2010;**39**:578–90.
10. Charpentier T. The PAW/GIPAW approach for computing NMR parameters: a new dimension added to NMR study of solids. *Solid State Nucl Magn Reson* 2011;**40**:1–20.
11. Harris RK, Hodgkinson P, Pickard CJ, Yates JR, Zorin V. Chemical shift computations on a crystallographic basis: some reflections and comments. *Magn Reson Chem* 2007;**46**:S174–86.
12. Jameson CJ, de Dios AC. Theoretical and physical aspects of nuclear shielding. In: *Nuclear magnetic resonance*. *Specialist periodical reports*, vol. 28–41. London: Royal Society of Chemistry; 1999–2012.
13. Chesnut DB. *Ab initio* calculations of NMR chemical shielding. *Annu Rep NMR Spectrosc* 1994;**29**:71–122.
14. de Dios AC, Jameson CJ. The NMR chemical shift. Insight into structure and environment. *Annu Rep NMR Spectrosc* 1994;**29**:1–69.
15. Autschbach J, Zheng S. Relativistic computations of NMR parameters from first principles: theory and applications. *Annu Rep NMR Spectrosc* 2009;**67**:1–95.

16. Wilson PJ. Density functional theory and its application to NMR shielding constants. *Annu Rep NMR Spectrosc* 2003;**49**:118–68.
17. Komorovsky S, Repisky M, Malkina OL, Malkin VG, Ondik IM, Kaupp M. A fully relativistic method for calculation of nuclear magnetic shielding tensors with a restricted magnetically balanced basis in the framework of the matrix Dirac–Kohn–Sham equation. *J Chem Phys* 2008;**128**:104101.
18. Cheng L, Xiao YL, Liu WJ. Four-component relativistic theory for NMR parameters: unified formulation and numerical assessment of different approaches. *J Chem Phys* 2009;**130**:144102.
19. Kutzelnigg W. Diamagnetism in relativistic theory. *Phys Rev A* 2003;**67**:032109.
20. Kutzelnigg W. Relativistic corrections to magnetic properties. *J Comput Chem* 1999;**20**:1199–219.
21. Kutzelnigg W, Liu WJ. Relativistic theory of nuclear magnetic resonance parameters in a Gaussian basis representation. *J Chem Phys* 2009;**131**:044129.
22. Xiao Y, Liu W, Cheng L, Peng D. Four-component relativistic theory for nuclear magnetic shielding constants: critical assessments of different approaches. *J Chem Phys* 2007;**126**:214101.
23. Hess BA. Relativistic theory and applications. In: von Rague´ Schleyer P, editor. *Encyclopedia of computational chemistry*. Chichester, NY: Wiley; 1998. p. 2499–508.
24. van Lenthe E, Baerends EJ, Snijders JG. Relativistic regular two-component Hamiltonians. *J Chem Phys* 1993;**99**:4597–610.
25. Cheng L, Xiao YL, Liu WJ. Four-component relativistic theory for nuclear magnetic shielding: magnetically balanced gauge-including atomic orbitals. *J Chem Phys* 2009;**131**:244113.
26. Xiao Y, Sun Q, Liu W. Fully relativistic theories and methods for NMR parameters. *Theor Chem Acc* 2012;**131**:1080.
27. Komorovsky S, Repisky M, Malkina OL, Malkin VG. Fully relativistic calculations of NMR shielding tensors using restricted magnetically balanced basis and gauge including atomic orbitals. *J Chem Phys* 2010;**132**:154101.
28. Olejniczak M, Bast R, Saue T, Pecul M. A simple scheme for magnetic balance in four-component relativistic Kohn–Sham calculations of nuclear magnetic resonance shielding constants in a Gaussian basis. *J Chem Phys* 2012;**136**:014108.
29. Sun Q, Liu W, Xiao Y, Cheng L. Exact two-component relativistic theory for nuclear magnetic resonance parameters. *J Chem Phys* 2009;**131**:081101.
30. Aucar GA, Romero RH, Maldonado AF. Polarization propagators: a powerful theoretical tool for a deeper understanding of NMR spectroscopic parameters. *Int Rev Phys Chem* 2010;**29**:1–64.
31. Maldonado AF, Aucar GA. The UKB prescription and the heavy atom effects on the nuclear magnetic shielding of vicinal heavy atoms. *Phys Chem Chem Phys* 2009;**11**:5615–27.
32. Arcisauskaite V, Melo JI, Hemmingsen L, Sauer SPA. Nuclear magnetic resonance shielding constants and chemical shifts in linear ^{199}Hg compounds: a comparison of three relativistic computational methods. *J Chem Phys* 2011;**135**:044306.
33. Cukras J, Sadlej J. Predicted NMR properties of noble gas hydride cations RgH^+. *Chem Phys Lett* 2008;**467**:18–22.
34. Seino J, Hada M. Magnetic shielding constants calculated by the infinite-order Douglas–Kroll–Hess method with electron-electron relativistic corrections. *J Chem Phys* 2010;**132**:174105.
35. Hrobárik P, Hrobáriková V, Meier F, Repiský M, Komorovský S, Kaupp M. Relativistic four-component DFT calculations of ^{1}H NMR chemical shifts in transition-metal hydride complexes: unusual high-field shifts beyond the Buckingham–Stephens model. *J Phys Chem A* 2011;**115**:5654–9.

36. Buckingham AD, Stephens PJ. Proton chemical shifts in the nuclear magnetic resonance spectra of transition-metal hydrides: octahedral complexes. *J Chem Soc* 1964;2747–59.
37. Melo JI, Maldonado A, Aucar GA. Relativistic effects on the shielding of SnH_2XY and PbH_2XY (X, Y = F, Cl, Br and I) heavy atom–containing molecules. *Theor Chem Acc* 2011;**129**:483–94.
38. Autschbach J, Zheng SH. Analyzing Pt chemical shifts calculated from relativistic density functional theory using localized orbitals: the role of Pt 5d lone pairs. *Magn Reson Chem* 2008;**46**:S45–55.
39. Krykunov M, Ziegler T, van Lenthe E. Implementation of a hybrid DFT method for calculating NMR shieldings using Slater-type orbitals with spin−orbital coupling included. Applications to ^{187}Os, ^{195}Pt, and ^{13}C in heavy-metal complexes. *J Phys Chem A* 2009;**113**:11495–500.
40. Dmitrenko O, Bai S, Dybowski C. Prediction of ^{207}Pb NMR parameters for the solid ionic lead(II) halides using the relativistic ZORA-DFT formalism: comparison with the lead-containing molecular systems. *Solid State Nucl Magn Reson* 2008;**34**:186–90.
41. Bagno A, Bini R. NMR spectra of terminal-oxo gold and platinum complexes: relativistic DFT predictions. *Angew Chem Int Ed* 2010;**49**:1083–6.
42. Nakanishi W, Hayashi S, Katsura Y, Hada M. Relativistic effect on ^{77}Se NMR chemical shifts of various selenium species in the framework of zeroth-order regular approximation. *J Phys Chem A* 2011;**115**:8721–30.
43. Le Guennic B, Autschbach J. $[Pt@Pb_{12}]^{2-}$ A challenging system for relativistic density functional theory calculations of ^{195}Pt and ^{207}Pb NMR parameters. *Can J Chem* 2011;**89**:814–21.
44. Wren JEC, Schreckenbach G. Neptunium(VII) in alkaline solutions: $[NpO_2(OH)_4]^{1-}$ or $[NpO_4(OH)_2]^{3-}$? *Can J Chem* 2009;**87**:1436–43.
45. Neto AC, Ducati LC, Rittner R, Tormena CF, Contreras RH, Frenking G. Heavy halogen atom effect on ^{13}C NMR chemical shifts in monohalo derivatives of cyclohexane and pyran. Experimental and theoretical study. *J Chem Theory Comput* 2009;**5**:2222.
46. Standara S, Malinakova K, Marek R, Marek J, Hocek M, Vaara J, et al. Understanding the NMR chemical shifts for 6-halopurines: role of structure, solvent and relativistic effects. *Phys Chem Chem Phys* 2010;**12**:5126–39.
47. Truflandier LA, Brendler E, Wagler J, Autschbach J. ^{29}Si DFT/NMR observation of spin–orbit effect in metallasilatrane sheds some light on the strength of the metal→silicon interaction. *Angew Chem Int Ed* 2011;**50**:255–9.
48. Bagno A, Saielli G. Relativistic DFT calculations of the NMR properties and reactivity of transition metal methane sigma-complexes: insights on C–H bond activation. *Phys Chem Chem Phys* 2011;**13**:4285–91.
49. Saielli G, Bini R, Bagno A. Computational ^{19}F NMR. 1. General features. *Theor Chem Acc* 2012;**131**:1140–50.
50. Auer AA, Gauss J, Stanton JF. Quantitative prediction of gas-phase ^{13}C nuclear magnetic shielding constants. *J Chem Phys* 2003;**118**:10407–17.
51. Harding ME, Lenhart M, Auer AA, Gauss J. Quantitative prediction of gas-phase ^{19}F nuclear magnetic shielding constants. *J Chem Phys* 2008;**128**:244111.
52. Ramsey NF. Magnetic shielding of nuclei in molecules. *Phys Rev* 1950;**78**:699–703.
53. Flygare WH. Spin-rotation interaction and magnetic shielding in molecules. *J Chem Phys* 1964;**41**:793–800.
54. Forgeron MAM, Wasylishen RE, Penner GH. Investigation of magnetic shielding in xenon difluoride using solid-state NMR spectroscopy and relativistic density functional theory. *J Phys Chem A* 2004;**108**:4751–8.
55. Jameson CJ, de Dios AC. Theoretical and physical aspects of nuclear shielding. In: Webb GA, editor. *Nuclear magnetic resonance*, vol. 38. London: Royal Society of Chemistry; 2009. p. 68–93 Chap. 2; 2012. p. 38–55 Chap. 2.

