
Applications of spin-spin couplings

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1 Introduction

The material in this chapter covers the period from 1 June 2010 to 31 May 2011. 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 IUPAC² 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 ¹H, D-²H, T-³H, Li-⁶Li, Be-⁹Be, B-¹¹B, C-¹³C, N-¹⁵N, O-¹⁷O, F-¹⁹F, Al-²⁷Al, Si-²⁹Si, P-³¹P, S-³³S, V-⁵¹V, Mn-⁵⁵Mn, Fe-⁵⁷Fe, Co-⁵⁹Co, Cu-⁶⁵Cu, As-⁷⁵As, Se-⁷⁷Se, Br-⁷⁹Br, Y-⁸⁹Y, Nb-⁹³Nb, Mo-⁹⁵Mo, Ru-⁹⁹Ru, Tc-⁹⁹Tc, Rh-¹⁰³Rh, Ag-¹⁰⁹Ag, Cd-¹¹³Cd, In-^{113/115}In, Sn-¹¹⁹Sn, