Applications of Spin-Spin Couplings

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1. Introduction

The material in this chapter covers the period from 1 June 2008 to 31 May 2009. It has been arranged as was done previously,[1] *i.e.* according to (i) the increasing atomic number of the nuclei involved, and (ii) the number of the bonds separating them. We follow the IUPAC[2] recommendations with one notable exception, namely, the nucleus with the smaller mass is given first. For the sake of simplicity the following symbols are used throughout the paper: H for ^{1}H, D–^{2}H, T–^{3}H, Li–^{6}Li, Be–^{9}Be, B–^{11}B, C–^{13}C, N–^{15}N, O–^{17}O, F–^{19}F, Al –^{27}Al, Si–^{29}Si, P–^{31}P, S–^{33}S, V–^{51}V, Mn–^{55}Mn, Fe–^{57}Fe, Co–^{59}Co, Cu–^{65}Cu, As– ^{75}As, Se–^{77}Se, Br – ^{79}Br, Y–^{89}Y, Nb–^{93}Nb, Mo–^{95}Mo, Ru–^{99}Ru, Tc – ^{99}Tc, Rh–^{103}Rh, Ag–^{109}Ag, Cd–^{113}Cd, In–$^{113/115}$In, Sn–^{119}Sn, Sb–^{121}Sb, Te–^{125}Te, I–^{127}I, Cs–^{133}Cs, W–^{183}W, Os–^{187}Os, Pt–^{195}Pt, Hg–^{199}Hg, Tl–^{205}Tl, Pb–^{207}Pb. All the other isotopes are described explicitly.

The recent developments in the quantum chemical calculation of NMR indirect spin-spin couplings have been discussed by Helgaker *et al.*[3] Solvent effects on shielding constants and spin-spin couplings have been reviewed by Bagno, Rastrelli and Saielli.[4] A review covering the application of chemical shifts, isotope effects on chemical shifts and couplings characterizing Schiff bases has been published by Hansen *et al.*[5]

The ^{15}N NMR data which also include $^{1}J_{NX}$ couplings have been collected by Pazderski[6] for 105 complexes of Pd(II), Pt(II), Au(III), Co(III), Rh(III), Ir(III), Pd(IV) as well as Pt(IV) complexes with simple azines such as pyridine, 2,2′-bipyridine, 1,10-phenanthroline, quinoline, isoquinoline, 2,2′-biquinoline, 1,2′:6,2′-terpyridine and their alkyl or aryl derivatives. A short review on the formation and structure of heterocycles obtained from condensation of trifluoromethanesulphonamide with different carbonyl compounds has been written by Shainyan and Meshcheryakov.[7] It contains NMR data including proton-proton couplings. A brief review (in Chinese) on ^{19}F NMR has been written by Li *et al.*[8]

An excellent review on the solid-state NMR including J_{SeX} data has been published by Demko and Wasylishen.[9] A review summarizing the progress in ^{119}Sn NMR spectroscopy has been written by Wrackmeyer.[10] A review devoted mainly to DFT computations of transition-metal shieldings has been published by Bühl.[11] It also contains important data on indirect spin-spin couplings involving transitions-metal nuclei as well as on nuclear quadrupole coupling tensors.

In the past decade residual dipolar couplings (RDCs) have revolutionized biomolecular NMR spectroscopy. Recent developments indicate that this

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technique can also be applied successfully to organic molecules to determine configuration and conformation, and to distinguish enantiomers. Two comprehensive reviews on RDCs in organic structure determination have been published, by Thiele,[12] and by Kummerlöwe and Luy.[13] In a short review Eliezer[14] has discussed recent advances in the application of several methods, including RDCs, for biophysical characterization of intrinsically disordered proteins. Several approaches for automated protein structure determination including those relying on RDCs have been reviewed by Güntert.[15]

2. New methods

NMR spectroscopic discrimination of optical enantiomers is most often carried out using ^{2}H spectra of chiral molecules aligned in a chiral liquid crystalline solvent. Recently, several novel spin selected correlation experiments have been designed by Suryaprakash and co-workers where proton instead of deuterium NMR was used. These are a simple, band selective small flip angle COSY[16] and Soft-COSY[17] which allow a separation and complete analyses of the overlapped and unresolved ^{1}H NMR spectra of enantiomers. The usefulness of these experiments has been demonstrated on several chiral model compounds such as (*R*/*S*)-3-butyn-2-ol, (*R*/*S*)-*β*-butyrolactone and (*R*/*S*)- propylene oxide; all the couplings including their signs have been determined for these compounds from the broad and featureless spectra. In another experiment natural abundant ^{13}C as a passive spin for the state selective 3Q-SQ correlation has been used.[18] Using the latter method it is possible to determine both homo- and heteronuclear couplings in a single experiment, and the measured parameters are precise due to upward scaling of the couplings. The same group of the authors[19] using the combination of homo- and heteronuclear multiple quantum experiments have measured the magnitudes and signs of the scalar and dipolar couplings of different isotopomers of doubly labelled acetonitrile ordered in liquid crystal.

It happens very often that the proton NMR spectra of even relatively small molecules, especially those containing several aromatic rings, are, due to the overlap of ^{1}H resonances, quite complex and difficult to interpret. It has been shown by Suryaprakash and co-workers, who used fluorinated benzamides as model compounds, that it is possible to separate the individual spectrum for each aromatic ring by spin system filtering employing the multiple-quantum-single-quantum correlation methodology.[20] The authors also have proposed a novel triple quantum experiment (SS3Q-*J*-resolved) for precise determination of the $^{3-5}J_{HH}$ and $^{3-5}J_{HF}$ values in those complex spectra.[21]

Several papers[22–25] have been devoted to the problems connected with accurate measurements of small *J* couplings under inhomogeneous field conditions. Two new NMR pulse sequences based on intermolecular multiple-quantum coherences have been designed by Lin *et al.*[22,23] which allow to obtain apparent *J* couplings with a scaling factor from one to infinity relative to the conventional *J* couplings. Two other pulse sequences, IDEAL-II[24] and heteronuclear CRAZED,[25] which allow to overcome the

difficulties connected with the acquisition of high-resolution NMR spectra in homogeneous field have been proposed by Chen *et al.*[24,25] It is worth noting that according to the authors the crucial spectral information, *i.e.* chemical shifts, multiplet patterns and relative peak areas for various peak systems is in these experiments fully retained and almost independent of the magnetic field inhomogeneity.

A 3D version of HSQC-TOCSY experiment for the measurement of heteronuclear couplings of organic compounds yielding complex spectra has been proposed by Misiak and Koźmiński.[26] The approach presented by these authors has been based on the optimized random sampling of the evolution time space followed by Multidimensional Fourier Transform, and applied to strychnine yielding all possible proton-carbon couplings in this molecule including their signs.

Parish and Szyperski[27] have introduced the concept named simultaneously cycled (SC) NMR which allows to record highly resolved ECOSY spectra twelve times faster than using conventional phase cycled ECOSY. Enthart *et al.*[28] have introduced the CLIP/CLAP HSQC for the measurement of one- bond heteronuclear coupling without phase distortions. Pell and Killer[29] have presented a method for recording *J*-spectra in the absorption mode.

Lendel and Damberg[30] have presented a 3D *J*-resolved experiment for fast measurement of $^{3}J_{\mathrm{HNH}\alpha}$ couplings in proteins with very high resolution. The method combines a phase sensitive *J*-resolved experiment with a $^{1}\mathrm{H}$–$^{15}\mathrm{N}$ SOFAST-HMQC.

Grzesiek and co-workers have published detailed protocols for measurements of the hydrogen bond mediated $^{2h}J_{\mathrm{NN}}$ couplings in $^{15}\mathrm{N}$ labelled nucleic acids[31] and of the $^{3h}J_{\mathrm{C'N}}$ couplings in $^{13}\mathrm{C}/^{15}\mathrm{N}$ labelled proteins.[32] All the calibrations and tests required for 2D quantitative J_{NN} HNN-COSY spectrum have been described in the first protocol.[31] The second protocol[32] contains the description of the details of 2D long-range H(N)CO TROSY pulse sequence along with the reference experiment sequence which accounts for relaxation losses.

A band-selective-decoupled gradient-enhanced $^{15}\mathrm{N}$–$^{1}\mathrm{H}$ IPAP-HSQC experiment has been published by Bax and co-workers[33] for measuring the $^{1}J_{\mathrm{HN}}$ and $^{1}D_{\mathrm{HN}}$ couplings in protonated proteins with improved accuracy. Brutscher and co-workers[34] have offered a new BEST-TROSY experiment that combines transverse- and longitudinal-relaxation optimization to achieve optimal sensitivity for the $^{1}J_{\mathrm{HN}}$ and $^{1}D_{\mathrm{HN}}$ coupling measurements in nucleic acids.

Residual dipolar couplings (RDCs) are of great interest for the structure determination of biomacromolecules and organic molecules like synthetic or natural products. Their accurate measurement requires a proper degree of alignment for the molecule under investigation.

Recently, a remarkable apparatus for rapid and reversible gel stretching based on gelatine as the polymer gel has been developed by Kuchel *et al.*,[35] and its usefulness demonstrated by the distinctions of enantiomers using RDCs and other anisotropic parameters.[36] It has been demonstrated by Kummerlöwe *et al.*[37] that such an apparatus is not limited to gelatine, but can also be used with covalently cross-linked hydrogels and even with gels

with polar organic solvents like DMSO. Sucrose and a cyclic hexapeptide have been used as model compounds to demonstrate that this new device allows one to measure RDCs with high precision. The same group of authors[38] has proposed perdeuterated poly(styrene) as almost artefact-free and arbitrarily scalable alignment medium for measuring residual dipolar couplings and other anisotropic NMR parameters. By its use they were able to perform the configurational and conformational analysis of staurosporine, a natural product isolated from *Streptomyces staurosporens*.

It has been demonstrated by Wiench *et al.*[39] that in the case of Si-Si double-quantum techniques, the well known Carr-Purcell-Meiboom-Gill(CPMG) train of rotor-synchronised π pulses during the detection of silicon magnetization can be exploited to measure homonuclear $^{2}J_{\mathrm{Si\text{-}Si}}$ couplings.

The hetero-nuclear *J* coupling spectrum of 2,2,2-trifluoroethanol has been recorded by Qiu *et al.*[40] by the use of an EMF-NMR-SQUID (earth-NMR-superconducting quantum interference device) device. This experiment demonstrates that it is possible to record high resolution NMR spectra in the absence of magnetic shielding, which opens the door to a new class of relatively low-cost, mobile, flexible NMR and MRI scanners.

3. One-bond couplings to hydrogen

NMR spectroscopy has been applied by Guilera *et al.*[41] to characterize the complex $[(\mathrm{triphos})\mathrm{Fe(CO)H_2}]$, which after protonation gives the corresponding cationic complex of the form $[(\mathrm{triphos})\mathrm{Fe(CO)H}(\eta^2\text{-}\mathrm{H_2})]^+$ (triphos=$\mathrm{MeC(CH_2CH_2PPh_2)_3}$]. The cation complex decomposes above 250 K in solution, but the authors were able to measure T_1 min and J_{HD}; the obtained results indicate that it contains a stretched dihydrogen ligand.

A five-line pattern due to $^{1}J_{\mathrm{HB}}$ couplings with four equivalent hydrogens has been observed by Shane *et al.*[42] in liquid $\mathrm{LiBH_4}$, which can be used as indication that only slow exchange (or no exchange at all) of hydrogen atoms takes place between $\mathrm{BH_4}$ units.

Restricted magnetically balanced basis has been applied by Malkin and co-workers[43] for relativistic calculations of scalar nuclear spin-spin coupling tensors in the matrix Dirac-Kohn-Sham framework. Benchmark relativistic calculations have been carried out for the H–X and H–H couplings in the $\mathrm{XH_4}$ series where X = C, Si, Ge, Sn and Pb. One-bond couplings, $^{1}J_{\mathrm{H-X}}$, in the gas-phase have been determined by Antušek *et al.*[44] for $\mathrm{CH_4}$, $^{1}J_{\mathrm{HC}} = 125.3$ Hz, $\mathrm{SiH_4}$, $^{1}J_{\mathrm{HSi}} = (-)\ 201.0$ Hz, $\mathrm{GeH_4}$, $^{1}J_{\mathrm{HGe}} = (-)96.7$ Hz, and calculated theoretically. The calculations have been also performed for $^{1}J_{\mathrm{HSn}}$ whose experimental value in $\mathrm{SnH_4}$ has been reported by Laaksonen and Wasylishen.[45]

The electronic origin of substituent effects on the Fermi contact term of $^{1}J_{\mathrm{HC}}$ couplings in 1-X-cyclopropanes (X = H, Cl, Br, I, CN, COOH, CHO and $\mathrm{NH_2}$) has been investigated by Neto *et al.*[46] by the CLOPPA (Contributions from Localized Orbitals within the Polarization Propagator Approach) method. The results obtained have been interpreted in terms of hyperconjugative interactions.

The concentration dependence of $^{1}J_{\mathrm{HC}}$ in NMR and ν_{CH} in IR for binary water-tetrahydrofuran mixtures has been studied by Mizuno *et al.*,[47] who

found different trends for the two types of CH_2 groups in the five-membered ring. The authors suggested that the blue shift of $\nu_{C(2,5)H2/s}$ and the increase of $^1J_{HC(2,5)}$ up to $\chi_{H_2O} \approx 0.6$ are related to the formation of a 1:1 H-bonded complex, whereas those of $\nu_{C(3,4)H2/as}$ and $^1J_{HC(3,4)}$ at $\chi_{H_2O} > 0.6$ are connected to the formation of 1:2 clusters. Blue-shifting hydrogen bonds formed by fluoroform in solution with various proton acceptors including pyridine and acetonitrile have been studied by Golubev *et al.*[48] by the use of NMR spectroscopy. They have shown that experimental ^1H and ^{15}N shielding as well as the H/D isotope effect on ^{13}C shielding change monotonously with the calculated H-bond strengthening, whereas the ^{13}C chemical shielding and the H–C scalar coupling change non-monotonously; the extremum points are situated approximately in the region of transformation from blue- to red-shifting H-bonds.

$^1J_{HC}$ couplings have been measured by Niebel *et al.*[49] for two isomeric isobenzofuranone derivatives shown in Fig. 1 below. Due to the presence of intramolecular hydrogen bond, $^1J_{H_7C_7}$ coupling is significantly larger in compound **a** than in compound **b.** The corresponding $^1J_{H_7C_7}$ values are 172.7 and 167.0 Hz, respectively.

$^1J_{HC}$ couplings have been calculated theoretically and determined experimentally by Rozentsveig *et al.*[50] for a series of *N*-arene-sulphonamides in order to prove their configuration. The results obtained have shown that these compounds exist exclusively as *E* isomers.

Liu *et al.*[51] have shown that due to the isotope effects in the protein semideuterated sidechain amides, the values of the $^1J_{NHE(DZ)}$ couplings are by 1 to 4 Hz larger than the values of the $^1J_{NHZ(DE)}$ couplings. Individual $^1J_{HC}$ couplings within each methylene group have been determined by Guichard *et al.*[52] for oligoureas revealing uniform values through the oligourea sequence, with $^1J_{HC}$ systematically slightly larger for the *pro-S* hydrogen than for the *pro-R*. The $^1J_{HC}$ coupling values measured by Van Horn and co-workers[53] for uranyl-histidine complexes in water have indicated that interactions between histidine and uranyl cation occur at the carboxylate site.

During the past decade, a large amount of effort has been devoted to obtain experimental data which relate some NMR spectroscopic parameters, e.g. the imino (^{15}N) chemical shifts and scalar $^1J_{H14N}$ spin-spin couplings, with tautomeric forms of substituted *ortho*-hydroxylaryl Schiff bases. Recently, the theoretical studies on this topic have been carried out

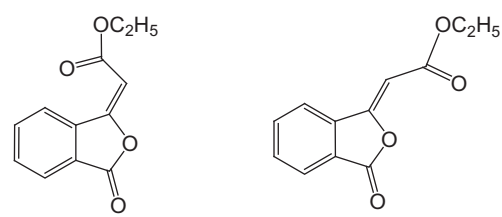


Fig. 1

by Zarycz and Aucar,[54] who concluded that a previous δ(N) *vs.* $^1J_{HN}$ linear depedence is better generalized to a cubic dependence, which seems to be more reliable. $^1J_{HN}$ spin-spin couplings have been determined by Rozwadowski and Nowak-Wydra[55] for some optically active Schiff bases derived from *ortho*-hydroxyaldehydes, and their values used as an indication of the presence of proton-transfer equilibrium.

Two papers have been devoted by Kupka[56,57] to calculate $^1J_{HO}$ and $^2J_{HH}$ couplings as well as isotropic shieldings in water using correlation-consistent and polarization-consistent basis sets in the Kohn-Sham basis set limit.

Theoretical studies devoted to anharmonic vibrational frequencies, vibrational averaged structures and NMR spin-spin couplings in FHF^- have been performed by Hirata *et al.*[58] The best theoretical estimates of vibrationally averaged $^1J_0$(HF) and $^2J_0$(FF) obtained by the authors are 124 and 186 Hz, respectively. The former agrees quantitatively with the reported by Shenderovich *et al.*[59] experimental value of 124 ± 3 Hz. The latter is consistent with the overall trend of the experimental and theoretical values of $^2J_0$(FF) in $[F(HF)_n]^-$ $(2 \leq n \leq 4)$ and may be considered to be the most accurate prediction for the experimentally inaccessible $^2J_0$(FF) in FHF^-.

It has been found by Ratajczyk and Szymański[60] that $^1J_{HSi}$ couplings in three 9-silyltriptycenes bearing chlorine, bromine and the methyl group in one of the *peri* positions are strongly diversified. These differences have been interpreted by the authors in terms of electron density transfers from the *peri* substituent causing the discrimination of the individual Si–H bonds.

It was pointed out some time ago by Ignatov *et al.*[61] that the sign of the H–Si coupling, rather than its absolute value, should be used as indication of the presence of non-classical bonding. Recently they have succeeded to determine experimentally the sign of J_{HSi} in some silyl hydrides of tantalum supported by cyclopentadienyl-imido ligand sets. In the compound $Cp(ArN)Ta(PMe_3)(H)(SiMePhH)$ the J_{HSi} has been found to be positive, which is in agreement with its classical silyl-hydride structure. In contrast, in the chlorosubstituted complexes, $Cp(ArN)Ta(PMe_3)(H)(SiMeCl_2)$ and $Cp(ArN)Ta(PMe_3)(H)(SiCl_3)$, the negative couplings of –40 and –50 Hz, respectively, have been found confirming the presence of significant inter-ligand Si–H interaction.

In-situ NMR studies have enabled Godard *et al.*[62] to detect and characterize a series of platinum dihydride bisphosphine complexes, *cis*-$Pt(L)(L')(H)_2$, where $L = PCy_3$ and $L' = PCy_2H$, PPh_3 or PCy_3, for which, among others, $^1J_{HPt}$ and $^1J_{PPt}$ couplings have been measured.

The non-relativistic Hartree-Fock and relativistic Dirac-Hartree-Fock methods have been applied by Cukras and Sadlej[63] to calculate the NMR shielding constants and, for the first time, the spin-spin couplings in noble gas hydride cations RgH^+, where Rg = Ne, Ar, Kr, Xe.

4. One-bond couplings not involving hydrogen

The empirical expression $^1J_{CLi} = L[n(a + d)]^{-1}$ has been proposed by Knorr *et al.*;[64] it claims a reciprocal dependence of the NMR coupling constant $^1J_{LiC}$ in a C-Li compound on two factors: (i) the number n of lithium nuclei in bonding contact with the observed carbanion centre and (ii) the sum

(a + d) of the numbers a of anions and d of donor ligands coordinated at the Li nucleus that generates the observed $^1J_{LiC}$ value.

$^1J_{7LiC}$ couplings have been observed by Fraenkel *et al.*[65] in four allylic lithium compounds prepared with a tethered ligand, $(CH_3OCH_2CH_2)_2NCH_2C(CH_3)_2$-L, attached to a terminal allyl carbon. These were equimolar equilibrium mixtures of 3-*endo*-L-allyllitium with 3-*exo*-L-allyllitium, and 1-*exo*-TMS-3-*endo*-L-allyllitium with 1-*exo*-TMS-3-*exo*-L-allyllitium where $^1J_{C7Li}$ of 5.2, 9.1, 3.5 and 6.8 Hz, respectively, have been observed for C-1; the couplings between the lithium and C-2 nuclei were considerably smaller, of *ca.* 2 Hz or less.

One-bond B–N and B–H couplings have been calculated by Yáñez *et al.*[66] for a series of neutral and anionic five-membered rings containing BN bonds. Computed $^1J_{BN}$ couplings range from −10.4 to −34.8 Hz in the neutral rings, thereby bracketing the value of $^1J_{BN}$ for borazine, −28.7 Hz. An even greater range for $^1J_{BN}$ has been computed for the anions, from −3.0 to −35.7 Hz.

Temperature dependence of the $^1J_{BF}$ spin-spin coupling of the gaseous BF_3 molecule in a wide range of temperatures has been studied by Jackowski *et al.*[67] The extrapolation of the measured values to the zero-density limit yielded the coupling free from intermolecular effects.

Density functional calculations of the nuclear magnetic shielding and indirect nuclear spin-spin couplings including J_{CC}s have been performed by Lutnæs *et al.*[68] by the use of different exchange-correlation functionals for three isomers of C_{20}, the ring, the bowl and the cage. León *et al.*[69] have performed calculations of one-bond carbon-carbon couplings and chemical shifts in carbon nanostructures for NMR quantum computing. The postulated systems are finite carbon nanotubes and finite graphene nanoribond enriched with ^{13}C atoms and finished on the edges with hydrogen atoms.

It has been suggested by Boulho *et al.*,[70] who studied several niobium complexes of the type $Tp^{Me2}NbX(c\text{-}C_3H_5)MeC{\equiv}CMe$, X = Cl, Ph, Me, that the observed reduction of $^1J_{C1C3}$ spin-spin couplings measured for cyclopropyl ring is a reliable and sensitive probe of α-C–C agostic character. The $^1J_{CC}$ and $^1J_{HC}$ couplings for two phakellins and two isophakellins, tetracyclic pyrrole-imidazole alkaloids, have been published by Meyer and Köck,[71] who reviewed the structure elucidation of these compounds using modern NMR methods. Special attention has been paid by these authors to the application of ADEQUATE NMR pulse sequences.

J couplings relevant for acetylene and derived from it complexes have been collected by Grotjahn[72] in his perspective paper. Generally, carbon-carbon couplings measured for complexes are dramatically smaller than the $^1J_{CC}$ coupling in acetylene itself, and range from 56.5 up to 118.7 Hz; a typical example is shown in Fig. 2 below.

NMR chemical shifts and $^1J_{C\alpha C\beta}$ couplings calculated by Rowley *et al.*[73] for substituted and unsubstituted ruthenacyclobutanes have been found to be in good agreement with experiment. Moreover, the calculations confirmed that the difference between metallacycle $^1J_{C\alpha C\beta}$ couplings correlate to C_α–C_β activation.

Schmidt and co-workers[74] have analysed all possible C_α-related one-bond couplings in proteins, $^1J_{C\alpha C\beta}$, $^1J_{C\alpha C'}$, $^1J_{C\alpha N}$ and $^1J_{H\alpha C\alpha}$ (more than 3000

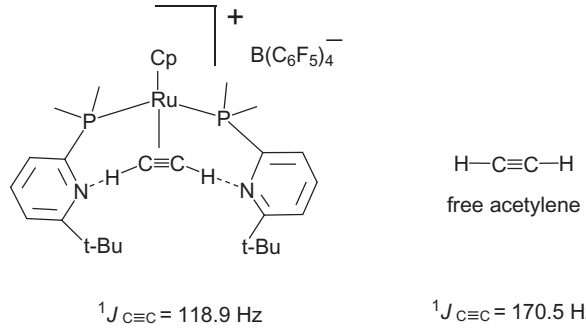


Fig. 2

total). Using analysis of variances they found that the most predominant factors influencing the values of those couplings are ϕ and ψ torsion angles, *i.e.* patterns of ^{1}J couplings may allow tentative annotation of secondary structure elements of protein.

Isotopic ^{13}C enrichment and $^{1,2}J_{CC}$ couplings have been a great help in tracing the biosynthetic route of the 3,4-dihydrobenzoate moieties of the siderophore petrobactin, produced by *Bacollus anthracis* str. Sterne[75] and in investigation of biosynthetic pathways to hydroxycoumarins during post-harvest physiological deterioration in cassava roots.[76]

^{13}C-NMR chemical shift data of cellulose $I\alpha$ have been determined by Hesse-Ertelt *et al.*[77] by INADEQUATE and RAI techniques applied to uniformly ^{13}C-labelled bacterial celluloses of different *Gluconacetobacter xylinus* strains. The robustness of the refocused INADEQUATE MAS NMR pulse sequence for probing through-bond connectivities has been demonstrated by Cadars *et al.*[78] in a large range of solid-state applications. The authors present a detailed account that combines product-operator analysis, numerical simulations and experiments of the behaviour of a three-spin system during the refocused INADEQUATE pulse sequence.

Heteronuclear solid-state magic-angle spinning (MAS) NMR experiments for determination of N–O dipolar and J couplings have been presented by Hung *et al.*[79] for [^{2}H(^{14}NH$_3$),1-^{13}C,^{15}N,^{17}O$_2$]glycine and [^{15}N$_2$, ^{17}O$_2$]uracil. For glycine ^{2}HCl $^{1}J_{CO}$(C═O) = 24.7 ± 0.2, $^{1}J_{CO}$(C–OH) = 25.3 ± 0.3 have been extracted from the fits of spin-echo (τ/2-π-τ/2) intensities; the experimental data obtained are in excellent agreement with the data calculated by the CASTEP code, 24.9, 25.7 and 7.9 Hz, respectively.

Relative importance of first and second derivatives of NMR chemical shifts and spin-spin couplings for vibrational averaging has been assessed by Dračínský *et al.*[80] The calculations have been performed for a model set of methane derivatives, differently charged alanine forms and sugar models. Among others, the results for one-bond C–F couplings have been discussed. Zeolites basicity has been investigated by Sánchez-Sánchez *et al.*[81] by the use of chlorodifluoromethane as a probe molecule for which ^{19}F NMR chemical shifts and $^{1}J_{CF}$ couplings have been determined by the nature of the extraframework atoms and not by the framework basicity.

Spin-spin couplings, $^1J_{CAl} = 94 \pm 5$ Hz, and $^1J_{CB} = 52 \pm 2$ Hz, have been determined by Wrackmeyer and Klimkina[82] for tri(*tert*-butyl)alane, $AlBu^t_3$, and the corresponding borane, BBu^t_3, respectively, by measurement of the line width of the ^{13}C NMR signals and of the relaxation rates of the quadrupolar ^{27}Al and ^{11}B nuclei. This is the first example of $^1J_{CAl}$ coupling determined for a monomeric trialkylalane.

Quite a number of 1-silacyclopent-2-ene derivatives have been obtained by Wrackmeyer and co-workers[83] by the consecutive 1,2-hydroboration and intramolecular 1,1-organoboration of alkyn-1-yl(vinyl)silanes. For all compounds obtained the one- and two-bond C-Si couplings have been measured and for some of them DFT calculations have been performed; reasonably good agreement has been observed between the computed and experimental data.

Extraordinarily large apical $^1J_{CP}$ couplings have been observed by Kobayashi and Kawashima[84] in the spectra of 5-carbaphosphatranes obtained by the reaction of 1-hydro-5-carbaphosphatrane with nucleophiles and subsequent intramolecular oxidative cyclization.

$^1J_{CCo}$ couplings ranging from 90 to 110 Hz have been determined by Ooms *et al.*[85] for a series of ^{13}C-methylcobalt(III) complexes with amine ligands of general formula $[trans\text{-}Co(en)_2(X)(^{13}CH_3)]^{n+}$ where en = ethylenediamine, $X = CN^-$, N_3^-, NH_3, NO_2^- or H_2O, $n = 1$, 2, as well as $[Co(NH_3)_5{}^{13}CH_3]^{2+}$. Although the DFT calculations performed for $[Co(en)_2(NO_2)(^{13}CH_3)]^{n+}$ and $[Co(en)_2(N_3)(^{13}CH_3)]^{n+}$ underestimate the magnitude of the coupling, they suggest that $^1J_{CCo}$ is positive, a result that cannot be determined from the experiments performed by the authors.

The $^1J_{CCu}$ and $^1J_{NCu}$ couplings of 590 and –120 Hz, respectively, have been determined by Aguiar and Kroeker[86] for $CuCN \cdot N_2H_4$ and used as indication that the cyanide ligands are static and their magnitudes reflect the deviation of the C–Cu–N angle when compared with other copper cyanides.

$^1J_{C69/71Ga}$ of 182 Hz/232 Hz and $^1J_{C115In} = 310 \pm 10$ Hz couplings have been determined by Wrackmeyer and Klimkina[87] for lithium tetra(*tert*-butyl)gallate and -indate, respectively; DFT calculations at the B3LYP/6-311 + G(d,p) level of theory have been performed by the authors for tri(*tert*-butyl)gallium, trimethylgallium and tetramethylgallate in order to predict $^1J_{CGa}$ couplings.

$^1J_{CSn}$ and $^2J_{HSn}$ couplings measured by Sadiq-ur-Rehman *et al.*[88] for organotin(IV) esters of (*E*)-3-furanyl-2-phenyl-2-propenoic acid indicated a four-coordinated environment around the tin atom in triorganotin(IV) and five-coordinated in diorganotin(IV) carboxylates in non-coordinating solvents. The $^1J_{CSn}$ couplings of about 325 to 363 Hz measured for organotin(IV) derivatives of 4-[(2,4-dinitrophenyl)amino)]-4-oxo-2-butenoic acid and 2-{[(2,4-dinitrophenyl)amino)]carbonyl}benzoic acid indicate that the tin atom in the compounds studied is four-coordinated in solution.[89]

The magnitude of the $^1J_{CPt}$ couplings of the range 2800–2814 Hz has been observed by Shin *et al.*[90] for a series of heteroleptic binuclear platinum(II) complexes containing 1,2-bis(diphenylphosphino)acetylene and 1,2-benzenedithiolate ligands, and invoked as evidence that the phosphine ligands are *cis* coordinated.

The first calculations of $^{1}J_{NN}$ couplings in N_5^-, HN_5^-, N_5^- and $MeOC_6H_5N_3$ have been performed by Perera *et al.*[91] with the aim to solve existing in the literature controversies concerning the structure of HN_5 and its pentazole anion.

Theoretical study on cation dinitrogen complexes $[N_2 \cdots X \cdots N_2]^+$ $X^+ = H^+, Li^+, Na^+, Be^{2+}, Mg^{2+}$ performed at the MP2/6-311 + + G(d,p) level by Alkorta and Elguero[92] included calculations of $^{1}J_{NN}$, $^{1}J_{HN}$ and $^{2h}J_{NN}$ spin-spin couplings. The effect of orbital instabilities for spin-symmetry breaking perturbations, namely the Fermi-contact and spin-dipole contributions to the indirect nuclear spin-spin couplings has been investigated by Auer and Grass.[93] The calculations have been performed for the CO and N_2 molecules.

Measurements of the chemical shifts and of a number of couplings, including those across one bond between the nitrogen nuclei, have been performed by Silva *et al.*[94] for three azines, benzalazine (1,2-dibenzylidenehydrazine), cinnamaldazine 1,2–bis(*E*–phenylallylidene)hydrazine and acetophenoneazine (1,2–bis(1–phenylethylidene)hydrazine); the first two were also labelled on both nitrogen atoms. The experimental results have been compared with the calculated data and reasonably good agreement has been found.

$^{1}J_{NRh}$ couplings of *ca.* 15 and 20 Hz for the amino and amido nitrogens, respectively, have been observed by Blacker *et al.*[95] for relevant to transfer hydrogenation half-sandwich pentamethylcyclopentadienyl rhodium amido complexes of general formula, Cp*RhCl(*S*,*S*-4-$RC_6H_4SO_2NCHPhCHPhNH_2$ (Cp* = η^5-C_5Me_5, R = Me, *t*-Bu, F).

Spin-spin couplings between nitrogen and silver nuclei, $^{1}J_{NAg}$, and ^{109}Ag chemical shifts provided useful structural information on silver complexes obtained by Scheele *et al.*[96] in the reaction of 3,5-bis[3-(2,4,6-trimethylphenyl)imidazolium-1-ylmethyl]-1*H*-pyrazole bishexafluorophosphate and 3,5-bis[3-(2,6-diisopropylphenyl)imidazolium-1-ylmethyl]-1*H*-pyrazole bishexafluorophosphate with Ag_2O. The latter complex is not stable in solution but exists in equilibrium with tetra- and hexanuclear complexes.

Silver-containing layered materials and their interactions with primary amines have been studied by Schurko and co-workers[97] by the use of solid-state ^{109}Ag and ^{15}N NMR spectroscopy. In particular, the combination of ^{109}Ag and ^{15}N NMR experiments on starting materials and samples prepared with both ^{15}N-labelled and unlabelled amines allowed the authors to measure accurately indirect $^{1}J_{NAg}$ and $^{1}J_{14NAg}$ couplings, which provided valuable information on the structure and bonding in these systems.

The variation of $^{1}J_{FP}$ couplings with the nature of the auxiliary ligand (X) in the $[RuX_2(\eta^6\text{-cymene})(PF_3)]$ (X = Cl, Br, I) complexes and the related compound, $PF_2(NMe_2)$, has been observed by Boshaala *et al.*[98] The coupling values decrease in order: free ligand PF_3 (or $PF_2(NMe_2)$) > Cl > Br > I, which has been interpreted by the authors in terms of the reduction of the phosphorus-fluorine bond order.

$^{1}J_{FP}$ of (–)713 ± 5 Hz and $^{1}J_{PRh}$ of (–)110 ± 10 Hz couplings have been determined by Bernard *et al.*[99] for solid [*tris*(dimethylphenylphosphine)](2,5-norbornadiene) rhodium (I) hexafluorophosphate. The negative sign has

been assigned to both couplings on the basis of data already reported in the literature.

The structure of β-Pb_2ZnF_6 has been determined by Martineau *et al.*[100] by the use of multinuclear solid state NMR, powder XRD and *ab initio* calculations. $^1J_{FPb}$ couplings of 1.7 up to 3.0 kHz have been measured for this compound and further used to select the fluorine resonances depending on the number of neighbouring lead ions, leading to an unambiguous assignment of the ^{19}F NMR spectrum.

Phosphanes with bulky oligosilyl substituents have been synthesized and characterized by NMR spectroscopy by Hassler and co-workers;[101] among others, $^1J_{SiP}$ coupling of 92.4 Hz across the P–$SiCl_3$ bond and $^1J_{SiP} = 85.5$ Hz across the P-hypersilyl bond have been observed in the spectrum of the hypersilyl(trichlorosilyl)trimethylsilylphosphane $[(SiMe_3)_3Si](SiMe_3)P(SiCl_3)$ compound. Another paper published by this group of authors[102] was devoted to silicon-phosphorus and silicon-arsenic cage compounds; for two of them, sodium hexamethyl-2,3,6,7-tetrasila-1-phosphanido-3,5-diphosphabicyclo[3.2.1]octane and decamethyl-3-trimethylsilyl-1,3,5-triphospha-2,4,6,7-tetrasilabicyclo[3.2.1]octane, $^1J_{SiP}$ couplings have been measured.

The electronic structure of some transition metal phosphides has been studied by Bekaert *et al.*[103] by the use of CP MAS spectra. In the spectrum of one of them, *i.e.* FeP_4, $^1J_{PP}$ coupling of 280 Hz has been observed providing evidence that a covalent P–P bond exists in this compound.

Large one-bond couplings, $^1J_{PP} = 549.7$ Hz in 1-methyl-3,5-bis(2,4,6-tri-*tert*-butylphenyl)-1*H*-[1,2,4]triphosphole and $^1J_{PP} = 553.3$ Hz in 1-benzyl-3,5-bis(2,4,6-tri-*tert*-butylphenyl)-1*H*-[1,2,4]triphosphole, have been used by Ionkin *et al.*[104] as evidence of a significant delocalization of the electron density in these polyphosphorus heterocycles.

The ^{31}P CP MAS spectra of new copper complexes, $[Cu(NCS)\{L\text{-}N)_2$ or $(L'\text{-}N\hat{}N)\}(PPh_3)]$, where L-*N*, L′-*N*^*N* = aromatic nitrogen base, studied by Pettinari *et al.*[105] exhibited distorted quartets, which allowed the authors to estimate the $^1J_{PCu}$ magnitude. The values of $^1J_{P63/63Cu}$ and $^2J_{PP}$ couplings have been reported by Sokolov *et al.*[106] in the CP MAS spectra of $[Cu(PPh_3)_2L]$ complex of *N*-(diisopropoxythiophosphinyl)-*N*′-phenylthiourea (HL). The couplings observed correspond to the PPh_3 ligands and equal 1124 and 922 Hz for the ^{63}Cu isotope, and 1204 and 977 Hz for the ^{65}Cu one; $^2J_{PP} = 121$ Hz.

A shielding of the phosphorus atom and an increase of the $^1J_{PSe}$ coupling from 746 to 765 Hz have been observed by Jakob *et al.*[107] upon progressive replacement of phenyl by ferrocenylethynyl in phosphane selenides $(FcC{\equiv}C)_nPh_{3-n}P{=}Se$ (n=1–3 and Fc = ferrocenyl = η^5–C_5H_4)(η^5–C_5H_5)Fe).

One-bond P-W couplings, $^1J_{PW}$, have been measured by Carlton *et al.*[108] for a large series of *cis* and *trans* isomers of $[W(CO)_4(PPh_3)(PR_3)]$ (PR_3 = phosphine, phosphite) complexes and correlated with Tolman electronic factor ν. The properties of the 2,6-dixylyl-4-phenylphosphabarrelene (^{x}PB) as a ligand have been explored by Wallis *et al.*[109] through the preparation of a series of complexes with selected transition metals. In the case of the complexes with tungsten, $W(CO)_5(^x$PB), and platinum, *cis*-$Pt(^x PB)_2Cl_2$, the one-bond couplings between the phosphorus and metal nuclei, $^1J_{PW}$ and $^1J_{PPt}$, respectively, have been analysed in order to understand the nature of

the metal-phosphorus bond; the *cis* structure has been assigned to the platinum complex on the basis of the $^1J_{PPt}$ value of about 3600 Hz.

$^1J_{PAu}$ coupling of about 120 Hz has been extracted by Healy *et al.*[110] from the ^{31}P CP MAS NMR spectrum of the [Au(dppey)$_2$]I complex where dppey = *cis*-bis(diphenylphosphino)ethylene. The observed $^1J_{PAu}$ value is in agreement with that reported for the [Au(dppey)$_2$]Cl complex, $^1J_{PAu}$ of *ca.* 200 Hz.[111] Both these values are significantly smaller than those obtained for the two-coordinated complexes, [Au(Ph_3P)X] (412–521) and [Au(Me_3P)X] (553–648 Hz).

The one-bond P-Pt couplings have been used by Rigamonti *et al.*[112] to evaluate the *cis* influence of a series of anionic ligands X and Y in *trans*-[PtXY(PPh_3)$_2$] complexes. The order of decreasing *cis* influence was found to be I > Cl > SePh > SPh > SEt > NO_2 > AcO > NO_2 > Me > mtc (mtc = *N*,*N*-dimethylmononthiocarbamato-*S*); moreover, the *cis* influences of the various ligands have been found to be additive.

One-, two-, three- and four-bond Se-Se couplings have been measured by Brownridge *et al.*[113] to corroborate the structures of the complex equilibrium mixture of cations formed upon dissolution of $(Se_6I_2)[AsF_6]_2 \cdot 2SO_2$ in liquid SO_2. The authors conclude that generally the couplings show a trend consistent with the expected bond alternations within the cations studied and that, additionally to the Fermi contact term dependence, also the through-space mechanism involving lone-pair electrons should be taken into account when the coupling magnitudes are analysed.

The results of DFT calculations of $^1J_{SnX}$ (X = H, F, Cl, Be, I, Me) indirect couplings performed for a series of SnX_4 compounds have been published by Matczak.[114]

The novel bicyclic compound [Sn{N($SiMe_3$)$_2$}CH_2SiMe_2N($SiMe_3$)]$_2$ containing a tin-tin bond has been obtained by Veith *et al.*[115] from bis(hexamethyldisilazyl)-tin(II) under fission of a C-H bond and characterized by NMR spectroscopy; $^1J_{117Sn119Sn}$ coupling in this compound equals 9529 Hz.

The structure of a bimetallic complex of general formula [Yb_2L_3(THF)] (for detailed structure see Fig. 3) has been confirmed by the presence of one-bond f-block-element-f-block-element coupling; $^1J_{YbYb} = 76.1$ Hz measured by Dietel *et al.*[116] for this compound in solution.

Computations of indirect spin-spin couplings using two-component relativistic hybrid DFT with a hybrid functional has been reported by Autschbach.[117] In particular, for the isotropic coupling and the coupling anisotropy of Tl-X (X = F, Cl, Br, I), the PBE0 hybrid functional yielded considerably improved agreement with experiment.

5. Two-bond couplings to hydrogen

The structure of a series of platinum dihydride bisphosphine complexes, *cis*-Pt(L)(L′)(H)$_2$ (L = PCy_3 and L′ = PCy_2H, PPh_3 or PCy_3) studied by Godard *et al.*[62] has been proved by the observation of $^2J_{HH}$ and $^2J_{HP}$ couplings; $^2J_{HH} = 8$ Hz, $^2J_{HP\,trans} = 175$ Hz and $^2J_{HP\,cis} = -20$ Hz have been extracted for the *cis*-Pt(PCy_3)$_2$(H)$_2$ complex from the spectrum of the type AA′XX′.

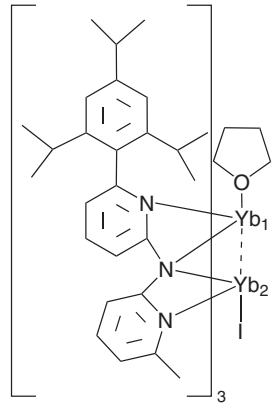


Fig. 3

The accurate value of $^{2}J_{HD} = -1.082 \pm 0.030$ Hz of HOD dissolved in chloroform-d_1 and the H/D isotopic shift of 0.0307(1) ppm have been reported for the first time.[118]

$^{2,3}J_{HH}$ couplings have been measured and analysed by Manimekalai *et al.*[119] for some cyanomethylene derivatives of piperidines, and by Parthiban *et al.*[120] for variously substituted *N*-methylpiperidin-4-one-*O*-benzyloximes.

$^{2-4}J_{HH}$ couplings and ^{1}H,^{13}C,^{15}N chemical shifts have been calculated by Enchev and Angelova[121] for some selected tautomers and isomers of 3-metyl- and 1-methyl-3-ethyl substituted 4-nitroso-5-pyrazolones in order to rationalize the previously derived experimental data for these compounds and to gain insight into their tautomeric behaviour.