56. Aucar IA, Gómez SS, Ruiz de Azúa MC, Giribet CG. Theoretical study of the nuclear spin-molecular rotation coupling for relativistic electrons and non-relativistic nuclei. *J Chem Phys* 2012;**136**:204119.
57. Keal TW, Tozer DJ. Selenium chemistry with DFT: molecular structures and ^{77}Se NMR shielding constants. *Mol Phys* 2005;**103**:1007–11.
58. Keal TW, Tozer DJ. The exchange-correlation potential in Kohn–Sham nuclear magnetic resonance shielding calculations. *J Chem Phys* 2003;**119**:3015–24.
59. Keal TW, Tozer DJ, Helgaker T. GIAO shielding constants and indirect spin–spin coupling constants: performance of density functional methods. *Chem Phys Lett* 2004;**391**:374–9.
60. Keal TW, Tozer DJ. A semiempirical generalized gradient approximation exchange-correlation functional. *J Chem Phys* 2004;**121**:5654–60.
61. Peach MJG, Kattirtzi JA, Teale AM, Tozer DJ. Shielding constants and chemical shifts in DFT: influence of optimized effective potential and coulomb-attenuation. *J Phys Chem A* 2010;**114**:7179–86.
62. Perdew JP, Ruzsinszky A, Tao J, Staroverov VN, Scuseria GE, Csonka GI. Prescription for the design and selection of density functional approximations: more constraint satisfaction with fewer fits. *J Chem Phys* 2005;**123**:062201.
63. Arbuznikov AV, Kaupp M. Advances in local hybrid exchange-correlation functionals: from thermochemistry to magnetic-resonance parameters and hyperpolarizabilities. *Int J Quantum Chem* 2011;**111**:2625–38.
64. Arbuznikov AV, Kaupp M. Nuclear shielding constants from localized local hybrid exchange-correlation potentials. *Chem Phys Lett* 2007;**442**:496–503.
65. Kaupp M, Arbuznikov A, Bahmann H. On occupied-orbital dependent exchange-correlation functionals. From local hybrids to Becke's B05 model. *Z Phys Chem* 2010;**224**:545–7.
66. Arbuznikov AV, Kaupp M, Bahmann H. From local hybrid functionals to "localized local-hybrid" potentials: formalism and thermochemical tests. *J Chem Phys* 2006;**124**:204102.
67. Arbuznikov AV, Kaupp M. Coupled-perturbed scheme for the calculation of electronic g-tensors with local hybrid functionals. *J Chem Theory Comput* 2009;**5**:2985–95.
68. Teale AM, Cohen AJ, Tozer DJ. Transition metal NMR chemical shifts from optimized effective potentials. *J Chem Phys* 2007;**126**:074101.
69. Shen Y, Bax A. Protein backbone chemical shifts predicted from searching a database for torsion angle and sequence homology. *J Biomol NMR* 2007;**38**:289–302.
70. Czinki E, Csaszar AG. Empirical isotropic chemical shift surfaces. *J Biomol NMR* 2007;**38**:269–87.
71. Vila JA, Scheraga HA. Factors affecting the use of $^{13}C^{\alpha}$ chemical shifts to determine, refine, and validate protein structures. *Proteins* 2008;**71**:641–54.
72. Tang S, Case DA. Vibrational averaging of chemical shift anisotropies in model peptides. *J Biomol NMR* 2007;**38**:255–66.
73. Precechtelova J, Novak P, Munzarova ML, Kaupp M, Sklenar V. Phosphorus chemical shifts in a nucleic acid backbone from combined molecular dynamics and density functional calculations. *J Am Chem Soc* 2010;**132**:17139–48.
74. Suitchmezian V, Jess I, Sehnert J, Seyfarth L, Senker J, Nather C. Structural, thermodynamic, and kinetic aspects of the polymorphism and pseudopolymorphism of prednisolone (11,17 alpha,21-trihydroxy-1,4-pregnadien-3,20-dion). *Cryst Growth Des* 2008;**8**:98–107.
75. Heider EM, Harper JK, Grant DM. Structural characterization of an anhydrous polymorph of paclitaxel by solid-state NMR. *Phys Chem Chem Phys* 2007;**9**:6083–97.
76. Ashbrook SE, Berry AJ, Frost DJ, Gregorovic A, Pickard CJ, Readman JE, et al. ^{17}O and ^{29}Si NMR parameters of $MgSiO_3$ phases from high-resolution solid-state NMR spectroscopy and first-principles calculations. *J Am Chem Soc* 2007;**129**:13213–24.

77. Sroka-Bartnicka A, Olejniczak S, Ciesielski W, Nosal A, Szymanowski H, Gazicki-Lipman M, et al. Solid state NMR study and density functional theory (DFT) calculations of structure and dynamics of poly(p-xylylenes). *J Phys Chem B* 2009;**113**:5464–72.
78. Salager E, Day GM, Stein RS, Pickard CJ, Elena B, Emsley L. Powder crystallography by combined crystal structure prediction and high-resolution ^{1}H solid-state NMR spectroscopy. *J Am Chem Soc* 2010;**132**:2564–6.
79. Garro Linck Y, Chattah AK, Graf R, Romanuk CB, Olivera ME, Manzo RH, et al. Multinuclear solid state NMR investigation of two polymorphic forms of ciprofloxacin-saccharinate. *Phys Chem Chem Phys* 2011;**13**:6590–6.
80. Johnston KE, Griffin JM, Walton RI, Dawson DM, Lightfoot P, Ashbrook SE. ^{93}Nb NMR and DFT investigation of the polymorphs of $NaNbO_3$. *Phys Chem Chem Phys* 2011;**13**:7565–76.
81. Liu W, Wang WD, Wang W, Bai S, Dybowski C. Influence of structure on the spectroscopic properties of the polymorphs of piroxicam. *J Phys Chem B* 2010;**114**:16641–9.
82. Lee J, Lu H, Moudrakovski IL, Ratcliffe CI, Ohmura R, Alavi S, et al. ^{13}C NMR studies of hydrocarbon guests in synthetic structure H gas hydrates: experiment and computation. *J Phys Chem A* 2011;**115**:1650–7.
83. Bifulco G, Riccio R, Gaeta C, Neri P. Quantum mechanical calculations of conformationally relevant ^{1}H and ^{13}C NMR chemical shifts of N-, O-, and S-substituted calixarene systems. *Chem Eur J* 2007;**13**:7185–94.
84. Webber AL, Elena B, Griffin JM, Yates JR, Pham TN, Mauri F, et al. Complete ^{1}H resonance assignment of β-maltose from ^{1}H–^{1}H DQ-SQ CRAMPS and ^{1}H (DQ-DUMBO)–^{13}C SQ refocused INEPT 2D solid-state NMR spectra and first principles GIPAW calculations. *Phys Chem Chem Phys* 2010;**12**:6970–83.
85. Bagno A, Rastrelli F, Saielli G. Prediction of the ^{1}H and ^{13}C NMR spectra of α-d-glucose in water by DFT methods and MD simulations. *J Org Chem* 2007;**72**:7373–81.
86. Mocci F. Torsion angle relationship of the ^{17}O NMR chemical shift in α, β-unsaturated carbonyl compounds. *Magn Reson Chem* 2009;**47**:862–7.
87. Dong RY, Marini A. Conformational study of a bent-core liquid crystal: ^{13}C NMR and DFT computation approach. *J Phys Chem B* 2009;**113**:14062–72.
88. Ruiz EJ, Sears DN, Pines A, Jameson CJ. Diastereomeric Xe chemical shifts in tethered cryptophane cages. *J Am Chem Soc* 2006;**128**:16980–8.
89. Sears DN, Vukovic L, Jameson CJ. Xe NMR lineshapes in channels decorated with paramagnetic centers. *J Chem Phys* 2006;**125**:114708.
90. Yuan H, Murad S, Jameson CJ, Olson JD. Molecular dynamics simulation of Xe chemical shifts and solubility in n-alkanes. *J Phys Chem C* 2007;**111**:15771–83.
91. Yuan H, Jameson CJ, Gupta SK, Olson JD, Murad S. Prediction of Henry's constants of xenon in cyclo-alkanes from molecular dynamics simulations. *Fluid Phase Equil* 2008;**269**:73–9.
92. Ochsenfeld C, Brown SP, Schnell I, Gauss J, Spiess HW. Structure assignment in the solid state by the coupling of quantum chemical calculations with NMR experiments: a columnar hexabenzocoronene derivative. *J Am Chem Soc* 2001;**123**:2597–606.
93. Steiner E, Soncini A, Fowler PW. Full spectral decomposition of ring currents. *J Phys Chem A* 2006;**110**:12882–6.
94. Steiner E, Fowler PW, Soncini A, Jenneskens LW. Current-density maps as probes of aromaticity: global and π ring currents in totally resonant polycyclic aromatic hydrocarbons. *Faraday Discuss* 2007;**135**:309–23.
95. Pelloni S, Lazzeretti P. Magnetotropicity of five-membered heterocyclic molecules. *Theor Chem Acc* 2007;**117**:903–13.
96. Pelloni S, Faglioni F, Zanasi R, Lazzeretti P. Topology of magnetic-field induced current-density field in diatropic mono-cyclic molecules. *Phys Rev A* 2006;**74**:012506.

97. Pelloni S, Lazzeretti P, Zanasi R. Assessment of σ-diatropicity of the cyclopropane molecule. *J Phys Chem A* 2007;**111**:8163–9.
98. Pelloni S, Lazzeretti P, Zanasi R. Topological models of magnetic field induced current density field in small molecules. *Theor Chem Acc* 2009;**123**:353–64.
99. Pelloni S, Lazzeretti P. Ring current models for acetylene and ethylene molecules. *Chem Phys* 2009;**356**:153–63.
100. Okazaki T, Laali KK. Transannular π–π interactions in janusenes and in related rigid systems with cofacial aromatic rings; gauging aromaticity in the hydrocarbons and in model carbocations; a DFT study. *Org Biomol Chem* 2006;**4**:3085–95.
101. Corminboeuf C, King RB, Schleyer PV. Implications of molecular orbital symmetries and energies for the electron delocalization of inorganic clusters. *Chemphyschem* 2007;**8**:391–8.
102. Kleinpeter E, Koch A, Seidl PR. Visualization and quantification of the anisotropic effect of C=C double bonds on ^{1}H NMR spectra of highly congested hydrocarbons-indirect estimates of steric strain. *J Phys Chem A* 2008;**112**:4989–95.
103. Kleinpeter E, Koch A. Trisannelated benzenes–aromatic molecules or 1,3,5-cyclohexatriene derivatives subjected to magnetic properties. *J Mol Struct (Theochem)* 2008;**857**:89–94.
104. Kleinpeter E, Koch A, Sahoo HS, Chand DK. Anisotropic effect of the nitrate anion-manifestation of diamagnetic proton chemical shifts in the ^{1}H NMR spectra of NO_3-coordinated complexes. *Tetrahedron* 2008;**64**:5044–50.
105. Kleinpeter E, Mod S, Koch A. Endohedral and external through-space shieldings of the fullerenes C_{50}, C_{60}, C_{60}^{-6}, C_{70}, and C_{70}^{-6}–visualization of (anti)aromaticity and their effects on the chemical shifts of encapsulated nuclei. *J Org Chem* 2008;**73**:1498–507.
106. Kleinpeter E, Koch A, Shainyan BA. Cyclobutadiene dianion derivatives–planar 4c,6e or three-dimensional 6c,6e aromaticity? *J Mol Struct (Theochem)* 2008;**863**:117–22.
107. Shainyan BA, Fettke A, Kleinpeter E. Push-pull vs captodative aromaticity. *J Phys Chem A* 2008;**112**:10895–903.
108. Cuesta IG, Marin JS, de Meras AMJS. How nitrogen modifies the nuclear magnetic shielding in tetraazanaphthalenes. *Phys Chem Chem Phys* 2009;**11**:4278–85.
109. Periyasamy G, Burton NA, Hillier IH, Thomas JMH. Electron delocalization in the metallabenzenes: a computational analysis of ring currents. *J Phys Chem A* 2008;**112**:5960–72.
110. Kleinpeter E, Koch A. The anisotropic effect of functional groups in ^{1}H NMR spectra is the molecular response property of spatial NICS–the frozen conformational equilibria of 9-arylfluorenes. *Tetrahedron* 2011;**67**:5740–3.
111. Duma L, Abergel D, Tekely P, Bodenhausen G. Proton chemical shift anisotropy measurements of hydrogen-bonded functional groups by fast magic-angle spinning solid-state NMR spectroscopy. *Chem Commun* 2008;2361–3.
112. Yates JR, Pham TN, Pickard CJ, Mauri F, Amado AM, Gil AM, et al. An investigation of weak C–HO hydrogen bonds in maltose anomers by a combination of calculation and experimental solid-state NMR spectroscopy. *J Am Chem Soc* 2005;**127**:10216–20.
113. Cai L, Fushman D, Kosov DS. Density functional calculations of ^{15}N chemical shifts in solvated dipeptides. *J Biomol NMR* 2008;**41**:77–88.
114. Precechtelova J, Padrta P, Munzarova ML, Sklenar V. ^{31}P chemical shift tensors for canonical and non-canonical conformations of nucleic acids: a DFT study and NMR implications. *J Phys Chem B* 2008;**112**:3470–8.
115. Gajda J, Olejniczak S, Bryndal I, Potrzebowski MJ. Elucidation of structural restraints for phosphate residues with different hydrogen bonding and ionization states. *J Phys Chem B* 2008;**112**:14036–44.

116. Dong S, Ida R, Wu G. A combined experimental and theoretical ^{17}O NMR study of crystalline urea: an example of large hydrogen-bonding effects. *J Phys Chem A* 2000;**104**:11194–202.
117. Bryce DL, Sward GD, Adiga S. Solid-state $^{35/37}Cl$ NMR spectroscopy of hydrochloride salts of amino acids implicated in chloride ion transport channel selectivity: opportunities at 900 MHz. *J Am Chem Soc* 2006;**128**:2121–34.
118. Chapman RP, Bryce DL. A high-field solid-state $^{35/37}Cl$ NMR and quantum chemical investigation of the chlorine quadrupolar and chemical shift tensors in amino acid hydrochlorides. *Phys Chem Chem Phys* 2007;**9**:6219–30.
119. Kongsted J, Nielsen CB, Mikkelsen KV, Christiansen O, Ruud K. Nuclear magnetic shielding constants of liquid water: insights from hybrid quantum mechanics/molecular mechanics models. *J Chem Phys* 2007;**126**:034510.
120. Klamt A, Schüürmann G. COSMO: a new approach to dielectric screening in solvents with explicit expressions for the screening energy and its gradient. *J Chem Soc, Perkin Trans 2* 1993;799–805.
121. Miertuš S, Scrocco E, Tomasi J. Electrostatic interactions of a solute with a continuum. A direct utilization of ab initio molecular potentials for the pervision of solvent effects. *Chem Phys* 1981;**55**:117–29.
122. de Dios AC, Pearson JG, Oldfield E. Secondary and tertiary structural effects on protein NMR chemical shifts: an *ab initio* approach. *Science* 1993;**260**:1491–6.
123. de Dios AC, Oldfield E. Methods for computing nuclear magnetic resonance chemical shielding in large systems: multiple cluster and charge field approaches. *Chem Phys Lett* 1993;**205**:108–16.
124. de Dios AC, Laws DD, Oldfield E. Predicting carbon-13 nuclear magnetic resonance chemical shielding tensors in zwitterionic L-threonine and L-tyrosine via quantum chemistry. *J Am Chem Soc* 1994;**116**:7784–6.
125. Stueber D. The embedded ion method: a new approach to the electrostatic description of crystal lattice effects in chemical shielding calculations. *Concepts Magn Reson A* 2006;**28**:347–68.
126. Stefanovich EV, Truong TN. A simple method for incorporating Madelung field effects into *ab initio* embedded cluster calculations of crystals and macromolecules. *J Phys Chem B* 1998;**102**:3018–22.
127. Di Fiori N, Orendt AM, Caputo MC, Ferraro MB, Facelli JC. Modeling solid-state effects on NMR chemical shifts using electrostatic models. *Magn Reson Chem* 2004;**42**:S41–7.
128. Weber J, Schmedt auf der Günne J. Calculation of NMR parameters in ionic solids by an improved self-consistent embedded cluster method. *Phys Chem Chem Phys* 2010;**12**:583–603.
129. Buckingham AD. Solvent effects in nuclear magnetic resonance spectra. *Can J Chem* 1960;**38**:300–7.
130. Bishop DM, Cybulski SM. Ab-initio calculation of the nuclear magnetic shielding constants and shielding polarizabilities of the noble gases. *J Magn Reson A* 1994;**107**:99–101.
131. Cybulski SM, Bishop DM. Calculation of magnetic properties VII. Electron-correlated magnetizability polarizabilities and nuclear shielding polarizabilities for nine small molecules. *Mol Phys* 1998;**93**:739–50.
132. Pecul M, Saue T, Ruud K, Rizzo A. Electric field effects on the shielding constants of noble gases: a four-component relativistic Hartree-Fock study. *J Chem Phys* 2004;**121**:3051–7.
133. Gauss J. Shielding polarizabilities calculated at the coupled-cluster singles and doubles level augmented by a perturbative treatment of triple excitations. *J Chem Phys* 2002;**116**:869–77.

134. Stueber D, Jameson CJ. The chemical shifts of Xe in the cages of clathrate hydrate structure I and II. *J Chem Phys* 2004;**120**:1560–71.
135. Banyai DR, Murakhtina T, Sebastiani D. NMR chemical shifts as a tool to analyze first principles molecular dynamics simulations in condensed phases: the case of liquid water. *Magn Reson Chem* 2010;**48**:S56–60.
136. Truflandier LA, Sutter K, Autschbach J. Solvent effects and dynamic averaging of ^{195}Pt NMR shielding in *cis* platin derivatives. *Inorg Chem* 2011;**50**:1723–32.
137. Bagno A, Bonchio M, Autschbach J. Computational modeling of polyoxotungstates by relativistic DFT calculations of ^{183}W NMR chemical shifts. *Chem Eur J* 2006;**12**:8460–71.
138. Sugimori K, Kawabe H, Nagao H, Nishikawa K. *Ab initio* and DFT study of ^{31}P-NMR chemical shifts of sphingomyelin and dihydrosphingomyelin lipid molecule. *Int J Quantum Chem* 2009;**109**:3685–93.
139. Bai S, Dmitrenko O, Dybowski C. ^{15}N and ^{13}C NMR chemical shifts of 6-(fluoro, chloro, bromo, and iodo)purine 2'-deoxynucleosides: measurements and calculations. *Magn Reson Chem* 2010;**48**:61–7.
140. Stueber D, Orendt AM, Facelli JC, Parry RW, Grant DM. Carbonates, thiocarbonates, and the corresponding monoalkyl derivatives: III. The ^{13}C chemical shift tensors in potassium carbonate, bicarbonate and related monomethyl derivatives. *Solid State NMR* 2002;**22**:29–49.
141. Stueber D, Grant DM. ^{13}C and ^{15}N chemical shift tensors in adenosine, guanosine dihydrate, 2-deoxythymidine, and cytidine. *J Am Chem Soc* 2002;**24**:10359–551.
142. Barich DH, Clawson JS, Stueber D, Strohmeier M, Pugmire RJ, Grant DM. Determination of ^{13}C chemical shift tensors in the presence of hydrogen bonding and ^{14}N quadrupolar coupling: p-aminosalicylic acid, isaniazid, and pyrazinamide. *J Phys Chem A* 2002;**106**:11375–9.
143. Jameson CJ, Stueber D. The NMR lineshapes of Xe in the cages of clathrate hydrates. *J Chem Phys* 2004;**120**:10200–14.
144. Vaara J, Pyykkö P. Relativistic, nearly basis-set-limit nuclear magnetic shielding constants of the rare gases He–Rn: a way to absolute nuclear magnetic resonance shielding scales. *J Chem Phys* 2003;**118**:2973–6.
145. Hanni M, Lantto P, Illias M, Hansen HJ, Vaara J. Relativistic effects in the intermolecular interaction-induced nuclear magnetic resonance parameters of xenon dimer. *J Chem Phys* 2007;**127**:164313.
146. Hanni M, Lantto P, Vaara J. Pairwise additivity in the nuclear magnetic resonance interactions of atomic xenon. *Phys Chem Chem Phys* 2009;**11**:2485–96.
147. Hyvarinen M, Vaara J, Goldammer A, Kutzky B, Hegetschweiler K, Kaupp M, et al. Characteristic spin-orbit induced $^{1}H(CH_2)$ chemical shifts upon deprotonation of group 9 polyamine aqua and alcohol complexes. *J Am Chem Soc* 2009;**131**:11909–18.
148. Sears DN, Jameson CJ, Harris RA. Nuclear magnetic shielding and chirality IV. The odd and even character of the shielding response to a chiral potential. *J Chem Phys* 2004;**120**:3277–83.
149. Barra AL, Robert JR. Parity non-conservation and NMR parameters. *Mol Phys* 1996;**88**:875–86.
150. Sears DN, Jameson CJ, Harris RA. Nuclear magnetic shielding and chirality I. The shielding tensor of Xe interacting with Ne helices. *J Chem Phys* 2003;**119**:2685–90.
151. Sears DN, Jameson CJ, Harris RA. Nuclear magnetic shielding and chirality II. The shielding tensor of a naked spin in Ne helices. *J Chem Phys* 2003;**119**:2691–3.
152. Sears DN, Jameson CJ, Harris RA. Nuclear magnetic shielding and chirality III. The single electron on a helix model. *J Chem Phys* 2003;**119**:2694–701.