Two- and three-bond H–H couplings provided useful information on the stereochemistry of the products of hydrosilylation of norbornadiene carried out by Stosur and Szymańska-Buzar[122] by silanes R_3SiH and R_2SiH_2, and with molybdenum catalysts.

A complete assignment of ^{1}H and ^{13}C data including proton-proton couplings has been reported by Bacher *et al.*[123] for 27 pravastatin derivatives, and by Onajole *et al.*[124] for five novel penta-cycloundecane amine derivatives, potential antituberculosis agents.

The studies with a goal to explore the variability of biological responses from the perspective of sample purity have been performed by Jaki *et al.*[125] For this purpose nine different samples of the pentacyclic plant triterpene ursolic acid with purity certifications were obtained, and their purity was independently assessed by means of quantitative ^{1}H NMR. Biological evaluation consisted of determining MICs against two strains of virulent *Mycobacterium tuberculosis* and IC_{50} values in Vero cells. *Ab initio* structure elucidation provided unequivocal structural confirmation and included an extensive ^{1}H NMR spin system analysis, determination of nearly all J_{HH} couplings and the complete NOE pattern, which led to a revision of earlier reports.

$^{2}J_{HH}$ and $^{3}J_{HH}$ couplings have been applied by Ahmad *et al.*[126] to establish structures of two new triterpenoidal saponins isolated from *Stachys*

parviflora (Lamiaceace); these were stachyssaponin A, 3β,15α,19α, 21β, 22α-pentahydroxyolean-12-ene-28-oic acid 3-*O*-{α-L-rhamnopyranosyl-(1$\rightarrow$3)-β-D-glucopyranoside}-22-*O*-{α-L-arabinofuranosyl-(1$\rightarrow$3)-β-D-glucopyranoside and stachyssaponin B, 2 β, 3β,15α, 21β-tetrahydroxyolean-12-ene-28-oic acid 2-*O*-[α-L-arabinofuranoside]-3, 21-bis-*O*-[β-D-glucopyranoside]. Further examples include two series of new furostanol saponins isolated by Zou and co-workers[127,128] from *Tupistra chinensis* The computed and experimental $^{2}J_{HH}$, $^{3}J_{HH}$ and $^{4}J_{HH}$ couplings have been obtained by Brasil *et al.*[129] for cordatin, a furan diterpenoid with a clerodane skeleton isolated from *Croton palanostigma* Klotzsch (Euphorbiacea) and showing significant anti-ulcerogenic activity.

Complete ^{1}H and ^{13}C NMR assignments including two- and three-bond proton-proton couplings have been made by Araújo *et al.*[130] for novel pterocarpans from *Harpalyce brasiliana*; by Cui *et al.*[131] for an unprecedented new limonoid-based alkaloid, granatoine, and a new phragmalin, xylocarpin L isolated from the fruits of the Chinese mangrove plant *Xylocarpus granatum*; by Chen *et al.*[132] for two amide alkaloids, 3-benzylidene-8, 8a-dihydroxy-2-methyl-hexahydro-pyrrolo[1,2-*a*]pyrazine-1,4-dione and 4-hydroxy-6-(hydroxy-phenyl-methyl)-N(3-methyl-butyryl)nicotinamide, isolated from a mangrove endophytic fungus. The presence of signals typical of the α-methylene-γ-lactone moiety, $\delta_H = 6.30$ and 5.80 ppm, and $^{2}J_{HH}$ of about 2 Hz, has been observed by Huo *et al.*[133] in the ^{1}H NMR spectra of three sesquiterpene lactones, 4-oxo-5,(6), 11-eudesmadiene-9,12-olide, 4-oxo-11-eudesmaene-8,12-olide and (1(10)E)-5β-Hydroxygermacra-1(10),4(15), 11-trien-8,12-olide isolated from *Inula helenium*.

$^{2}J_{HH}$ and $^{3}J_{HH}$ couplings have been determined by da Silva *et al.*[134] to characterize three 7,7′-dihydroarylnaphtalene lignan lactones, and by Machida *et al.*[135] to perform structural elucidation of four neolignan glycosides with enantiomeric aglycones from *Osmanthus ilicifolius*.

The rat brain has been studied by Iltis *et al.*[136] under pentobarbital anesthesia; accurate quantification of *in vivo* spectra has been performed in the presence of propylene glycol (PG). Chemical shifts and proton-proton couplings have been measured for this compound at 37 °C and pH 7.1 and used for spectral simulation.

The stereochemistry of four 3β,7-dihydroxy-5,6-epoxycholestanes synthesized from cholesterols has been elucidated by Poza *et al.*[137] by the analysis of $^{3}J_{HH}$ and $^{2,3}J_{HC}$ couplings combined with DFT calculations. The same approach, developed originally by Murata *et al.*,[138] has been applied by Plaza *et al.*[139] to establish the structure of a series of new depsipeptides isolated from the marine sponge *Siliquariaspongia mirabilis*. Extensive spectroscopic studies including application of $^{2,3}J_{HC}$ couplings have been performed by Lu *et al.*[140] to elucidate the structures of two formosalides A and B, cytotoxic 17-membered ring macrolides with all-*cis* tetraenes, a tetrahydropyran ring and a tetrahydrofuran ring, isolated from a marine dinoflagellate *Prorocentrum* sp. Four novel oxylipins have been isolated by Benavides *et al.*[141] from the corms of *Dracontium loretense* and their relative configurations have been assigned on the basis of combined analysis of homonuclear, $^{2,3}J_{HH}$, and heteronuclear $^{2,3}J_{HC}$ couplings, along with ROE data.

The stereochemical behaviour of $^{2}J_{HC}$ and $^{1}J_{HC}$ couplings, involving nuclei in the vicinity of a carbonyl group has been investigated by Pedersoli *et al.*[142] in fluoro-, chloro-, bromo- and cyanoacetamides, and interpreted in terms of the hyperconjugative interactions and electrostatic effects. The large difference has been observed by Pérez *et al.*[143] for the experimental $^{2}J_{H\mathit{ald}C2}$ couplings in *syn* and *anti* conformers of four 5-X-furan-2-carboxyaldehyde derivatives ($X = CH_3$, Ph, NO_2, Br), and rationalized in terms of an unusual coupling pathway for the FC contribution to such couplings in the *syn* conformers.

The $^{2,3}J_{HC}$ couplings have been applied by Menche *et al.*[144] in stereochemical determination of etnangien, a potent novel analogue of the natural macrolide antibiotic – a highly potent RNA polymerase inhibitor from the mycobacterium *Sorangium cellulosum*.

Application of various geminal spin-spin couplings such as $^{2}J_{HC}$, $^{2}J_{HN}$ and $^{2}J_{HO}$ has been analysed critically by Contreras *et al.*[145] They have studied a set of compounds where their experimental $^{2}J_{XY}$ couplings through the X–C–Y fragment are predicted to be sensitive to hyperconjugative interactions involving either bonding or antibonding orbitals containing the C atom.

A very careful analysis of $^{2,3}J_{HN}$ and $^{1-4}J_{HC}$ couplings allowed Danilkina *et al.*[146] to determine structures of a series of 2-substituted 5-phenyl-7*H*-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-ones, which were obtained in a one-step reaction of 1-acylthiosemicarbazides.

A lab exercise which introduces students to the coupling effects of NMR active nuclei other than ^{1}H has been designed by Pohl and Schwarz.[147] It includes polymer-supported synthesis of 2-fluoroacetophenone and its identification by the use of $^{2}J_{HF}$ couplings.

The $H_3C–Sn–CH_3$ angles in four different dimethyltin complexes of Schiff bases derived from 2-amino-3-hydroxypyridine and different substituted salicylaldehydes have been estimated by Öztas *et al.*[148] using Lockhart's equations with the $^{2}J_{HSn}$ and $^{1}J_{CSn}$ coupling values.

$^{2}J_{HPt}$ coupling of 79 Hz has been found by De Crisci *et al.*[149] for the neutral platinum (IV) complex, [(*closo*-$CB_{11}H_6Br_6$)$PtMe_3$], containing the *closo*-$CB_{11}H_6Br_6^-$ anion bonded to the trimethylplatinum(IV) cation *via* three boron-bound bromines, and used as indicator of the donor strength of the tripodal cap. The authors concluded that *closo*-$CB_{11}H_6Br_6^-$ is a relatively weak donor towards the $PtMe_3^+$ cation.

6. Two-bond couplings not involving hydrogen

Two-bond intramolecular J couplings, $^{2}J_{CO} = 8.8 \pm 0.9$ Hz and $^{2}J_{N1N3} = 2.7 \pm 0.1$ Hz have been determined by Hung *et al.*[79] for glycine ^{2}HCl and uracil, respectively by the use of heteronuclear solid-state magic-angle spinning (MAS) experiments.

Solvent and temperature effects on $^{2}J_{C(O)F}$ and $^{2}J_{HF}$ couplings in α-fluoroacetophenone, *p*-nitro-α-fluoroacetophenone and *p*-nitro-α-fluoroacetophenone have been analysed by Fiorin *et al.*,[150] who studied the conformational equilibria in these three compounds.

Carbon-fluorine couplings across one and two bonds have been reported by Marchione and Buck[151] for a set of polyfluorinated acids and alcohols; typical J_{CF} values were about 270 Hz for the couplings across one bond and 30 Hz for those across two bonds.

The *fac* configuration of the $\{2\text{–}(CH_3CO)\text{-}C_4H_3N\}Re(PPh_3)(CO)_3$ complex studied by Mirebeau *et al.*[152] has been confirmed from the existence of a $^2J_{CP}$ coupling of 28.5 Hz and by X-ray analysis.

Spectroscopic study has been performed by Silva *et al.*[153] to elucidate the structures of diethylenetriaminepentaacetic acid complexed to copper and lead. In the case of the Pb complex the free and complexed carboxyl groups could be easily discriminated since the latter was broadened due to $^2J_{C=O\cdots Pb}$ coupling.

Two- and three-bond F-F couplings have been measured by Ghiviriga *et al.*[154] for 1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane and mono- and difluoronated derivatives; the geminal coupling of the bridge fluorines is 246 Hz if they have an *ortho* fluorine and 238 Hz if they do not.

Experimentally determined and theoretically calculated $^2J_{Si\text{–}O\text{–}Si}$ couplings have been used by Cadars *et al.*[155] to investigate the local structures of siliceous zeolites Sigma-2 and ZSM-12; the authors also evaluated the sensitivity of J couplings for detailed characterization analyses. $^2J_{SiOSi}$ coupling has been also investigated by Florian *et al.*[156] in two crystalline polymorphs and in a glass of ^{29}Si isotopically enriched wollastonite $CaSiO_3$ composition. In the crystalline samples $^2J_{SiOSi}$ couplings of 1.5, 3.6 and 8.0 Hz have been determined with a high accuracy of ± 0.1 Hz.

The enormous temperature dependence of the huge $^2J_{PP}$ coupling in $S(PF_2)_2$ and $Se(PF_2)_2$ has been explained by Reilly *et al.*[157] in terms of thermal interconversion of two conformers predicted theoretically for these two compounds. The computed couplings for the potential conformers of $S(PF_2)_2$ differ vastly and are -12.6 and 395.2 Hz.

A series of novel bisphosphoramidates, such as, for example, 2.3.16.μ'-(*N*-2-pyridinyl)-*N*′-phenyl phosphoramidic chloride-bis[(*N*″,*N*‴-phenyl) phosphoric triamide and 2.3.2.0.μ'-(*N*-phenyl)-*N*′-2-pyridinyl phosphoramidic chloride-bis[(*N*″,*N*‴-phenyl) phosphoric triamide, has been synthesized by Gholivand and co-workers;[158] the observed $^2J_{PP}$ coupling of 20 Hz confirmed the presence of the (O)P–N–P(O) linkage in these compounds.

Couplings between phosphorus nuclei across one and two bonds have been determined by Tattershall *et al.*[159] for three diastereoisomers, *R*(*SR*)*R*, *S*(*SR*)*R* and *R*(*SR*)*S*, of sterically crowded β-P_4S_3 diamide, *exo*,*exo*-β-$P_4S_3(pthiq)_2$, obtained from bicyclic β-$P_4S_3I_2$ and 1-phenyl-1,2,3,4-tetrahydroisoquinoline (Hpthiq) in the presence of triethylamine. For the unsymmetric diastereomer *R*(*SR*)*R* also the spectra of four rotamers, existing due to the hindered rotation around the P–N bonds, have been observed at low temperature; for three of them a full analysis has been performed yielding a set of P–P couplings and ^{31}P chemical shifts.

$^2J_{PSn}$ couplings, the parameter which so far has received little attention in the literature, have been used by Ben Dhia *et al.*[160] to distinguish between the *cis* and *trans* isomers of four octahedral complexes $SnCl_4 \cdot 2(O)PCl(NR_2)_2$ and $SnCl_4 \cdot 2(O)PCl_2NR_2$ (R=Me or Et). The experimentally

determined and calculated couplings in the *trans* isomers are significantly larger than in the *cis* compounds; for example, $^{2}J_{PSn}$ of 144 Hz (*cis*) and 186 Hz (*trans*) have been found in $SnCl_4 \cdot 2(O)PCl(NR_2)_2$. The couplings across two bonds between the P and Sn nuclei of 530 and 410 Hz have been observed by Olbert *et al.*[161] for monomeric bis(trimethylsilyl)amido tin(II) *N*-(diphenylphosphanyl)(2-pyridylmethyl)amide and homoleptic tin(II) bis[*N*-(diphenylphosphanyl)(2-pyridylmethyl)amide], respectively.

A series of highly stable platinum (II) and platinum (IV) pyrophosphato complexes containing ammine, *trans*-1,2-cyclohexanediamine and 1,2-ethanediamine as the amine ligands has been synthesized by Mishur *et al.*[162] and characterized by the use of NMR including $^{2}J_{PPt}$ couplings whose values varied from about 15 to 26 Hz. It is worth noting that the complexes studied exhibit excellent antitumor activities in human ovarian cells.

An application of ultra-high field for measurements of ^{31}P MAS NMR spectra of inorganic compounds containing Tl/Bi/P/S has allowed Gave *et al.*[163] to observe two-bond couplings between phosphorus and thallium nuclei. The $^{2}J_{PTl}$ coupling values extracted from the spectra of $Tl_4Bi_2(PS_4)_2(P_2S_6)$, $Tl_3Bi(PS_4)_2$ and $TlBiP_2S_7$ vary between 500 and 1600 Hz, and are in accord with the *J* values determined recently by the use of 9.4 T field.[164] These are the first examples of non-one bond P-Tl couplings reported in either the liquid or the solid state.