153. Buckingham AD, Malm S. Asymmetry in the nuclear magnetic shielding tensor. *Mol Phys* 1971;**22**:1127–30.
154. Ruiz EJ, Sears DN, Pines A, Jameson CJ. Diastereomeric Xe chemical shifts in tethered cryptophane cages. *J Am Chem Soc* 2006;**128**:16980–8.
155. Ruiz EJ, Spence MM, Rubin SM, Wemmer DE, Pines A, Winssinger N, et al. *43rd experimental NMR conference, April 14–19, Asilomar, CA*; 2002.
156. Buckingham AD, Fischer P. Direct chiral discrimination in NMR spectroscopy. *Chem Phys* 2006;**324**:111–6.
157. Harris RA, Jameson CJ. A note on chirality in NMR spectroscopy. *J Chem Phys* 2006;**124**:096101.
158. Allen BD, Cintrat JC, Faucher N, Berthault P, Rousseau B, O'Leary DJ. An isosparteine derivative for stereochemical assignment of stereogenic (chiral) methyl groups using tritium NMR: theory and experiment. *J Am Chem Soc* 2005;**127**:412–20.
159. Smith SG, Channon JA, Paterson I, Goodman JM. The stereochemical assignment of acyclic polyols: a computational study of the NMR data of a library of stereopentad sequences from polyketide natural products. *Tetrahedron* 2010;**66**:6437–44.
160. Smith SG, Goodman JM. Assigning stereochemistry to single diastereoisomers by GIAO NMR calculation: the DP4 probability. *J Am Chem Soc* 2010;**132**:12946–59.
161. Facelli JC, Grant DM. Determination of molecular symmetry in crystalline naphthalene using solid-state NMR data. *Nature* 1993;**365**:325–7.
162. Strohmeier M, Orendt AM, Alderman DW, Grant DM. Investigation of the polymorphs of dimethyl-3,6-dichloro-2,5-hydroxyterephthalate by ^{13}C solid-state NMR spectroscopy. *J Am Chem Soc* 2001;**123**:1713–22.
163. Hu JZ, Facelli JC, Alderman DW, Pugmire RJ, Grant DM. ^{15}N chemical shift tensors in nucleic acid bases. *J Am Chem Soc* 1998;**120**:9863–9.
164. Facelli JC, Pugmire RJ, Grant DM. Effects of hydrogen bonding in the calculations of ^{15}N chemical shift tensors: benzamide. *J Am Chem Soc* 1996;**118**:5488–9.
165. Anderson K, Merwin LH, Wilson WS, Facelli JC. ^{15}N chemical shifts in energetic materials: CP/MAS and ab initio studies of aminonitropyridines, aminonitropyrimidines, and their N-oxides. *Int J Mol Sci* 2002;**3**:858–72.
166. Pechkis DL, Walter EJ, Krakauer H. High sensitivity of ^{17}O NMR to p-d hybridization in transition metal perovskites: first principles calculations of large anisotropic chemical shielding. *J Chem Phys* 2009;**131**:184511.
167. Pechkis DL, Walter EJ, Krakauer H. First-principles calculations of ^{17}O nuclear magnetic resonance chemical shielding in $Pb(Zr_{1/2}Ti_{1/2})O_3$ and $Pb(Mg_{1/3}Nb_{2/3})O_3$: linear dependence on transition-metal/oxygen bond lengths. *J Chem Phys* 2011;**135**:114507.
168. Mauri F, Pfrommer BG, Louie SG. *Ab-initio* theory of NMR chemical shifts in solids and liquids. *Phys Rev Lett* 1996;**77**:5300–3.
169. Pickard CJ, Mauri F. All-electron magnetic response with pseudopotentials: NMR chemical shifts. *Phys Rev B* 2001;**63**:245101.
170. Clark SJ, Segall MD, Pickard CJ, Hasnip PJ, Probert MJ, Refson K, et al. *Zeit Kristallographie* 2005;**220**:567–70.http://www.castep.org/.
171. Canning A, Raczkowski D. Scaling first-principles planewave codes to thousands of processors. *Computer Physics Communications* 2004; 169: 449–453. PARATEC (PARAllel Total Energy Code) developed at Lawrence Berkeley National Laboratory by Pfrommer B, Raczkowski D, Canning A, Louie SG, (with contributions from F. Mauri, M. Côté, Y. Yoon, C. Pickard and P. Haynes) is heavily optimized for running on large parallel machines https://www.nersc.gov/users/software/applications/materials-science/paratec/. Accessed Aug. 14, 2012.
172. Giannozzi P, Baroni S, Bonini N, Calandra M, Car R, Cavazzoni C, Ceresoli D, Chiarotti GL, Cococcioni M, Dabo I, Dal Corso A, Fabris S, Fratesi G, de Gironcoli S,

Gebauer R, Gerstmann U, Gougoussis C, Kokalj A, Lazzeri M, Martin-Samos L, Marzari N, Mauri F, Mazzarello R, Paolini S, Pasquarello A, Paulatto L, Sbraccia C, Scandolo S, Sclauzero G, Seitsonen AP, Smogunov A, Umari P, Wentzcovitch RM. QUANTUM ESPRESSO: a modular and open-source software project for quantum simulations of materials. *J Phys Condens Matter* 2009;21:395502. Quantum ESPRESSO is available from http://www.quantum-espresso.org/. Accessed Aug. 14, 2012.

173. Sebastiani D, Parrinello M. A new ab-initio approach for NMR chemical shifts in periodic systems. *J Phys Chem A* 2001;**105**:1951–8.
174. J. Hutter, M. Parrinello, D. Marx, P. Focher, M. Tuckerman, W. Andreoni, A. Curioni, E. Fois, U. Roetlisberger, P. Giannozzi, T. Deutsch, A. Alavi, D. Sebastiani, A. Laio, J. VandeVondele, A. Seitsonen, S. Billeter, Computer code CPMD, version 3.5, Copyright IBM Corp. and MPI-FKF Stuttgart 1990–2002, http://www.cpmd.org. Accessed Aug. 14, 2012.
175. Weber V, Iannuzzi M, Giani S, Hutter J, Declerck R, Waroquier M. Magnetic linear response properties calculations with the Gaussian and augmented-plane-wave method. *J Chem Phys* 2009;**131**:014106.
176. VandeVondele J, Krack M, Mohamed F, Parrinello M, Chassaing T, Hutter J. Quickstep: fast and accurate density functional calculations using a mixed Gaussian and plane waves approach. *Comput Phys Commun* 2005;**167**:103–28.
177. The CP2K developers group, 2008, http:/cp2k.berlios.de/.
178. Thonhauser T, Ceresoli D, Mostofi AA, Marzari N, Resta R, Vanderbilt D. A converse approach to the calculation of NMR shielding tensors. *J Chem Phys* 2009;**131**:101101.
179. Thonhauser T, Ceresoli D, Marzari N. NMR shifts for polycyclic aromatic hydrocarbons from first-principles. *Int J Quantum Chem* 2009;**109**:3336–42.
180. Ceresoli D, Marzari N, Lopez MG, Thonhauser T. *Ab initio* converse NMR approach for pseudopotentials. *Phys Rev B* 2010;**81**:184424.
181. Skachkov D, Krykunov M, Kadantsev E, Ziegler T. The calculation of NMR chemical shifts in periodic systems based on gauge including atomic orbitals and density functional theory. *J Chem Theory Comput* 2010;**6**:1650–9.
182. Skachkov D, Krykunov M, Ziegler T. An improved scheme for the calculation of NMR chemical shifts in periodic systems based on gauge including atomic orbitals and density functional theory. *Can J Chem* 2011;**89**:1150–61.
183. P.H.T. Philipsen, G. te Velde, E.J. Baerends, J.A. Berger, P.L. de Boeij, J.A. Groeneveld, E.S. Kadantsev, R. Klooster, F. Kootstra, P. Romaniello, D.G. Skachkov, J.G. Snijders, G. Wiesenekker, T. Ziegler, BAND2012, SCM, Theoretical Chemistry, Vrije Universiteit, Amsterdam, The Netherlands, http://www.scm.com BAND, a periodic structure program for the study of bulk crystals, polymers, and surfaces in the Amsterdam Density Functional (ADF) package
184. Schwarz K, Blaha P, Trickey SB. Electronic structure of solids with WIEN2k. *Mol Phys* 2010;**108**:3147–66.
185. P. Blaha, K. Schwarz, G. Madsen, D. Kvasnicka and J. Luitz, WIEN2k, An Augmented Plane Wave Plus Local Orbitals Program for Calculating Crystal Properties, Institute for Materials Chemistry, Technical University Vienna. ©2001 by P. Blaha and K. Schwarz. Latest release December 14, 2007.
186. Laskowski R, Blaha P. Calculations of NMR chemical shifts with APW-based methods. *Phys Rev B* 2012;**85**:035132.
187. Gregor T, Mauri F, Car R. A comparison of methods for the calculation of NMR chemical shifts. *J Chem Phys* 1999;**111**:1815–22.
188. Mauri F, Pfrommer BG, Louie SG. *Ab initio* NMR chemical shift of diamond, chemical-vapor-deposited diamond, and amorphous carbon. *Phys Rev Lett* 1997;**79**:2340–3.
189. Yoon Y-G, Pfrommer BG, Mauri F, Louie SG. NMR chemical shifts in hard carbon nitride compounds. *Phys Rev Lett* 1998;**80**:3388–91.

190. Mauri F, Pfrommer BG, Louie SG. Signature of surface states on NMR chemical shifts: a theoretical prediction. *Phys Rev B* 1999;**60**:2941–5.
191. Mauri F, Pasquarello A, Pfrommer BG, Yoon Y-G, Louie SG. Si-O-Si bond-angle distribution in vitreous silica from first-principles ^{29}Si NMR analysis. *Phys Rev B* 2000;**62**:R4786–9.
192. Pfrommer BG, Mauri F, Louie SG. NMR chemical shifts of ice and liquid water: the effects of condensation. *J Am Chem Soc* 2000;**122**:123–9.
193. Blöchl PE. Projector augmented-wave method. *Phys Rev B* 1994;**50**:17953–79.
194. Mauri F, Vast N, Pickard CJ. Atomic structure of icosahedral B_4C boron carbide from a first principles analysis of NMR spectra. *Phys Rev Lett* 2001;**87**:085506.
195. Marques MAL, d'Avezac M, Mauri F. Magnetic response and NMR spectra of carbon nanotubes from *ab initio* calculations. *Phys Rev B* 2006;**73**:125433.
196. Profeta M, Mauri F, Pickard CJ. Accurate first principles prediction of ^{17}O NMR parameters in SiO_2: assignment of the zeolite ferrierite spectrum. *J Am Chem Soc* 2003;**125**:541–8.
197. Farnan I, Balan E, Pickard CJ, Mauri F. The effect of radiation damage on local structure in the crystalline fraction of $ZrSiO_4$: investigating the ^{29}Si NMR response to pressure in zircon and reidite. *Am Mineralogist* 2003;**88**:1663–7.
198. Charpentier T, Ispas S, Profeta M, Mauri F, Pickard CJ. First-principles calculation of ^{17}O, ^{29}Si, and ^{23}Na NMR spectra of sodium silicate crystals and glasses. *J Phys Chem B* 2004;**108**:4147–61.
199. Benoit M, Profeta M, Mauri F, Pickard CJ, Tuckerman ME. First-principles calculation of the ^{17}O NMR parameters of a calcium aluminosilicate glass. *J Phys Chem B* 2005;**109**:6052–60.
200. Gervais C, Profeta M, Babonneau F, Pickard CJ, Mauri F. *Ab-initio* calculations of NMR parameters of highly coordinated oxygen sites in aluminosilicates. *J Phys Chem B* 2004;**108**:13249–53.
201. Profeta M, Benoit M, Mauri F, Pickard CJ. First-principles calculation of the ^{17}O NMR parameters in Ca oxide and Ca aluminosilicates: the partially covalent nature of the Ca-O bond, a challenge for density functional theory. *J Am Chem Soc* 2004;**126**:12628–35.
202. Yates JR, Dobbins SE, Pickard CJ, Mauri F, Ghi PY, Harris RK. A combined first principles computational and solid-state NMR study of a molecular crystal: flurbiprofen. *Phys Chem Chem Phys* 2005;**7**:1402–7.
203. Gervais C, Dupree R, Pike KJ, Bonhomme C, Profeta M, Pickard CJ, et al. Combined first-principles computational and experimental multinuclear solid-state NMR investigation of amino acids. *J Phys Chem A* 2005;**109**:6960–9.
204. Ghi PY, Harris RK, Hammond RB, Ma C, Roberts KJ, Yates JR, et al. Solid-state NMR and computational studies of 4-methyl-2-nitroacetanilide. *Magn Reson Chem* 2006;**44**:325–33.
205. Yates JR, Pickard CJ, Payne MC, Dupree R, Profeta M, Mauri F. Theoretical investigation of oxygen-17 NMR shielding and electric field gradients in glutamic acid polymorphs. *J Phys Chem A* 2004;**108**:6032–7.
206. Harris RK, Ghi PY, Puschmann H, Apperley DC, Griesser UJ, Hammond RB, et al. Structural studies of the polymorphs of carbamazepine, its dihydrate, and two solvates. *Org Process Res Dev* 2005;**9**:902–10.
207. Yates JR, Pickard CJ, Mauri F. Calculation of NMR chemical shifts for extended systems using ultrasoft pseudopotentials. *Phys Rev B* 2007;**76**:024401.
208. Vanderbilt D. Soft self-consistent pseudopotentials in a generalized eigenvalue formalism. *Phys Rev B* 1990;**41**:7892–5.
209. Zhou B, Sherriff BL, Wang T. 27Al NMR spectroscopy at multiple magnetic fields and *ab initio* quantum modeling for kaolinite. *Am Mineralogist* 2009;**94**:865–71.

210. Ashbrook SE, Polles LL, Gautier R, Pickard CJ, Walton RI. ^{23}Na multiple-quantum MAS NMR of the perovskites $NaNbO_3$ and $NaTaO_3$. *Phys Chem Chem Phys* 2006;**8**:3423–31.
211. Harris RK, Cadars S, Emsley L, Yates JR, Pickard CJ, Jetti R, et al. NMR crystallography of oxybuprocaine hydrochloride, Modification II°. *Phys Chem Chem Phys* 2006;**9**:360–8.
212. Harris RK, Joyce SA, Pickard CJ, Cadars S, Emsley L. Assigning carbon-13 NMR spectra to crystal structures by the INADEQUATE pulse sequence and first principles computation: a case study of two forms of testosterone. *Phys Chem Chem Phys* 2006;**8**:137–43.
213. Webber AL, Emsley L, Claramunt RM, Brown P. NMR crystallography of Campho [2,3-c]pyrazole ($Z' = 6$): combining high-resolution ^{1}H-^{13}C solid-state MAS NMR spectroscopy and GIPAW chemical-shift calculations. *J Phys Chem A* 2010;**114**:10435–42.
214. Kücukbenli E, Sonkar K, Sinha N, de Gironcoli S. Complete ^{13}C NMR chemical shifts assignment for cholesterol crystals by combined CP-MAS spectral editing and *ab initio* GIPAW calculations with dispersion forces. *J Phys Chem A* 2012;**116**:3765–9.
215. Johnston JC, Iuliucci RJ, Facelli JC, Fitzgerald G, Mueller KT. Intermolecular shielding contributions studied by modeling the ^{13}C chemical-shift tensors of organic single crystals with plane waves. *J Chem Phys* 2009;**131**:144503.
216. Cuny J, Furet E, Gautier R, Le Polles L, Pickard CJ, d'Espinose de Lacaillerie CB. Density functional theory calculations of ^{95}Mo NMR parameters in solid-state compounds. *Chemphyschem* 2009;**10**:3320–9.
217. Widdifield CM, Bryce DL. Solid-state $^{79/81}$Br NMR and gauge-including projector-augmented wave study of structure, symmetry, and hydration state in alkaline earth metal bromides. *J Phys Chem A* 2010;**114**:2102–16.
218. Kibalchenko M, Yates JR, Pasquarello A. First-principles investigation of the relation between structural and NMR parameters in vitreous GeO_2. *J Phys: Condens Mat* 2010;**22**:145501.
219. Pedone A, Gambuzzi E, Malavasi G, Menziani MC. First-principles simulations of the ^{27}Al and ^{17}O solid-state NMR spectra of the $CaAl_2Si_3O_{10}$ glass. *Theor Chem Acc* 2012;**131**:1147.
220. De Gortari I, Portella G, Salvatella X, Bajaj VS, van der Wel PCA, Yates JR, et al. Time averaging of NMR chemical shifts in the MLF peptide in the solid state. *J Am Chem Soc* 2010;**132**:5993–6000.
221. Truflandier L, Paris M, Boucher F. Density functional theory investigation of 3d transition metal NMR shielding tensors in diamagnetic systems using the gauge-including projector augmented-wave method. *Phys Rev B* 2007;**76**:035102.
222. Yates JR, Pickard CJ, Payne MC, Mauri F. Relativistic nuclear magnetic resonance chemical shifts of heavy nuclei with pseudopotentials and the zeroth-order regular approximation. *J Chem Phys* 2003;**118**:5746–53.
223. http://www.gipaw.net.
224. Berghold G, Mundy C, Romero A, Hutter J, Parrinello M. General and efficient algorithms for obtaining maximally localized Wannier functions. *Phys Rev B* 2000;**61**:10040.
225. Piana S, Sebastiani D, Carloni P, Parrinello M. *Ab initio* molecular dynamics-based assignment of the protonation state of pepstatin A/HIV-1 protease cleavage site. *J Am Chem Soc* 2001;**123**:8730–7.
226. Keith TA, Bader RFW. Calculation of magnetic response properties using a continuous set of gauge transformations. *Chem Phys Lett* 1993;**210**:223–31.
227. Keith TA, Bader RFW. Calculation of magnetic response properties using atoms in molecules. *Chem Phys Lett* 1992;**194**:1–8.
228. Sebastiani D. Ab-initio calculations of NMR parameters In condensed phases. *Modern Phys Lett B* 2003;**17**:1301–19.