7. Three-bond hydrogen-hydrogen couplings

Analysis of vicinal proton-proton couplings for many years has remained an important source of information on the structure of organic compounds, and the number of papers where their application to establish conformation and configuration of molecules has been described is traditionally considerably larger than those where the other couplings are discussed.

Aguirre-Valderrama and Dobado[165] have presented a free web-accessible Java program to calculate vicinal H–C_{sp3}–C_{sp3}–H proton-proton couplings in organic molecules.

A user-friendly Matlab program for the pseudorotation analysis of saturated five-membered ring systems based on $^{3}J_{HH}$ couplings has been designed by Hendrickx and Martins.[166]

Vitalis and Pappu[167] have applied experimental $^{3}J_{H\alpha H\beta}$ couplings for dipeptides as one of the tests to assess the validity of the ABSINTH model, their new continuum solvation model for simulations of polypeptide structures in aqueous solutions. Theoretical and experimental vicinal proton-proton couplings have been found by Bouø and co-workers[168] to be quantitatively consistent with the Raman optical activity of four proline containing model dipeptides.

The $\langle {}^{3}J_{HNH\alpha} \rangle$ value calculated for alanine in GGAGG has been compared with the experimental one by Daggett and co-workers[169] in their studies of the intrinsic conformational propensities of that amino acid.

A simple method to determine the relative stereochemistry of statine amino acids (γ-amino-β-hydroxyacids) by using ^{1}H NMR spectroscopy has been described by Preciado and Williams.[170] They have shown that it is possible to assign the configuration of statine units within complex natural

Table 1 Peptides and proteins for which the solution structure has been calculated with $^3J_{HH}$

Name	[a]	[b]	Reference
a series of six model glycopeptides	2	5	171
[Pd(en)(Ac-HAAAH-NH_2-*N1,N2*)]$^{+2}$	5	3	172
Ac-MARAM-NH_2 with Ru^{2+} clip	5	4	173
Ac-Phe-[Orn-Pro-D-Cha-Trp-Arg]	6	3	174
three bifunctional peptide derivatives of δ-preferring opioid agonists and NK1 antagonists	8	5	175
the $A\beta_{21-30}$ peptide	10	9	176
the C-terminal segment of p21 protein	20	18	177
varv F, a cyclotide from the European field pansy, *Viola arvensis*	29	29	178
the PinA WW domain from *Aspergillus nidulans*	53	39	179
parvulustat (Z-2685) from *Streptomyces parvulus* FH-1641	78	51	180
human apolipoprotein CIII	79	74	181
human matrix metalloproteinase 12 (MMP-12) – inhibitor complex	165	135	182
porcine amelogenin, the tooth enamel protein[c]	172	69	183

[a] the number of amino acid residues. [b] the total number of vicinal backbone and side chain proton-proton couplings measured. [c] 2D structure only.

Table 2 Carbohydrates for which $^3J_{HH}$ has been used as a structural parameter

Name	Reference
LPS-6, lipopolysaccharide	185
methyl α(2,8)-di/trisialosides	186
vesparoside B, a glycosphingolipid from *Spheciospongia vesparia*	187
the β-1,3-glucan, laminarahexose	188

products by using a combination of chemical shift and coupling information derived from the α-methylene ABX system. The authors provided 73 examples whose complexity ranges from simple statine units to cyclic depsipeptides, such as tamandarin B.

In Table 1 are listed peptides and proteins for which vicinal proton-proton couplings were used in their structure calculations.

Solution structure of the nonamer of *N*,*N*′-linked oligourea has been determined with the help of $^3J_{HH}$ couplings by Miclet and co-workers.[52]

$^3J_{HH}$ couplings have been used by Vázquez and co-workers[184] in the studies of conformational domino effect in a series of *β*-D-glucopyranosyl-(1→6)-α-D-glucopyranosides. Several other examples of carbohydrate structures obtained with the help of $^3J_{HH}$ couplings are given in Table 2.

NMR data including $^3J_{HH}$ couplings have been reported by Noté *et al.*[189] for the aglycons and the sugar moieties of tetrapterosides A and B, two new oleanane-type saponins isolated from *Tetrapleura tetraptera*. The compounds' structures are 3-*O*-{6-*O*-[(2*E*,6*S*)-2,6-dimethyl-6-hydroxyocta-2,7-dienoyl)-*β*-D-glucopyranosyl-(1→2)-*β*-D-glucopyranosyl-(1→3)-*β*-D-glucopyranosyl-(1→4)-[*β*-D-glucopyranosyl-(1→2)]-*β*-D-glucopyranosyl}-3,27-dihydroxyoleanolic

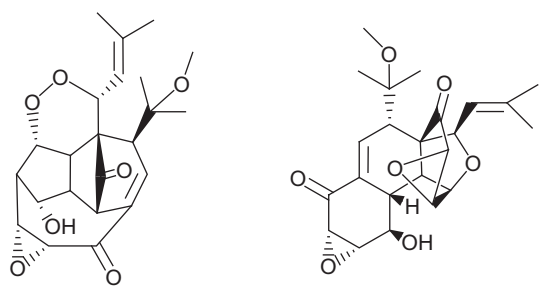
acid and 3-*O*-{*β*-D-glucopyranosyl-(1→2)-6-*O*-[(*E*)-feruloyl-*β*-D-glucopyranosyl-(1→3)-*β*-D-glucopyranosyl-(1→4)-[*β*-D-glucopyranosyl-(1→2)]-*β*-D-glucopyranosyl}-3,27-dihydroxyoleanolic acid.

A simple matching scheme based on $^3J_{HH}$ couplings has been proposed by Gheysen *et al.*[190] as a new tool for rapid attribution of the TOCSY traces originating from the anomeric ^{1}H resonances towards the underlying monosaccharide type. The application of this scheme to rapid identification of common hexapyranose monosaccharide units has been demonstrated by the authors with the PS7F polysaccharide from *Streptococcus pneumonia*.

An extensive use of $^3J_{HH}$ couplings has been made by Paquette *et al.*[191] to elucidate the stereochemical relationships in the eight members of the cyclooctanose family of carbasugars and their precursor intermediates. Two new carbasugars have been isolated by Sedmera *et al.*[192] from *Streptomyces lincolnensis* along with streptol (valienol), gabosine (valienone) and glucosylglycerate, and characterized by NMR.

Recently, a lively discussion has taken place in the literature concerning hexacyclinol, a novel complex molecule isolated from the basidiomycete *Panus rudis*, for which two different structures, although containing many similar functional groups, have been proposed (Fig. 4). The theoretical calculations of ^{1}H NMR spectra of these two structures performed by Saielli and Bagno[193] clearly show that structure 2 is the correct one. A strong argument in favour of 2 followed from the fact that the ^{1}H NMR calculated spectrum of 2 reveals almost identical coupling and chemical shift patterns with those observed experimentally, whereas the theoretical spectrum predicted for 1 is far from the one provided by the experiment.

Vicinal $^3J_{HH}$ couplings have been extensively applied by many authors in structural and stereochemical studies of natural products. Thus, they have been used by Guo and co-workers[194] to establish the structure of four new α-methylene-γ-lactone-bearing cembrane diterpenoids from *Lobophytum crassum*. Further examples include two new sesquiterpenes isolated from *Cyperus rotundus* L. by Xu *et al.*;[195] three new eudesmanolides, ten sesquiterpenes extracted from *Inula helenium*, by Ma *et al.*;[196] two new sesquiterpene lactone xylosides isolated by Michalska *et al.*[197] from *Lactuca triangulata*, and the tricyclic sesquiterpenoid longifolene studied by Subramaniam.[198] It has been shown by the authors in the latter case that the



1 **2**

Fig. 4

flexible seven-membered ring of longifolene adopts a twist-chair conformation.

Complete spectral assignments including three-bond proton-proton couplings have been made by Diniz *et al.*[199] for two novel cordiaquinones from the roots of *Cordia leucocephala*; by Chen *et al.*[200] for five new xanthones isolated from the bark of *Garcinia xanthochymus*; by Ma *et al.*[201] for eight flavonoids isolated from *Sorphora flavescens*, and by Iftikhar *et al.*[202] for two quercusides A and B, new flavonoid glucosides, isolated from *Quercus incana*. Further examples include three new stigmastane glycosides isolated by Suo and Yang from *Vernonia cumingiana*;[203] isoprenylated flavanones from *Sophora tonkinensis* studied by Li *et al.*;[204] prenylated isoflavones from *Flemingia philippinensis*;[205] four new coumaronochromone analogues, aervins A-D, isolated by Imran *et al.*[206] from *Aerva persica*; salisomide and salisoflavan, two new secondary metabolites from *Salsola imbricata*,[207] and two new indolic enamide diastereomers from a mangrove endophytic fungus *Aspergillus* sp.[208] The three-dimensional molecular structure of the isoflavan glabridin, 4-[(3*R*)-8,8-dimethyl-3,4-dihydro-2*H*-pyrano[6,5-*f*]chromen-3-yl]benzene-1,3-diol, isolated from the root of *Licorice*, has been established by Kim *et al.*[209] as equatorial Ph-3 half-chair chroman ring on the basis of semi-empirical PM3 calculations and refined by the use of proton-proton couplings. Unequivocal assignments of flavonoids from *Tefrosia* sp. (Fabaceae) have been carried out by Arriaga *et al.*[210] allowing the authors to correct some erroneous literature data. The relative stereochemistry of a novel benzophenone glycoside and a new flavonoid from the leaves of *Aquilaria sinensis* has been established by Qi *et al.*[211]

$^{3}J_{HH}$ couplings have been used by Wright and co-workers[212] to characterize karlotoxin 1, a new toxin from *Karlodinium veneficum* and by Ye and co-workers[213] in structure elucidation of six new phochinenins A-F from *Pholidota chinensis*.

Experimental and theoretical $^{3}J_{HH}$ couplings have been extensively used by Mendoza-Espinoza *et al.*[214] to establish the absolute configuration and conformation of hypurticin, hyptolide and spicigerolide, representatives of polyacyloxy-6-heptenyl-5,6-dihydro-2*H*-pyran-2-ones, natural products occurring in several members of the mint family (Lamiaceae). All these compounds are highly flexible and a correct elucidation of their structures is important in view of the fact that all of them reveal a significant cytotoxicity.

$^{3}J_{HH}$ couplings together with ^{13}C chemical shifts have been calculated by Chini *et al.*[215] for kedarcidin chromofore and palau'amine in the attempt to establish the correct configuration of these two compounds prior to their total synthesis. Kedarcidin chromofore is a compound that belongs to the enediyne family of antitumor antibiotics, whereas palau'amine is an oroidin dimer, belonging to the class of pyrrole-imidazole alkaloid family isolated from the sponge *Stylotella aurantium*. Populations of conformers in three cinchona alkaloid *O*-ethers at ambient and low temperatures have been estimated by Busygin *et al.*[216]

Vicinal proton-proton couplings have been applied by Riddell *et al.*[217] to characterize hexachlorocyclopentenyldibromocyclooctane (HCDBCO),

i.e. [(1*R*,2*R*,5*R*,6*R*,9*S*,10*S*)-5,6-dibromo-1,10,11,12,13,13-hexachlorotricyclo [8,2,1,$0^{2,9}$]-tridec-11-ene)]. The measured dihedral angles from the X-ray structure correlated very well with those calculated from the proton-proton couplings, indicating that the conformations in solution and in the solid state are probably very similar. However, it is worth noting that a preferred conformation derived by computer modelling differed significantly from the one assigned, and the proton-proton couplings expected for this conformation are not consistent with those observed.

Spectroscopic studies that illuminate the three-dimensional structures of highly substituted tetrahydropyran dioxocarbenium ions have been carried out by Yang and Worpel.[218] By comparing the ^{1}H NMR couplings of both mono and multiple substituted dioxocarbenium ions with those predicted by computational methods, the authors established the conformational preferences of these compounds and came to the conclusion that in the absence of severe steric interactions electrostatic forces dictate the conformational preferences.

Four vicinal proton-proton couplings determined experimentally for tetrahydrofuran and tetrahydrothiophene have been used by Chertkov *et al.*[219] to evaluate the parameters of the dynamic structure of these two molecules by the use of conformational analysis scheme which involves the quantum-chemical description of the dynamic systems in terms of large-amplitude oscillations. In the final step of this approach the inverse structural problem has been solved by the authors with refinement of the potential parameters according to the criterion of best fit of the calculated and experimental couplings. The good agreement between the calculated and experimental J values supported the conclusions drawn for the structure of the studied molecules. The conformational isomerism of 2-chloro- and 2-bromocyclopentanones has been determined by Martins *et al.*[220] through the solvent dependence of the $^{3}J_{HH}$ couplings, theoretical calculations and infrared data, using the solvation theory for the treatment of NMR data. Diastereoselective, three-component cascade synthesis of tetrahydrofurans and tetrahydropyrans employing the tandem Mukaiyama aldol-lactonization process has been described by Mitchell *et al.*[221] The stereochemical outcome of this process was determined by NOE correlations, $^{3}J_{HH}$ coupling analysis and X-ray crystallography of the derived oxygen heterocycles.

Large coupling values, of *ca.* 11 Hz, observed by Olah and co-workers[222] between the H1 and H2 protons in the spectra of chiral benzylic carbocations generated from the corresponding benzylic alcohols, have been used by the authors as an indication of the antiperiplanar position of these two hydrogen atoms.

Roberts and co-workers have continued their studies on conformational preferences of 1,2-disubstituted ethanes extensively using vicinal proton-proton couplings. The present paper[223] has been devoted to the influence of pH and solvent on the conformation of 3-(dimethylazinoyl)propanoic acid. The results obtained by the authors indicate that the conjugate acid and neutral forms of this compound have essentially statistical preferences for *gauche* in water and alcohols as protic solvents, unperturbed by intramolecular hydrogen bonding. With its neutral form in aprotic solvents, intramolcular hydrogen bonding strongly stabilizes the *gauche* conformer,

while for the anion, a smaller preference observed for the *gauche* conformer may involve attraction between the carboxylate and the amine oxide nitrogen.

Stereospecific synthesis of allylic and homoallylic alcohols from functionalized propargyllic alcohols has been described by Sydnes *et al*.,[224] and the configuration around the double bond in these products assigned on the basis of $^{3}J_{HH}$ values.

Although *o*-nitrosobenzoic acid was synthesized more than a hundred years ago, its NMR spectra have been reported only recently by Schaper.[225] This is due to the fact that this compound exists in the monomer-dimer (*E* and *Z*) equilibrium, which leads to rather complex NMR spectra. Schaper has performed a full analysis of them which also yielded the relevant $^{3}J_{HH}$ and $^{4,5}J_{HH}$ couplings for the compound and dimers studied.

Proton-proton couplings have been measured by Incerti *et al*.[226] for three novel benzo[*d*]isothiazole derivatives: methyl 2-amino-3-(benzo[*d*]isothiazol-3-yl)propanoate, 3-amino-5-methylbenzo[*d*]isothiazole and *N*-(*t*-butyloxycarbonyl)-2-aminobenzo[*d*]isothiazol-3(2*H*)-one, and desulphurated isostere of the latter compound, *N*-(*t*-butyloxycarbonyl)-2-aminoisoindolin-1-one.

$^{3}J_{HH}$ couplings have been determined by Culf *et al*.[227] to characterize two novel and stable nitrocyclohexadienyl spirobicyclic zwitterionic Janovsky anionic hydantoin σ-complexes, rac-1,3-diisopropyl-6-nitro-2,4-dioxo-1,3-diazaspiro[4,5]deca-6,9-dien-8-ylideneazinate, ammonium internal salt and 1,3-diisopropyl-2,4-dioxo-1,3-diazaspiro[4,5]deca-6,9-dien-8-ylideneazinate, ammonium internal salt.

$^{3}J_{HH}$ couplings in the polymethine chain have been used by Mustroph *et al*.[228] to characterize the bond localisation in the ground state. The authors have shown that different heterocyclic terminal groups induce different bond localisations in the electronic ground state, and indicated that the intensity distribution among the vibrational sub-bands can be explained by the Franck-Condon principle together with the $^{3}J_{HH}$ couplings.

The couplings between vicinal protons have been applied by Bollikolla *et al*.[229] to assign the conformations of some substituted 2-aryl-*trans*-decahydroquinolin-4-ols.

$^{3}J_{HH}$ couplings for four 2*r*-aryl-6*c*-phenylthian-4-ones, their 1-oxides and 1,1-dioxides have been analysed by Devanathan and Pandiarajan,[230] who came to the conclusion that in all these compounds the heterocyclic ring adopts a chair conformation with equatorial orientations of the aryl and phenyl groups.

Surprisingly small $^{3}J_{HH}$ couplings have been observed by Bender *et al*.[231] for 2:1 adduct of benzyne with 2-methylanizole, which has been shown to have the bisbenzotricyclic structure 6,6a,11,11a-tetrahydro-5-methoy-6-methyl-5,6,11-metheno-5*H*-benzo[*a*]fluorene.

Gold(I)-triphenylphosphine-arylazoimidazole complexes have been characterized by Byabartta and Laguna[232] by the use of NMR spectroscopy including proton-proton couplings.

8. Three-bond couplings to hydrogen

Unique H-Li couplings of 0.45 and 0.89 Hz through the Li–N–C–H network have been observed by Willard and co-workers[233] in the spectrum of a

chiral enolate aggregate containing a lithium enolate and a chiral lithium amide. This is a second example of such coupling reported in the literature. For the first time scalar coupling of 0.80 Hz between proton and lithium nuclei across the H–C–C–Li path was reported by Günther and co-workers in 1993.[234]

For a short alanine peptide (Ala_5) Best *et al.*[235] have quantified the agreement between experimental $^{3}J_{HNC'}$, $^{3}J_{H\alpha C'}$, $^{3}J_{HNC\alpha}$ $^{3}J_{HNC\beta}$, $^{3}J_{H\alpha H\beta}$, $^{1}J_{NC\alpha}$, $^{2}J_{NC\alpha}$ and $^{3}J_{CC'}$ couplings and their calculated averaged values obtained from the simulations using twelve different force fields. The calculated α-helical content is generally too high and in poor agreement with experiment.

$^{1-3}J_{HC}$ and $^{1-2}J_{CC}$ couplings have been calculated and measured by Serianni and co-workers[236] for detection and quantification of acyclic keto, keto hydrate and enol forms of ^{13}C-labelled *N*-acetyl-neuraminic acid.

The conformational change of spermidine upon interaction with adenosine triphosphate in aqueous solution has been studied by Maruyoshi *et al.*,[237] who successfully determined $^{3}J_{HC}$ and $^{3}J_{HH}$ couplings for a spermidine-ATP complex.

Several examples of carbohydrates and nucleotides whose structures were solved by means of heteronuclear couplings are listed in Table 3.

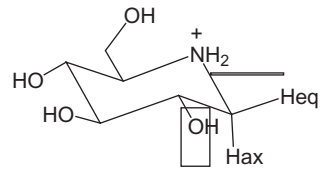
The redundant set of experimental vicinal proton-carbon, $^{3}J_{HC}$, and proton-proton, $^{3}J_{HH}$, couplings involving the OH protons of α and β anomers of a D-glucopyranoside derivative has been applied by Köver *et al.*[243] in order to elucidate the OH-rotamer equilibrium in polyalcohols. The populations of the lowest energy conformers obtained on the basis of the experimental data were similar to those derived by the use of the quantum-mechanical approach. Good agreement has been also observed between the experimental and calculated *J* values.

Vicinal hydrogen-carbon couplings have been determined by Yamaguchi *et al.*[244] for ammonium containing C–N–C–H systems using HMBC experiments. 1-Deoxynojirimycin hydrochloride has been used as a model compound, for which the *anti*-periplanar and *gauche* couplings have been measured, 7.3 and 1.6 Hz, respectively (Fig. 5).

Table 3 Nucleosides and carbohydrates for which heteronuclear vicinal couplings have been used as a structural parameter

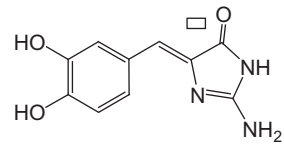
Name	[a]	Reference
a series of prolinol-based nucleoside phosphonic acids	$^{2}J_{HP}$, $^{1,3}J_{CP}$	238
ApA, ApC, CpA and CpC RNA dinucleoside monophosphates	$^{3}J_{HC}$, $^{3}J_{HP}$, $^{2,3}J_{CP}$	239
carbohydrates:		
the amylopectin trisaccharide building blocks	$^{3}J_{HC}$	240
two 3′*O*- and 6′;-*O*-phosphorylated maltoses	$^{3}J_{HC}$	241
the neutral exopolysaccharide from *Lactobacillus delbrueckii* ssp. *bulgaricus* LBB.B26	$^{1}J_{HC}$	242

[a] type of vicinal heteronuclear couplings measured.



$^{3}J_{H1eqC5}$ (*anti*) = 7.3 Hz
$^{3}J_{H1axC5}$ (*gauche*) = 1.6 Hz

Fig. 5



$^{3}J_{H6C4}$ = 5.4 Hz

Fig. 6

Detailed maps of long-range proton-carbon and proton-nitrogen couplings for a selection of derivatives of pyrazinecarboxylic acid have been obtained by Holzer *et al.*[245] In the case of J_{HC} couplings also those across one bonds have been determined.

A set of proton-carbon couplings for 4(7)nitro- and 5(6)-nitrobenzotriazoles and their methyl derivatives has been measured by Larina and Milata,[246] who studied the tautomerism of these compounds by ^{1}H, ^{13}C and ^{15}N spectroscopy. $^{n}J_{HC}$ couplings ($n = 1$–3) have been measured and calculated by Şenyel *et al.*[247] for 3-piperidino-propylamine.

$^{3}J_{HC}$ couplings of 5.4 Hz have been observed by Davis *et al.*[248] between the vinylic protons and the imidazolone carbonyl in the spectra of stereoselectively synthesized polyandrocarpamines A and B providing evidence that the coupled nuclei are *Z* arranged (Fig. 6).

The biotransformation of 2,3,3,3-tetrafluoropropene, a non-ozone depleting fluorocarbon replacement, yielded, as a major metabolite, *N*-acetyl-S-(3,3,3-trifluoro-2-hydroxy-propyl)-L-cysteine, whose structure has been established by Schuster *et al.*[249] by the use of proton-fluorine couplings.

It has been indicated by Larina *et al.*[250] that ^{31}P NMR spectroscopy provides the most convenient and unambiguous tool for the investigation of the *E*–*Z* isomeric structures of phosphorylated enamines. Couplings between the vinylic protons and phosphorus have been reported by the authors for a series of the products of chlorophosphorylation of *N*-vinylazoles.

A theoretical study of the conformational behaviour of geminal and vicinal H–P couplings in a series of vinylphosphine and vinylphosphine chalcogenides has been performed by Fedorov *et al.*[251] The authors established that both types of couplings reveal very marked stereospecifity

towards the orientational phosphorus lone pair effect and that of the P = X double bonds (X = O, S, Se).

$^3J_{HCNP}$ couplings of *ca.* 25 Hz have been reported by Gholivand *et al.*[252] for a series of new 1,3,2-diazaphosphorinanes with formula 4-X-$C_6H_4NHP(O)[NHCH_2C(CH_3)_2CH_2NH]$ where X = F, Cl, Br, I, OCH_3; and related to $H_{eqatorial}$ with P–N–C–H torsion angle near to 180 degrees obtained from X-ray crystallography.

A simple and convenient 1D ^{31}P experiment based on the observation of $^2J_{HP}$ and $^3J_{HP}$ coupling patterns has been adapted by Sharma *et al.*[253] for direct detection of alkylphosphonic acids in environmental matrices.

It has been shown by Rusakov *et al.*[254] that $^3J_{HSe}$ couplings determined experimentally and calculated theoretically for divinylselenide strongly depend on the conformation of this compound. The same applies to geminal H-Se and C-Se couplings.

Three-bond couplings, $^3J_{HCd} = 44.4$ Hz, have been observed by Salehzadeh *et al.*[255] between the imine proton and 111/113-cadmium nuclei in the spectrum of the Cd(II) complex of a new hexadendate base ligand derived from an asymmetric tripodal tetraamine and 2-pyridinecarboxaldehyde.

$^3J_{HSn}$ and $^2J_{HSn}$ couplings have been applied by Ancin *et al.*[256] to characterize four penta coordinated organotin(IV) Schiff base complexes, such as, for example, [*N*-(3-hydroxypyridine-2-yl)-5-chlorosalicylideneiminato]dimethyltin, in which the metal is coordinated to tridentate ligands containing nitrogen and oxygen donors.

Two $^3J_{HHg}$ couplings have been determined by Chen *et al.*[257] for a novel bismercury(II) complex of bidendate N^{21},N^{22}-bridged porphyrin, [((benzamido-κ*N*)phenylmercury-κ*Hg*-N^{21},N^{22})-*meso*-tetraphenyl-porphyrinato-N^{23}, N^{24}] phenylmercury(II) toluene solvate, 188 and 177 Hz for Hg(1) and Hg(2), respectively; these results provided information on the coordination numbers of the Hg atoms.

$^3J_{HPt}$ and $^3J_{CPt}$ couplings have been applied by Rochon *et al.*[258] to characterize the novel Pt(II) complexes of the types *cis*- and *trans*-Pt(Ypy)(pyrazine)Cl_2, $K_2[Cl_3Pt(\mu\text{-pyrazine})PtCl_3]$ and *trans*, *trans*-$(Ypy)Cl_2Pt(\mu\text{-pyrazine})Pt(Ypy)Cl_2$ where Ypy = pyridine derivative. Typically, larger $^3J_{HPt}$ couplings have been observed for the *cis* than for *trans* isomers. In another set of the mixed complexes studied by these authors[259] the pyrazine ligand has been substituted by pyrimidine.

9. Three-bond couplings not involving hydrogen

$^3J_{C'C\gamma}$ and $^3J_{C\gamma N}$ couplings have been used by Vila and Scheraga[260] in the validation test for a set of calculated ubiquitin conformations in their studies on factors affecting the $^{13}C_\alpha$ chemical shifts.

Several examples of proteins whose solution structure was elucidated with the help of heteronuclear couplings are listed in Table 4.

Improved pulse sequences for measurement of $^3J_{CSi}$ and $^2J_{CSi}$ couplings at natural abundance of both nuclei have been proposed by Blechta and Schraml.[263] They allow to avoid the negative effect of $^1J_{HSi}$ couplings on the sensitivity of experiment by using non-gradient versions (INEPT-(Si,C)-COSY) or by switching proton decoupling off during gradient pulses

Table 4 Peptides and proteins for which heteronuclear couplings have been used as a structural parameter in 3D structure calculations

Name	[a]	[b]	[c]	Reference
PhI p 3, a major allergen from timothy grass pollen	97	25	$^3J_{HN}$, $^3J_{CC}$, $^3J_{CN}$	261
productive and non-productive complexes between IIA^{Man} and IIB^{Man}	136 + 164	37/22	$^3J_{CC}$, $^3J_{CN}$	262

[a] number of residues. [b] total number of vicinal couplings measured. [c] types of heteronuclear couplings measured.

(modified INEPT-(Si, C, Si)gHMQC pulse sequence. To show the usefulness of this new approach $^3J_{CSi}$ and $^2J_{CSi}$ couplings have been measured for $(EtO)_2SiMe_2$ and $(EtO)_2SiHMe$ as model compounds. Spin-spin couplings between carbon and silicon nuclei over three, two and one bond as well as other NMR parameters have been measured and calculated by Sykora *et al.*[264] for a series of trimethylsilylated alcohols of the types $Me_3Si–O–(CH_2)_nCH_3$ and $Me_3Si–O–CH_{3-n}$-R_n ($n = 0–3$; R = Me, Ph, or Si). The authors suggest that the signs of the couplings determined by them for selected compounds are likely be extended to all such compounds, which is supported by their theoretical calculations.

A simple method has been presented by McIntosh *et al.*[265] for identification and assignment of phosphorylated serine and threonine residues in ^{13}C- and $^{13}C/^{15}N$-labelled proteins. The method is based on $^3J_{CP}$, $^2J_{CP}$ and $^3J_{HP}$ couplings.

Probable conformation states of ions of the tetra-acid 2-hydroxyethyl-imino-bis(methylenephosphonic acid) and its ring condensation product, the triacid 2-hydroxy-2-oxo-4-phosphonemethyl-1,4,2-oxazaphosphorinane, have been estimated by Demadis *et al.*[266] by means of the dependence of $^3J_{CP}$ and $^3J_{HH}$ vicinal couplings.