229. Sebastiani D, Goward G, Schnell I, Parrinello M. NMR chemical shifts in periodic systems from first principles. *Comput Phys Commun* 2002;**147**:707–10.
230. Sebastiani D, Goward G, Schnell I, Spiess HW. NMR chemical shifts in proton conducting crystals from first principles. *J Mol Struct (Theochem)* 2003;**625**:283–8.
231. Schmidt J, Hoffmann A, Spiess HW, Sebastiani D. Bulk chemical shifts in hydrogen-bonded systems from first-principles calculations and solid-state-NMR. *J Phys Chem B* 2006;**110**:23204–10.
232. Ceresoli D, Gerstmann U, Seitsonen AP, Mauri F. First-principles theory of orbital magnetization. *Phys Rev B* 2009;**81**:060409.
233. Ceresoli D, Thonhauser T, Vanderbilt D, Resta R. Orbital magnetization in crystalline solids. *Phys Rev B* 2006;**74**:24408.
234. Widdifield CM, Bryce DL. Solid-state ^{127}I NMR and GIPAW DFT study of metal iodides and their hydrates: structure, symmetry, and higher-order quadrupole-induced effects. *J Phys Chem A* 2010;**114**:10810–23.
235. Abou-Hamad E, Babaa M-R, Bouhrara M, Kim Y, Saih Y, Dennler S, et al. Structural properties of carbon nanotubes derived from ^{13}C NMR. *Phys Rev B* 2011;**84**:165417.
236. Pickard CJ, Salager E, Pintacuda G, Elena B, Emsley L. Resolving structures from powders by NMR crystallography using combined proton spin diffusion and plane wave DFT calculations. *J Am Chem Soc* 2007;**129**:8932–3.
237. Bryce DL, Bultz EB. Alkaline earth chloride hydrates: chlorine quadrupolar and chemical shift tensors by solid-state NMR spectroscopy and plane wave pseudopotential calculations. *Chem Eur J* 2007;**13**:4786–96.
238. Attrell RJ, Widdifield CM, Korobkov I, Bryce DL. Weak halogen bonding in solid haloanilinium halides probed directly via chlorine-35, bromine-81, and iodine-127 NMR spectroscopy. *Cryst Growth Des* 2012;**12**:1641–53.
239. Burgess KMN, Korobkov I, Bryce DL. A combined solid-state NMR and X-ray crystallography study of the bromide ion environments in triphenylphosphonium bromides. *Chem Eur J* 2012;**18**:5748–58.
240. Vasconcelos F, Cristol S, Paul J-F, Tricot G, Amoureux J-P, Montagne L, et al. ^{17}O solid-state NMR and first-principles calculations of sodiumtrimetaphosphate ($Na_3P_3O_9$), tripolyphosphate ($Na_5P_3O_{10}$), and pyrophosphate ($Na_4P_2O_7$). *Inorg Chem* 2008;**47**:7327–37.
241. Olejniczak S, Mikua-Pacboczyk J, Hughes CE, Potrzebowski MJ. ^{15}N and ^{13}C high-resolution solid-state NMR study of the polymorphism of the L-enantiomer of N-benzoylphenylalanine. *J Phys Chem B* 2008;**112**:1586–93.
242. Macholl S, Lentz D, Borner F, Buntkowsky G. Polymorphism of N, N″-diacetylbiuret studied by solid-state ^{13}C and ^{15}N NMR spectroscopy, DFT calculations, and X-ray diffraction. *Chem Eur J* 2007;**13**:6139–49.
243. Ashbrook SE, Le Polles L, Pickard CJ, Berry AJ, Wimperis S, Farnan I. First-principles calculations of solid-state ^{17}O and ^{29}Si NMR spectra of Mg_2SiO_4 polymorphs. *Phys Chem Chem Phys* 2007;**9**:1587–98.
244. Filhol J-S, Deschamps J, Dutremez SG, Boury B, Barisien T, Legrand L, et al. Polymorphs and colors of polydiacetylenes: a first principles study. *J Am Chem Soc* 2009;**131**:6976–88.
245. Bryce DL, Bultz EB, Aebi D. Calcium-43 chemical shift tensors as probes of calcium binding environments. Insight into the structure of the vaterite $CaCO_3$ polymorph by ^{43}Ca solid-state NMR spectroscopy. *J Am Chem Soc* 2008;**130**:9282–92.
246. Lizarraga R, Holmstrom E, Parker SC, Arrouvel C. Structural characterization of amorphous alumina and its polymorphs from first-principles XPS and NMR calculations. *Phys Rev B* 2011;**83**:094201.
247. Aliev AE, Mann SE, Rahman AS, McMillan PF, Corà F, Iuga D, et al. High-resolution solid-state ^{2}H NMR spectroscopy of polymorphs of glycine. *J Phys Chem A* 2011;**115**:12201–11.

248. Griffin JM, Knight F, Hua G, Ferrara J, Hogan S, Woollins JD, et al. ^{77}Se solid-state NMR of inorganic and organoselenium systems: a combined experimental and computational study. *J Phys Chem C* 2011;**115**:10859–72.
249. Caruso F, Chan EJ, Hanna JV, Marchetti F, Pettinari C, Di Nicola C, et al. The question of *cis* versus trans configuration in octahedral metal diketonates: an in-depth investigation on diorganobis(4-acyl-5-pyrazolonato)tin(IV) complexes. *Eur J Inorg Chem* 2012;1369–79.
250. Sadoc A, Body M, Legein C, Biswal M, Fayon F, Rocquefelte X, et al. NMR parameters in alkali, alkaline earth and rare earth fluorides from first principle calculations. *Phys Chem Chem Phys* 2011;**13**:18539–50.
251. Truflandier L, Paris M, Payen C, Boucher F. First-principles calculations within periodic boundary conditions of the NMR shielding tensor for a transition metal nucleus in a solid state system: the example of ^{51}V in $AlVO_4$. *J Phys Chem B* 2006;**110**:21403–7.
252. Griffin JM, Yates JR, Berry AJ, Wimperis S, Ashbrook SE. High-resolution ^{19}F MAS NMR spectroscopy: structural disorder and unusual J couplings in a fluorinated hydroxy-silicate. *J Am Chem Soc* 2010;**132**:15651–60.
253. Ispas S, Charpentier T, Mauri F, Neuville DR. Structural properties of lithium and sodium tetrasilicate glasses: molecular dynamics simulations versus NMR experimental and first-principles data. *Solid State Sciences* 2010;**12**:183–92.
254. Angeli F, Villain O, Schuller S, Ispas S, Charpentier T. Insight into sodium silicate glass structural organization by multinuclear NMR combined with first-principles calculations. *Geochim Cosmochim Acta* 2011;**75**:2453–69.
255. Kibalchenko M, Yates JR, Massobrio C, Pasquarello A. Structural composition of first-neighbor shells in $GeSe_2$ and $GeSe_4$ glasses from a first-principles analysis of NMR chemical shifts. *J Phys Chem C* 2011;**115**:7755–9.
256. Charpentier T, Kroll P, Mauri F. First-principles NMR structural analysis of vitreous silica. *J Phys Chem C* 2009;**113**:7917–27.
257. Soleilhavoup A, Delaye J-M, Angeli F, Angeli F, Caurant D, Charpentier T. Contribution of first-principles calculations to multinuclear NMR analysis of borosilicate glasses. *Magn Reson Chem* 2010;**48**:S159–70.
258. Forler N, Vasconcelos F, Cristol S, Paul JF, Montagne L, Charpentier T, et al. New insights into oxygen environments generated during phosphate glass alteration: a combined ^{17}O MAS and MQMAS NMR and first principles calculations study. *Phys Chem Chem Phys B* 2010;**12**:9053–62.
259. Pedone A, Charpentier T, Menziani MC. The structure of fluoride-containing bioactive glasses: new insights from first-principles calculations and solid state NMR spectroscopy. *J Mater Chem* 2012;**22**:12599–608.
260. Mitchell MR, Carnevale D, Orr R, Whittle KR, Ashbrook SE. Exploiting the chemical shielding anisotropy to probe structure and disorder in ceramics: ^{89}Y MAS NMR and first-principles calculations. *J Phys Chem C* 2012;**116**:4273–86.
261. Mitchell MR, Reader SW, Johnston KE, Pickard CJ, Whittle KR, Ashbrook SE. ^{119}Sn MAS NMR and first-principles calculations for the investigation of disorder in pyrochlore ceramics. *Phys Chem Chem Phys* 2011;**13**:488–97.
262. Sebastiani D. Current densities and nucleus-independent chemical shift maps from reciprocal-space density functional perturbation theory calculations. *Chemphyschem* 2006;**7**:164–75.
263. Brunklaus G, Koch A, Sebastiani D, Spiess HW. Selectivity of guest–host interactions in self-assembled hydrogen-bonded nanostructures observed by NMR. *Phys Chem Chem Phys* 2007;**9**:4545–51.
264. Cuny J, Sykina K, Fontaine B, Le Polle's L, Pickard CJ, Gautier R. ^{95}Mo nuclear magnetic resonance parameters of molybdenum hexacarbonyl from density functional theory: appraisal of computational and geometrical parameters. *Phys Chem Chem Phys* 2011;**13**:19471–9.

265. Koelling DD, Harmon BN. A technique for relativistic spin-polarized calculations. *J Phys C* 1977;**10**:3107–14.
266. E. D. Glendening, A. E. Reed, J. E. Carpenter, F. Weinhold, NBO, Version 3.1; Chemistry Department, University of Wisconsin: Madison, WI, 1995.
267. Harper JK, Doebbler JA, Jacques E, Grant DM, Von Dreele RB. A combined solid-state NMR and synchrotron X-ray diffraction powder study on the structure of the antioxidant (+)-catechin 4.5-hydrate. *J Am Chem Soc* 2010;**132**:2928–37.
268. Alderman DW, Sherwood MH, Grant DM. Comparing, modeling, and assigning chemical-shift tensors in the Cartesian, irreducible spherical, and icosahedral representations. *J Magn Reson A* 1993;**101**:188–97.
269. Cadars S, Lesage A, Pickard CJ, Sautet P, Emsley L. Characterizing slight structural disorder in solids by combined solid-state NMR and first principles calculations. *J Phys Chem A* 2009;**113**:902–11.
270. Klintenberg MK, Derenzo SE, Weber MJ. Accurate crystal fields for embedded cluster calculations. *Comput Phys Commun* 2000;**131**:120–8.
271. Chen X, Zhan C-G. First-principles studies of C-13 NMR chemical shift tensors of amino acids in crystal state. *J Mol Struct (Theochem)* 2004;**682**:73–82.
272. Strohmeier M, Stueber D, Grant DM. Accurate ^{13}C and ^{15}N chemical shift and ^{14}N quadrupolar coupling constant calculations in amino acid crystals: zwitterionic, hydrogen-bonded systems. *J Phys Chem A* 2003;**107**:7629–42.
273. Zheng A, Liu S-B, Deng F. ^{13}C Shielding tensors of crystalline amino acids and peptides: theoretical predictions based on periodic structure models. *J Comput Chem* 2009;**30**:222–35.
274. Zheng A, Yang M, Yue Y, Ye C, Deng F. ^{13}C NMR shielding tensors of carboxyl carbon in amino acids calculated by ONIOM method. *Chem Phys Lett* 2004;**399**:172–6.
275. Brey WS, Richardson D, Bechtel B, Aksenov A. Spin-spin coupling and substituent and halogen isotope shift effects in the fluorine NMR spectra of fluorinated cyclopropanes and cyclopropyl ethers. *Magn Reson Chem* 2007;**45**:205–19.
276. Spink E, Hewage C, Malthouse JPG. Determination of the structure of tetrahedral transition state analogues bound at the active site of chymotrypsin using ^{18}O and ^{2}H isotope shifts in the ^{13}C NMR spectra of glyoxal inhibitors. *Biochemistry* 2007;**46**:12868–74.
277. Rozwadowski Z. Deuterium isotope effect on ^{13}C chemical shifts of tetrabutylammonium salts of Schiff bases amino acids. *Magn Reson Chem* 2006;**44**:881–6.
278. West-Nielsen M, Dominiak PM, Wozniak K, Hansen PE. Strong intramolecular hydrogen bonding involving nitro- and acetyl groups. Deuterium isotope effects on chemical shifts. *J Mol Struct* 2006;**789**:81–91.
279. Chmielewski P, Ozeryanskii VA, Sobczyk L, Pozharskii AF. Primary H-1/H-2 isotope effect in the NMR chemical shift of $HClO_4$ salts of 1,8-bis(dimethylamino) naphthalene derivatives. *J Phys Org Chem* 2007;**20**:643–8.
280. Golubev NS, Detering C, Smirnov SN, Shenderovich IG, Denisov GS, Limbach HH, et al. H/D isotope effects on NMR chemical shifts of nuclei involved in a hydrogen bridge of hydrogen isocyanide complexes with fluoride anion. *Phys Chem Chem Phys* 2009;**11**:5154–9.
281. Golubev NS, Denisov GS, Macholl S, Smirnov SN, Shenderovich IG, Tolstoy PM. NMR study of blue-shifting hydrogen bonds formed by fluoroform in solution. *Z Phys Chem* 2008;**222**:1225–45.
282. Tiainen M, Maaheimo H, Soininen P, Laatikainen R. ^{13}C isotope effects on ^{1}H chemical shifts: NMR spectral analysis of ^{13}C-labelled D-glucose and some ^{13}C-labelled amino acids. *Magn Reson Chem* 2010;**48**:117–22.
283. Abildgaard J, Hansen PE, Manalo MN, LiWang A. Deuterium isotope effects on ^{15}N backbone chemical shifts in proteins. *J Biomol NMR* 2009;**44**:119–26.