The effect of PNCC dihedral angles on the $^3J_{CaliphaticP}$ in a series of several new carbacylamidophosphates of general formula $(X)C(O)NHP(O)(NC_6H_{12})_2$, X = CH_2Cl, $CHCl_2$, CCl_3, CF_3, MeC_6H_4, BrC_6H_4, ClC_6H_4, has been studied by Gholivand and co-workers.[267]

The C-Tl couplings to the *ortho* (52 Hz), *meta* (70 Hz) and *para*-carbons (37 Hz) of the dipp ring have been observed by Zhu *et al.*[268] in the spectrum of $[C_6H_3$-2,6-$(C_6H_3$-2,6-*i*-$Pr_2)_2OTl]_2$, which provided evidence that the Tl-arene contacts in the crystal structure of this compound are preserved in solution.

It is generally assumed that $^3J_{FF}$ couplings are very small in perfluorinated groups. However, the detailed analysis of the spectra of perfluorobutyric acid and 2,2,3,3,4,4,4-heptafluorobutanol performed by Newmark[269] has shown that the actual values of these couplings are quite large; moreover, they can adopt opposite signs, which makes the range covered by them larger than expected.

Ab initio equation of motion coupled cluster singles and doubles (EOM-CCSD) calculations of spin-spin couplings for difluoroacetylene have been performed by Del Bene *et al.*[270] with special attention being paid to a small

three-bond F-F coupling. The experimental value reported by Bürger and Sommer,[271] $^3J_{FF} = 2.2$ Hz, could be reproduced by the authors only when the experimental geometry was applied. When the calculations were performed using geometries obtained at different levels of theory, not only was the calculated absolute value of this coupling far from that determined experimentally but also its sign changed from positive to negative.

Homo-, FF, and heteronuclear, HF, long-range scalar couplings have been extensively discussed and applied by Wormald *et al.*[272] in their studies on the chemical structure and the composition of a vinylidene fluoride telomer. The authors draw the reader's attention to the fact that it is possible for groups in straight-chain fluorinated compounds to have vicinal $^3J_{FF}$ couplings near to zero, whereas $^4J_{FF}$ coupling can be quite large, about 10 Hz. This must be taken into consideration when assigning couplings and thereby determining the structure.

10. Couplings over more than three bonds and through space

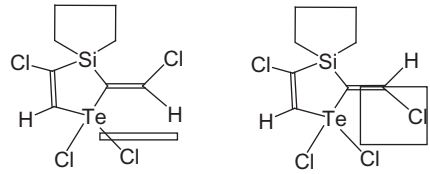
The benzylic couplings, $^{4,5,6}J_{H,CH3}$, in toluene, in a series of 4-mono- and 3,5-disubstituted toluene derivatives as well as in 4-picoline have been determined by Pérez-Hernández *et al.*[273] by the use of the recently modified *J* doubling in the frequency domain method. All these experimental benzylic couplings have been correctly estimated by DFT calculations at the B3LYP/aug-cc-pVTZ level of theory.

A set of $^{2-5}J_{HH}$ couplings have been reported by Montalvo-González[274] for five exocyclic alkenes and fifteen different ketimines obtained from cyclohexanone and its derivatives. An analysis of the coupling values allowed them to establish relative stereochemical and preferential conformations in the studied compounds.

NMR studies of novel Schiff bases derived from L-α-amino methyl esters and 3-hydroxypyridin-4-carboxaldehyde have been carried out by Perona *et al.*,[275] who have also reported $^3J_{HH}$ and $^4J_{HH}$ couplings for a large series of these compounds.

Proton-proton couplings including those across four bonds have provided useful information on the structures of two regioisomeric 7-arylidene hexahydroindazoles, chiral (3*S*,3a*R*,6*R*,7*E*)-7-(4-methoxybenzylidene)-3,4,5,7-hexahydro-3-(4-methoxyphenyl)-2,6-dimethyl-2*H*-indazole and (3*S*,3a*R*,4*R*,7*E*)-7-(4-methoxybenzylidene)-3,5,6,7-hexahydro-3-(4-methoxyphenyl)-2,4-dimethyl-2*H*-indazole studied by Pivnenko *et al.*[276] The long-range couplings between protons have also been reported for a large set of new 1-alkyl-3-benzoyl-pyrazole and 1-alkyl-3-benzoyl-pyrazoline derivatives studied by Lopez-Cara *et al.*,[277] and for substituted 5*H*-[1,3]thiazolo[2,3-*b*]quinazolin-5-one and 12*H*-[1,3]benzothiazolo[2,3-*b*]quinazolin-12-one investigated by Palacios *et al.*[278]

The effect of sulphur oxidation on the transmission mechanism of $^4J_{HH}$ couplings in a series of 1,3-dithiane derivatives has been studied by Gauze *et al.*[279] The results have been rationalized in terms of the hyperconjugation interactions involving the S=O group; the compounds studied were: 1,3-dithiane-1-oxide, *cis*-1,3-dithiane-1,3-dioxide, 1,3-dithiane-1,1,3-trioxide and 1,3-dithiane-1,1,3,3-tetraoxide.



$^5J_{HH}$ not observed $^5J_{HH}$ = 0.5 Hz

Fig. 7

The influence of solvents and temperature on proton-proton couplings in 2-bromocyclohexanone has been studied Coelho *et al.*[280] with special attention being paid to the $^4J_{H2H6}$ long-range coupling.

A new class of tellurium-silicon containing heterocycles, 4,4-diorganyl-1,1,3,6-tetrachloro-1,4-tellura(IV)silafulvenes, has been characterized spectroscopically by Amosova *et al.*;[281] for compounds with *Z* configuration very characteristic long-range $^5J_{HH}$ couplings of 0.2–0.5 Hz have been observed (Fig. 7).

Homoallylic, $^5J_{HH}$, and allylic couplings, $^4J_{HH}$, have been used by Gao *et al.*[282] to elucidate the structure of (4*R**, 5*S**, 6*S**, 8*S**, 13*R**)-1-(2,8-dihydroxy-1,2.6-trimethyl-1,2,6,7,8,8a-hexahydro-naphtalen-1-yl)-3-methoxy-propan-1-one, a polyketide-originated metabolite isolated from a marine sponge-derived fungus *Mycelia sterilia*.

A new method for the determination of the configuration and conformation of push-pull perfluoroalkyl-containing olefinic derivatives by the use of the long-range coupling, $^4J_{CF}$, has been discussed by El Kharrat *et al.*[283]

$^4J_{CF}$, $^5J_{HF}$ and $^5J_{FF}$ and couplings have been measured by Reiter *et al.*[284] for a series of 2-amino-4-phenylthiazoles and analysed together with nuclear Overhauser effects from the point of view of conformational preferences of these compounds. This was a part of their studies on molecular features crucial to the activity of pyrimidine benzamide-based thrombopoietin receptor agonists.

The effects of fluoro substitution on the properties of 4-bromodiphenyl ether have been studied by Klösener *et al.*,[285] who measured spectra of the pattern compound and its five corresponding monofluorinated analogues, analysis of which yielded, among others, J_{CF} couplings for fluoro derivatives including those across four bonds.

An analysis of the ^1H, ^{13}C and ^{19}F spectra of *peri*-difluoronaphtalene measured by Emsley *et al.*[286] in the nematic liquid crystalline solvent ZLI 1695 led the authors to the conclusion that there is strong evidence for a significant contribution of J_{FFzz}(aniso) to residual total anisotropic spin-spin coupling T_{FF}. A full set of *J* couplings measured in $CDCl_3$ including the indirect through-space F–F coupling of 58.90 Hz has been also obtained for this molecule.

Using density functional theory (DFT) with different exchange-correlation functionals and the polarization consistent basis sets optimized for *J*-coupling as well as the second order polarization propagator

approximation, Jaszuñski and Vaara[287] have calculated all the coupling tensors involving the F nuclei in *peri*-difluoronaphtalene. Besides the $^{4}J_{FF}$ tensor, significant anisotropic contributions have been also found for the long-range C–F and H–F coupling tensors.

Unexpectedly large $^{5}J_{FF}$ couplings of about 14 Hz, apparently a manifestation of the highly crowded structure, have been observed by Thomas *et al*.[288] in four copper β-octakis(trifluoromethyl)corrole complexes.

The fluorine-fluorine scalar coupling interactions have been found to be especially informative in structural investigations of a selection of various mono- and di-substituted octafluoro[2.2]paracyclophanes carried out by Roche and Marchione.[289] In addition to $^{2}J_{FF}$ and $^{3}J_{FF}$ couplings, these compounds also provided quite large, of about 2 Hz, couplings across seven, and in some cases even eight bonds.

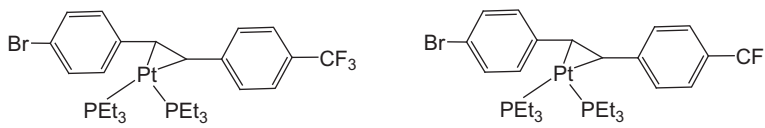
A through-space F–P coupling (formally across six bonds) has been observed by Kruck *et al*.[290] in the spectra of one distereoisomer only, out of two possible *N*,*N*–dimethylphosphoramidites, obtained from the reaction of 3-trifluoromethylsulphonyl-2′2-dihydroxy-1,1′-binaphtalene with hexamethylphosphorous triamide. This coupling reveals a remarkable, up to 400%, dependence on temperature and solvent internal pressure.

Unusually large spin-spin couplings between F and Pt over seven bonds, $^{7}J_{FPt} = 2.9$ Hz, and between F and P over eight bonds, $^{8}J_{FP} = 11.8$ Hz, have been observed by Zenkina *et al*.[291] for four analogous platinum stilbene- and stilbazole-based complexes, whose structures are shown in Fig. 8 below. These heteronuclear interactions are independent of temperature, solvent and concentration, which is indicative of through-bond spin-spin coupling.

A comparison of conformations of 1,1′,2-tris(diphenylphosphino)-3′,4-di-*tert*-butylferrocene and 1,1′,2-tris(diphenylphosphino)-3′-(triphenyl)methyl-4-*tert*-butylferrocene allowed Smaliy *et al*.[292] to determine, for the first time, the conditions of an efficient control of the orientation of the phosphino substituents on the ferrocene backbone in the absence of an ansabridge. It has been found by the authors that through-space couplings between heteroannular phosphorus atoms, $J_{PP} > 10$ Hz, are especially useful for assessing the conformation of the ferrocene backbone in solution of the studied compounds.

11. Couplings through hydrogen bonds

Bu and co-workers[293] have studied *in silica* the influence of metal ion binding to Watson-Crick base pairs on the values of internucleotide $^{2h}J_{NN}$



$^{7}J_{FPt}$ = 13. 2 Hz
$^{8}J_{FPtrans}$ = 3.1 Hz

$^{7}J_{FPt}$ = 11. 8 Hz
$^{8}J_{FPtrans}$ = 2.9 Hz

Fig. 8

Table 5 Compounds for which scalar couplings have been measured through the hydrogen bond

Name	[a]	[b]	[c]	Reference
PKWT, the wild type minimal conserved human TER pseudoknot	N–H···N	$^{2h}J_{NN}$	18	294
PKDU, ΔU177 pseudoknot	N–H···N	$^{2h}J_{NN}$	18	294
Xist RNA A-repeat 14-mer	N–H···N	$^{2h}J_{NN}$	4	295
Xist RNA A-repeat 26-mer	N–H···N	$^{2h}J_{NN}$	4	295
a complex of an acylguanidine derivative in an artificial arginine receptor	N–H··· $^{-}$O–P	$^{2h}J_{HP}$	1	296

[a] hydrogen bond type, symbols of nuclei involved are given in bold. [b] type of couplings measured. [c] number of couplings measured.

couplings. They explored the subject by the combined use of DFT and molecular simulations.

In Table 5 one can find several examples of compounds for which couplings through hydrogen bonds were used in structural analysis.

Hung *et al.*[79] have measured $^{2h}J_{NO}$ intermolecular couplings in the crystals of uracil.

Yates and co-workers.[297] have calculated solid state $^{1h}J_{HN}$ and $^{2h}J_{NN}$ couplings in two 6-aminofulvene-1-aldimine derivatives and a deoxyguanosine derivative, and compared them to those experimentally measured.[298,299] The authors have also calculated $^{2h}J_{NO}$ couplings and found that they are of similar magnitude as $^{2h}J_{NN}$.

Spin-spin couplings transmitted through Ir–H···H–N dihydrogen bonds have been calculated by Olejniczak and Pecul,[300] and good agreement has been observed with the experimental data reported by Lee *et al.*[301] The authors analysed the dependence of $^{1h}J_{HH}$ couplings in a series of model compounds on the distance between the coupled hydrogen nuclei, and came to the conclusion that this is not the parameter influencing the coupling magnitude. According to their opinion, also some other structural parameters, such as, for example, the dihedral angle H–Ir–N–C should be taken into account.

A large number of couplings were measured by Fritz *et al.*[302,303] in 1974 and 1975 for the 2-fluorobenzamide labelled with ^{15}N, and some of them assigned to couplings through intramolecular N–H···H hydrogen bonds. These couplings change dramatically when $CDCl_3$ is replaced by DMSO. A DFT and AIM analysis has been recently performed by Alkorta *et al.*[304] to justify the existence of a weak hydrogen bond in 2-fluorobenzamide and related compounds in the absence of solvent.

Theory and implementation of calculation of spin-spin couplings within combined quantum mechanics/molecular mechanics methods have been applied by Møgelhøj *et al.*[305] for prediction of spin-spin couplings in liquid water and acetylene in aqueous solution. They have also discussed the role of a solvent on spin-spin couplings across hydrogen bonds in the water dimer.

The dependence of calculated $^{3h}J_{C'N}$ couplings of force field parameters has been assessed by Schmid and Meuwly.[306] They have shown that the

increased polarity of the hydrogen bond improves the calculated $^{3h}J_{C'N}$ couplings and shifts the conformational ensemble sampled from the molecular dynamics simulations towards the experimentally measured one.

A theoretical structural analysis of the factors that affect $^{1}J_{HN}$, $^{1h}J_{HN}$ and $^{2h}J_{NN}$ couplings in N–H$\cdots$N hydrogen-bonded complexes has been performed by Alkorta *et al.*[307], who studied 27 complexes containing N–H$\cdots$H hydrogen bonds. The main conclusion was that the hybridization of N atom of the hydrogen bond donor is much more important than that of the hydrogen bond acceptor.

The DFT calculations at the B3LYP/6–311 + + G(d,p) level of theory have been performed by Ebrahimi *et al.*[308] in order to get insight into relationship between the calculated NMR data including $^{1}J_{HF}$ and $^{2h}J_{NF}$ in X-pyridine$\cdots$HF complexes.