284. Takeda M, Jee J, Terauchi T, Kainosho M. Detection of the sulfhydryl groups in proteins with slow hydrogen exchange rates and determination of their proton/ deuteron fractionation factors using the deuterium-induced effects on the ^{13}C NMR signals. *J Am Chem Soc* 2010;**132**:6254–60.
285. Kitevski-LeBlanc JL, Evanics F, Prosser RS. Approaches for the measurement of solvent exposure in proteins by ^{19}F NMR. *J Biomol NMR* 2009;**45**:255–64.
286. Makulski W. ^{1}H, ^{13}C and ^{17}O nuclear magnetic shielding of methanol and its deuterated isotopomers from gas phase measurements. *J Mol Struct* 2008;**872**:81–6.
287. Makulski W. An H-2(D) isotope shift in the H-1 NMR spectra of water in gaseous environment of fluoromethanes. *J Mol Struct* 2007;**839**:90–3.
288. Ullah S, Ishimoto T, Williamson MP, Hansen PE. *Ab initio* calculations of deuterium isotope effects on chemical shifts of salt-bridged lysines. *J Phys Chem B* 2011;**115**:3208–15.
289. Jameson CJ. Variation of chemical shielding with internal coordinates. Applications to diatomic molecules. *J Chem Phys* 1977;**66**:4977–82.
290. Jameson AK, Schuett K, Jameson CJ, Cohen SM, Parker H. The temperature dependence of chemical shielding in diatomic molecules: CO, F_2, ClF, HBr and HCl. *J Chem Phys* 1977;**67**:2821–4.
291. Kantola AM, Lantto P, Vaara J, Jokisaari J. Carbon and proton shielding tensors in methyl halides. *Phys Chem Chem Phys* 2010;**12**:2679–92.
292. Willans MJ, Wasylishen RE, McDonald R. Polymorphism of potassium ferrocyanide trihydrate as studied by solid-state multinuclear NMR spectroscopy and X-ray diffraction. *Inorg Chem* 2009;**48**:4342–53.
293. Hansen MR, Schnitzler T, Pisula W, Graf R, Mullen K, Spiess HW. Cooperative molecular motion within a self-assembled liquid-crystalline molecular wire: the case of a TEG-substituted perylenediimide disc. *Angew Chem Int Ed* 2009;**48**:4621–4.
294. Wei YY, Graf R, Sworen JC, Cheng CY, Bowers CR, Wagener KB, et al. Local and collective motions in precise polyolefins with alkyl branches: a combination of ^{2}H and ^{13}C solid-state NMR spectroscopy. *Angew Chem Int Ed* 2009;**48**:4617–20.
295. Lee YJ, Clark CG, Graf R, Wagner M, Mullen K, Spiess HW. Solid-state organization of semifluorinated alkanes probed by ^{19}F MAS NMR spectroscopy. *J Phys Chem B* 2009;**113**:1360–6.
296. Mallamace F, Corsaro C, Broccio M, Branca C, Gonzalez-Segredo N, Spooren J, et al. NMR evidence of a sharp change in a measure of local order in deeply supercooled confined water. *Proc Natl Acad Sci USA* 2008;**105**:12725–9.
297. Gajda J, Pacholczyk J, Bujacz A, Bartoszak-Adamska E, Bujacz G, Ciesielski W, et al. Structure and dynamics of L-selenomethionine in the solid state. *J Phys Chem B* 2006;**110**:25692–701.
298. Car R, Parinello M. Unified approach for molecular dynamics and density-functional theory. *Phys Rev Lett* 1985;**55**:2471–4.
299. Bagno A, D'Amico F, Saielli G. Computing the ^{1}H NMR spectrum of a bulk ionic liquid from snapshots of Car-Parrinello molecular dynamics simulations. *Chemphyschem* 2007;**8**:873–8.
300. Parrinello M. Simulating complex systems without adjustable parameters. *Comput Sci Eng* 2000;**2**:22–7.
301. Barnett RN, Landman U. Born Oppenheimer molecular-dynamics simulations of finite systems: structure and dynamics of $(H_2O)_2$. *Phys Rev B* 1993;**48**:2081–97.
302. Heine T, Vietze K, Seifert G. ^{13}C NMR fingerprint characterizes long time-scale structure of $Sc_3N@C_{80}$ endohedral fullerene. *Magn Reson Chem* 2004;**42**:S199–201.
303. Sebastiani D, Parrinello M. *Ab-initio* study of NMR chemical shifts of water under normal and supercritical conditions. *Chemphyschem* 2002;**3**:675–9.

304. Murakhtina T, Heuft J, Meijer EJ, Sebastiani D. First principles and experimental ^{1}H N MR signatures of solvated ions: the case of $HCl_{(aq)}$. *Chemphyschem* 2006;**7**:2578–84.
305. Komin S, Gossens C, Tavernelli I, Rothlisberger U, Sebastiani D. NMR solvent shifts of adenine in aqueous solution from hybrid QM/MM molecular dynamics simulations. *J Phys Chem B* 2007;**111**:5225–32.
306. Schiffmann C, Sebastiani D. Hydrogen bond networks: structure and dynamics via first-principles spectroscopy. *Phys Status Solidi B* 2012;**249**:368–75.
307. Sebastiani D, Rothlisberger U. Nuclear magnetic resonance chemical shifts from hybrid DFT QM/MM calculations. *J Phys Chem B* 2004;**108**:2807–15.
308. Jameson CJ, Lim H-M. *Ab initio* studies of the nuclear magnetic resonance chemical shifts of a rare gas atom in a zeolite. *J Chem Phys* 1995;**103**:3885–94.
309. Sears DN, Jameson CJ. Theoretical calculations of Xe chemical shifts in cryptophane cages. *J Chem Phys* 2003;**119**:12231–44.
310. Sears DN, Jameson CJ. The Xe shielding surfaces for Xe interacting with linear molecules and spherical tops. *J Chem Phys* 2004;**121**:2151–7.
311. Jameson CJ, Sears DN, de Dios AC. The ^{129}Xe nuclear shielding tensor surfaces for Xe interacting with rare gas atoms. *J Chem Phys* 2003;**118**:2575–80.
312. Chesnut DB, Rusiloski BE. A study of NMR chemical shielding in water clusters derived from molecular dynamics simulations. *J Mol Struct (Theochem)* 1994;**314**:19–30.
313. Malkin VG, Malkina OL, Steinebrunner G, Huber H. Solvent effect on the NMR chemical shieldings in water calculated by a combination of molecular dynamics and density functional theory. *Chem Eur J* 1996;**2**:452–7.
314. Vaara J, Lounila J, Ruud K, Helgaker T. Rovibrational effects, temperature dependence, and isotope effects on the nuclear shielding tensors of water: a new ^{17}O absolute shielding scale. *J Chem Phys* 1998;**109**:8388–97.
315. Pennanen TS, Vaara J, Lantto P, Sillanpää AJ, Laasonen K, Jokisaari J. Nuclear magnetic shielding and quadrupole coupling tensors in liquid water: a combined molecular dynamics simulation and quantum chemical study. *J Am Chem Soc* 2004;**126**:11093–102.
316. Jameson CJ, Jameson AK, Lim HM. Competitive adsorption of xenon and krypton in zeolite NaA. ^{129}Xe NMR and grand canonical Monte Carlo simulations. *J Chem Phys* 1997;**107**:4364–72.
317. Jameson CJ, Jameson AK, Kostikin P, Baello BI. Adsorption of xenon and CH_4 mixtures in zeolite NaA. ^{129}Xe NMR and grand canonical Monte Carlo simulations. *J Chem Phys* 2000;**112**:323–34.
318. Jameson CJ. The Xe chemical shift tensor in silicalite and SSZ-24 zeolite. *J Am Chem Soc* 2004;**126**:10450–6.
319. Jameson CJ. Calculations of Xe lineshapes in model nanochannels. Grand canonical Monte Carlo averaging of the ^{129}Xe NMR chemical shift tensor. *J Chem Phys* 2002;**116**:8912–29.
320. Moudrakovski I, Soldatov DV, Ripmeester JA, Sears DN, Jameson CJ. Xe NMR lineshapes in channels of peptide molecular crystals. *Proc Natl Acad Sci USA* 2004;**101**:17924–9.
321. Jameson CJ, Sears DN, Murad S. Molecular dynamics averaging of Xe chemical shifts in liquids. *J Chem Phys* 2004;**121**:9581–92.
322. Standara S, Kulha´nek P, Marek R, Hornı´cˇek J, Bourˇ P, Straka M. Simulations of ^{129}Xe NMR chemical shift of atomic xenon dissolved in liquid benzene. *Theor Chem Acc* 2011;**129**:677–84.
323. Truflandier LA, Autschbach J. Solvent effects and dynamic averaging of ^{195}Pt NMR Shielding in *cis* platin derivatives. *J Am Chem Soc* 2010;**132**:3472–83.
324. Dumez J-N, Pickard CJ. Calculation of NMR chemical shifts in organic solids: accounting for motional effects. *J Chem Phys* 2009;**130**:104701.