Ab initio equation of motion coupled cluster singles and doubles (EOM-CCSD) calculations of spin-spin couplings have been performed by Del Bene *et al.*[309] for F–F and H–F couplings in cyclic FH polymers $(FH)_n$, $n = 2$–6. The authors conclude that although both the Fermi contact term and $^{2h}J_{FF}$ couplings increase and become positive when the cluster size increases, the FC term is not a good quantitative approximation to $^{2h}J_{FF}$.

12. Residual dipolar couplings

A combination of *J* couplings, NOEs and RDCs readily available in the 24-membered macrocyclic ring of archazolide A has been applied by Farès *et al.*[310] to establish the structure of this complex polyketide (see Fig. 9) and permitted the correct relative configuration of the macrolactone ring to be singled out from 64 ($2^{(7-1)}$) pairs of enantiomers with 7 stereocentres.

The relaxation dispersion results together with T_2 data and ^{1}H residual dipolar couplings have been discussed by Ayalur-Karunakaran *et al.*[311] from the point of view of polymer dynamics in a partially filled porous matrix.

Cramer *et al.*[312] have measured $^{1}D_{HC}$ couplings for cylindramide and used them to refine the calculated structure of its macrolactame ring.

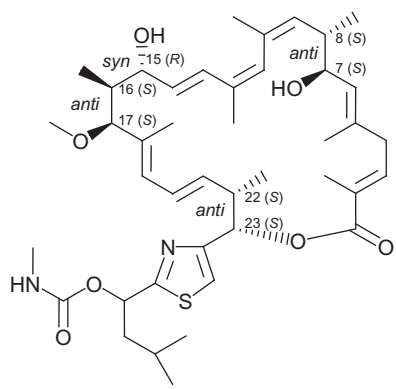


Fig. 9

Stoll *et al.*[313] have conducted a structural investigation of the photoswitchable catalyst on the basis of $^{1}D_{CN}$ residual couplings.

Lanthanide binding peptides containing a single cysteine residues placed at different positions have been attached to proteins *via* a disulphide bond by Otting and co-workers[314] with the aim to generate different molecular alignments of the protein in a magnetic field and to obtain independent sets of residual dipolar couplings. Bax and co-workers[315] have shown that G-tetrameric DNA aligns in a magnetic field and is well suited for the RDC measurements of larger proteins. Tjandra and co-workers[316] have described a new collagen gel system that can weakly align the molecule for solution NMR spectroscopy.

Bax and co-workers[317] have analysed the very high precision RDC data measured for the perdeuterated mutants of GB3 which allowed them to obtain the effective amide $^{1}H–^{15}N$ bond length, ($r_{eff} = 1.015$ Å).

Residual dipolar couplings have been calculated for four disordered proteins of different sizes with secondary structure propensities by Forman-Kay and co-workers[318] using local alignment tensors and compared with the measured RDCs. Using simulations of RDCs in partially unfolded polyalanine chains Jensen and Blackledge[319] have shown that the appearance of the NMR dipolar waves may provide information on the behaviour of the neighbouring capping strands. Bryson *et al.*[320] have presented REDCRAFT (*Re*sidual *D*ipolar *C*oupling *R*esidue *A*ssembly and *F*iltering *T*ool), a new software tool that uses only experimental data (including RDCs) for structure characterization and identification of dynamics of proteins and polypeptides.

For the first time Hus *et al.*[321] have shown that 16 different solutions consistent with the measured RDCs exist for the peptide plane. The authors have discussed conditions under which the correct solution can be identified.

Recently, several new approaches for retrieving biomolecular structures from residual dipolar couplings have been proposed. Zweckstetter[322] has described the protocol of PALES (*P*rediction of *AL*ignm*E*nt from *S*tructure) applicable to proteins, nucleic acids and oligosaccharides. The software provides opportunity for prediction of an alignment tensor (and thus RDCs) from the known molecular coordinates and takes into account both, the molecular shape and charge distribution of the molecule. Tolman and co-workers[323] have proposed a new protocol called RSDC (*R*igid *S*tructure from *D*ipolar *C*ouplings) which allows to determine de novo vector orientations and alignment tensors from only three good quality independent sets of RDCs. Valafar and co-workers[324] have introduced a novel algorithm that uses unassigned RDC data acquired from multiple alignment media for estimation of relative order tensors and for reconstruction of vectors in space. Sattler and co-workers[325] have employed RDC orientational restraints in their developed earlier Crystallography and NMR Systems (CNS); this approach is applicable to multidomain proteins and complexes with known single-domain high resolution structures. Valafar and co-workers[326] have combined unassigned backbone RDCs and probability density profile analysis (PDPA) for rapid classification of protein structure.

Vögeli *et al.*[327] have very precisely measured intraresidue $^{3}D_{HNH\alpha}$ and sequential $^{4}D_{HNH\alpha}$ residual dipolar couplings and carefully analysed the

impact of protein backbone motions on their values. Griesinger and co-workers[328] have developed a robust and independent of structural noise approach called SCRM (*S*elf-*C*onsistent *R*DC-based *M*odel-free analysis) for the determination of supra-τ_c protein dynamics. They utilized 36 $^1D_{HN}$ couplings data sets of ubiquitin including 13 sets measured by them. The same group of the authors have also carried out crossvalidated ensemble refinement called EROS (*E*nsemble *R*efinement with *O*rientational *R*estraints), which allowed them to extract structural ensemble of ubiquitin from combined RDC and NOE data,[329] and describe different conformations that ubiquitin adopts upon binding to different recognition proteins.[330] On the basis of this analysis they have proposed the conformational selection to explain the molecular recognition dynamics of ubiquitin.

For fast two-site exchanging protein-ligand systems with small ligand amount Kay and co-workers have quantified $^{1,2}D_{HC}$ couplings[331] of the low populated bound state of protein (called the invisible, excited state by the authors). They have also proposed a general approach that allows determination of the structure of the low populated bound state of protein.[332] The approach is based on the measurements of residual chemical shift anisotropies and residual dipolar couplings of protein dissolved in small amount of alignment media.

Markley and co-workers[333] have measured $^1D_{HN}$ and $^1D_{H\alpha C\alpha}$ couplings for iron-sulphur cluster cochaperone HscB and compared them with those calculated from the crystal structure. The comparison revealed that the solution structure of the protein is rigid and similar to that in the solid state.

Similarly, Grzesiek and co-workers[334] have compared $^1D_{HN}$ RDCs measured in solution with those calculated from the crystal structure to characterize conformations of ABL kinase in a complex with three clinical inhibitors; Jasco *et al*.[335] have investigated structural differences of MalF-P2 in solution and in the crystalline state; Sattler and co-workers[336] have compared solution and crystal structures of the extended Tudor domain of *D. melanogaster* Tudor-SN; Zweckstetter and co-workers[337] have compared RDCs calculated for X-Ray and model structures of CesT with those measured in solution to point that this protein exists in solution as the unswapped dimer. In a similar manner Clore and co-workers[338] have studied the impact of phosphorylation on structure and interactions between N-terminal domain of enzyme I (EIN) and the histidine phosphocarrier protein (HPr). Table 6 provides several examples of proteins whose structures were solved or refined using RDCs.

Residual dipolar couplings have been applied by Xia and Margulis[370] in their software tool to produce predictions of complexed sugar structures.

Al-Hashimi and co-workers[371] have presented a detailed protocol for rapid determination of the relative orientation and dynamics of A-form helices in RNA using RDCs. The protocol does not require complete resonance assignments. The limits of applicability are discussed, such as the choice of the RDCs to be measured or uncertainty of RDCs. The protocol contains the procedure of the average interhelix alignment and characterization of interhelix motions.

The same group have presented a theoretical approach to the analysis of domain motions in biomolecules using RDCs.[372] They have shown that

Table 6 Proteins for which the solution structure has been calculated with RDCs

Name	[a]	[b]	[c]	Reference
EW	2	8	$^{1}D_{HC}$	339
L-Pro-*cis*-β-ACC-L-Pro-OBn	3	23	$^{1}D_{HC}$, $^{2,3}D_{HH}$	340
Ac-SFVG-OMe	4	13	$^{1}D_{HC}$	339
the coiled-coiled domain (RHCC) of Rab11-FIP2 monomer/dimmer	40/80	30/68	$^{1}D_{HN}$	341
TM23, the second and third transmembrane domains of the human glycine receptor	61	42	$^{1}D_{HC}$, $^{1}D_{HN}$, $^{1}D_{CC}$	342
the CD2-cpSRP54$_{pep}$ complex	57 + 14	[d]	$^{1}D_{HN}$	343
Human apolipoprotein CIII	79	70	$^{1}D_{HN}$	181
the C-terminal domain of Sendai virus nucleoprotein, partially folded	82	280	$^{1}D_{HC}$, $^{1}D_{HN}$, $^{1}D_{CN}$, $^{2}D_{HC}$	344
the GUCT domain from human RNA helicaseII/Guβ	85	129	$^{1}D_{HN}$, $^{1}D_{CC}$	345
ArgN-LBT complexes with Tm^{3+}	78 + 15	*ca.* 30	$^{1}D_{HN}$	314
PhI p 3, a major allergen from timothy grass pollen	97	138	$^{1}D_{HC}$, $^{1}D_{HN}$	261
the S100A1-TRTK12-Ca^{2+} complex	93 + 12	248	$^{1}D_{HC}$, $^{1}D_{HN}$	346
the *tv*Myb$_{135-141}$/DNA complex	107 + 16nt	74	$^{1}D_{HN}$	347
the inner DysF domain of myoferlin	118	87	$^{1}D_{HN}$	348
SMTNL1-CH, the caponin homology domain from the smoothelin-like 1 protein	119	104	$^{1}D_{HN}$	349
the Ca^{2+}-bound C2A domain of rabphiln-3A	125	90	$^{1}D_{HN}$	350
Rv1761c from *Mycobacterium tuberculosis*	127	113	$^{1}D_{HN}$	351
the U4 spliceosomal RNP complex	128 + 33nt	121	$^{1}D_{HC}$, $^{1}D_{HN}$	352
RD3 antifreeze protein from the Antarctic eel pout	134	~130	$^{1}D_{HN}$	353
Ca^{2+}-binding domain 1 of the Na^{+}/Ca^{2+} exchanger	139	95	$^{1}D_{HN}$	354
the C terminus of human galectin-3-carbohydrate complex	155 + 355		37 + 11	$^{1}D_{HC}$, $^{1}D_{HN}$, $^{3}D_{HH}$
the CaM/DAPk/ Ln^{3+} complex (Ln = Tm, Tb, Dy)	148 + 19	*ca.* 110	$^{1}D_{HC}$, $^{1}D_{HN}$	356
the CaM/DRP-1/Ln^{3+} complex (Ln = Tm, Tb, Dy)	148 + 26	*ca.* 110	$^{1}D_{HC}$, $^{1}D_{HN}$	356
the C-terminal domain of EMILIN1	162	234	$^{1}D_{HN}$, $^{1}D_{CC}$, $^{1}D_{CN}$	357
human matrix metalloproteinase 12 (MMP-12) – inhibitor complex	165	263	$^{1}D_{HN}$, $^{1}D_{CC}$, $^{1}D_{CN}$, $^{2}D_{HC}$	182
the *SyB*-Cph1 (GAF) domain of a cyanobacterial phytochrome	172	235	$^{1}D_{HN}$, $^{1}D_{HC}$	358
	63 + 110	76		359

Table 6 (*Continued*)

Name	[a]	[b]	[c]	Reference
the interlukin-2 tyrosine kinase SH3/SH2			$^1D_{HC}$, $^1D_{HN}$	
the Ca^{2+}-bound rat S100B	91×2	157	$^1D_{HN}$, $^1D_{CC}$	360
the S100A1-RyRP12 complex	$93 \times 2 + 12$	116	$^1D_{HC}$, $^1D_{HN}$	361
Alg13, the sugar donor subunit of a yeast N-acetylglucosamine transferase	202	117	$^1D_{HN}$	362
human securing, intrinsically disordered	202	85	$^1D_{HN}$	363
the dynamic cytochrome *c*/Adx complex + CLaNP5	$103 + 108$	64	$^1D_{HN}$	364
the GluR2 S1S2 domain	253	121	$^1D_{HN}$	365
productive and non-productive complexes between IIA^{Man} and IIB^{Man}	$136 + 164$	377	$^1D_{HN}$, $^1D_{CN}$, $^2D_{CN}$	262
the EMILIN1 globular C1q domain	162×3	234	$^1D_{HN}$, $^1D_{CC}$, $^1D_{CN}$	366
the Pdx°-CYP101°, putidaredoxin-cytochrome P450cam complex	$405 + 106$	59	$^1D_{HN}$	367
the DnaK /NRLLLTG/ADP complex	$638 + 7$	231	$^1D_{HN}$	368
the ATCase-nucleotide complex	463×6	46	$^1D_{HC(methyl)}$	369

[a] number of residues. [b] the total number of residual dipolar couplings measured. [c] types of residual dipolar couplings measured. [d] number not specified.

Table 7 Oligonucleotides and carbohydrates for which the solution structure has been calculated with RDCs

Name	[a]	[b]	[c]	Reference
PKWT, the wild type minimal conserved human TER pseudoknot	29	63	$^1D_{HC}$, $^1D_{HN}$	294
PKDU, ΔU177 pseudoknot	28	74	$^1D_{HC}$, $^1D_{HN}$	294
a *let-7* miRNA:*lin-41* mRNA complex from *Caenorhabditis elegans*	33	51	$^1D_{HN}$	375
E. coli $tRNA^{Val}$, (RDC and SAXS data)	76	27	$^1D_{HN}$	376
carbohydrates:				
the $Glc_3ManOMe$	4	25	$^1D_{HC}$	377
LPS-6, lipopolysaccharide	4	38	$^1D_{HC}$, $^1D_{HN}$, $^3D_{HH}$	185
human milk sugars: LNF-1, LND-1, LNF-2, LNF-3, LNnT, LNT	4-6	20	$^1D_{HC}$	370

[a] the number of nucleotides or sugar units. [b] the total number of residual dipolar couplings measured. [c] types of residual dipolar couplings measured.

using five independent alignments, twenty five internal order parameters can be found providing a means to characterize domain motions with very high resolution Latham and Pardi[373] have tested the usefulness of the BEST-Jcomp-HMQC2 experiment proposed earlier by Schanda *et al*.[374] for measurement of imino D_{HH} residual dipolar couplings in RNA; they were able to measure D_{HH} for IRE RNA and for native *E. coli* $tRNA^{Val}$. Residual dipolar couplings have been also measured and applied in structural analysis of nucleic acids and carbohydrates listed in Table 7.

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