325. Robinson M, Haynes PD. Dynamical effects in *ab initio* NMR calculations: classical force fields fitted to quantum forces. *J Chem Phys* 2010;**133**:084109.
326. Drac˘´ınsky´ M, Bour P. Vibrational averaging of the chemical shift in crystalline α-glycine. *J Comput Chem* 2012;**33**:1080–9.
327. Jameson CJ. The dependence of 19F nuclear magnetic shielding on internal coordinates in CF_4, SiF_4, and BF_3. *J Chem Phys* 1977;**67**:2814–20.
328. Jameson CJ, Osten HJ. Theoretical aspects of the isotope effect on nuclear shielding. *Annu Rep NMR Spectrosc* 1986;**17**:1–78.
329. Rossano S, Mauri F, Pickard CJ, Farnan I. First-principles calculation of ^{17}O and ^{25}Mg NMR shieldings in MgO at finite temperature: rovibrational effect in solids. *J Phys Chem B* 2005;**109**:7245–50.
330. Fileti EE, Georg HC, Coutinho K, Canuto S. Isotropic and anisotropic chemical shifts in liquid water. A sequential QM/MM. *J Braz Chem Soc* 2007;**18**:74–84.
331. Pennanen TS, Lantto P, Sillanpää AJ, Vaara J. Nuclear magnetic resonance chemical shifts and quadrupole couplings for different hydrogen-bonding cases occurring in liquid water: a computational study. *J Phys Chem A* 2007;**111**:182–92.
332. Fowler PW, Riley G, Raynes WT. Dipole moment, magnetizability and nuclear shielding surfaces for the water molecule. *Mol Phys* 1981;**42**:1463–81.
333. Lazzeretti P, Zanasi R, Sadlej AJ, Raynes WT. Magnetizability and carbon-13 shielding surfaces for the methane molecule. *Mol Phys* 1987;**62**:605–16.
334. Jameson CJ, de Dios AC, Jameson AK. Nuclear magnetic shielding of nitrogen in ammonia. *J Chem Phys* 1991;**95**:1069–79.
335. Jameson CJ, de Dios AC, Jameson AK. The ^{31}P shielding in phosphine. *J Chem Phys* 1991;**95**:9042–53.
336. Harper JK, Grant DM. Enhancing crystal structure prediction with NMR tensor data. *Crystal Growth Design* 2006;**6**:2315–21.
337. Elena B, Emsley L. Powder crystallography by proton solid-state NMR spectroscopy. *J Am Chem Soc* 2005;**2005**(127):9140–6.
338. Elena B, Pintacuda G, Mifsud N, Emsley L. Molecular structure determination in powders by NMR crystallography from proton spin diffusion. *J Am Chem Soc* 2006;**128**:9555–60.
339. Mou Y, Tsai TWT, Chan JCC. Determination of the backbone torsion psi angle by tensor correlation of chemical shift anisotropy and heteronuclear dipole-dipole interaction. *Solid State Nucl Magn Reson* 2007;**31**:72–81.
340. Brouwer DH, Alavi S, Ripmeester JA. NMR crystallography of *p*-tert-butylcalix[4]arene host–guest complexes using ^{1}H complexation-induced chemical shifts. *Phys Chem Chem Phys* 2008;**10**:3857–60.
341. Salager E, Stein RS, Pickard CJ, Elena B, Emsley L. Powder NMR crystallography of thymol. *Phys Chem Chem Phys* 2009;**11**:2610–21.
342. Bradley JP, Velaga SP, Antzutkin ON, Brown SP. Probing intermolecular crystal packing in (γ-indomethacin by high-resolution ^{1}H solid-state NMR spectroscopy. *Cryst Growth Des* 2011;**11**:3463–71.
343. Brouwer DH. A structure refinement strategy for NMR crystallography: an improved crystal structure of silica-ZSM-12 zeolite from ^{29}Si chemical shift tensors. *J Magn Reson* 2008;**194**:136–46.
344. Aguiar PM, Kroeker S. Cyanide orientational ordering and copper electric field gradients in $CuCN{\cdot}N_2H_4$. *Phys Chem Chem Phys* 2009;**11**:834–40.
345. Tjandra N, Bax A. Large variations in ^{13}C chemical shift anisotropy in proteins correlate with secondary structure. *J Am Chem Soc* 1997;**119**:9576–7.
346. Walling AE, Pargas RE, de Dios AC. Chemical shift tensors in peptides: a quantum mechanical study. *J Phys Chem A* 1997;**101**:7299–303.

347. Brouwer DH, Moudrakovski IL, Darton RJ, Morris RE. Comparing quantum-chemical calculation methods for structural investigation of zeolite crystal structures by solid-state NMR spectroscopy. *Magn Reson Chem* 2010;**48**:S113–21.
348. Byrne PJ, Warren JE, Morris RE, Ashbrook SE. Structure and NMR assignment in AlPO-15: a combined study by diffraction, MAS NMR and first-principles calculations. *Solid State Sci* 2009;**11**:1001–6.
349. Chen F, Wasylishen RE. Structural characterization of silver dialkylphosphite salts using solid-state ^{109}Ag and ^{31}P NMR spectroscopy, IR spectroscopy and DFT calculations. *Magn Reson Chem* 2010;**48**:270–5.
350. Sehnert J, Senker J. A concerted approach for the determination of molecular conformation in ordered and disordered materials. *Chem Eur J* 2007;**13**:6339–50.
351. Paramasivam S, Balakrishnan A, Dmitrenko O, Godert A, Begley TP, Jordan F, et al. Solid-state NMR and density functional theory studies of ionization states of thiamin. *J Phys Chem B* 2011;**115**:730–6.
352. Scheer M, Gregoriades LJ, Zabel M, Bai J, Krossing I, Brunklaus G, et al. Self-assemblies based on $[Cp_2Mo_2(CO)_4(\mu,\eta^2\text{-}P_2)]$-solid-state structure and dynamic behaviour in solution. *Chem Eur J* 2008;**14**:282–95.
353. Dmitrenko O, Bai S, Beckmann PA, van Bramer S, Vega AJ, Dybowski C. The relationship between ^{207}Pb NMR chemical shift and solid-state structure in Pb(II) compounds. *J Phys Chem A* 2008;**112**:3046–52.
354. Yamauchi K, Okonogi M, Kurosu H, Tansho M, Shimizu T, Gullion T, et al. High field ^{17}O solid-state NMR study of alanine tripeptides. *J Magn Reson* 2008;**190**:327–32.
355. Chizallet C, Costentin G, Lauron-Pernot H, Che M, Bonhomme C, Maquet J, et al. Study of the structure of OH groups on MgO by 1D and 2D ^{1}H MAS NMR combined with DFT cluster calculations. *J Phys Chem C* 2007;**111**:18279–87.
356. Bradley JP, Pickard CJ, Burley JC, Martin DR, Hughes LP, Cosgrove SD, et al. Probing intermolecular hydrogen bonding in sibenadet hydrochloride polymorphs by high-resolution ^{1}H double-quantum solid-state NMR spectroscopy. *J Pharmaceutical Sci* 2012;**101**:1821–30.
357. Kim SM, Kim DH. Determination of the structure of 1,1'-diethyl-2,2'-carbocyanine iodide using NMR spectra and GIAO-HF/DFT calculations. *Dyes Pigment* 2008;**79**:1–6.
358. Tomlinson JH, Ullah S, Hansen PE, Williamson MP. Characterization of salt bridges to lysines in the protein G B1 domain. *J Am Chem Soc* 2009;**131**:4674–84.
359. Wong A, Kotch FW, Kwan ICM, Davis JT, Wu G. Probing the Na^+ binding site in a calix[4]arene–guanosine conjugate dimer by solid-state ^{23}Na NMR and quantum chemical calculation. *Chem Commun* 2009;2154–6.
360. Comotti A, Bracco S, Sozzani P, Hawxwell SM, Hu CH, Ward MD. Guest molecules confined in amphipathic crystals as revealed by X-ray diffraction and MAS NMR. *Crystal Growth Des* 2009;**9**:2999–3002.
361. Alumasa JN, Gorka AP, Casabianca LB, Comstock E, de Dios AC, Roepe PD. The hydroxyl functionality and a rigid proximal N are required for forming a novel non-covalent quinine-heme complex. *J Inorg Biochem* 2011;**105**:467–75.
362. Jameson CJ, de Dios AC. *Ab initio* calculations of the intermolecular chemical shift in nuclear magnetic resonance in the gas phase and for adsorbed species. *J Chem Phys* 1992;**97**:417–34.
363. Jameson CJ, de Dios AC. Xe nuclear magnetic resonance lineshapes in nanochannels. *J Chem Phys* 2002;**116**:3805–21.
364. Anedda R, Soldatov DV, Moudrakovski IL, Casu M, Ripmeester JA. A new approach to characterizing sorption in materials with flexible micropores. *Chem Mat* 2008;**20**:2908–20.

365. Comotti A, Bracco S, Sozzani P, Horike S, Matsuda R, Chen J, et al. Nanochannels of two distinct cross-sections in a porous Al-based coordination polymer. *J Am Chem Soc* 2008;**130**:13664–72.
366. Brouwer DH, Moudrakovski IL, Udachin KA, Enright GD, Ripmeester JA. Guest loading and multiple phases in single crystals of the van der Waals host *p*-tert-butylcalix[4]arene. *Cryst Growth Des* 2008;**8**:1878–85.
367. Zurek E, Pickard CJ, Walczak B, Autschbach J. Density functional study of the ^{13}C NMR chemical shifts in small-to-medium-diameter infinite single-walled carbon nanotubes. *J Phys Chem A* 2006;**110**:11995–2004.
368. Zurek E, Pickard CJ, Autschbach J. A density functional study of the ^{13}C NMR chemical shifts in functionalized single-walled carbon nanotubes. *J Am Chem Soc* 2007;**129**:4430–9.
369. Zurek E, Pickard CJ, Autschbach J. A density functional study of the ^{13}C NMR chemical shifts in fluorinated single-walled carbon nanotubes. *J Phys Chem A* 2009;**113**:4117–24.
370. Zurek E, Pickard CJ, Autschbach J. Density functional study of the ^{13}C NMR chemical shifts in single-walled carbon nanotubes with Stone-Wales defects. *J Phys Chem C* 2008;**112**:11744–50.
371. Vasconcelos F, Cristol S, Paul J-F, Montagne L, Mauri F, Delevoye L. First-principles calculations of NMR parameters for phosphate materials. *Magn Reson Chem* 2010;**48**: S142–50.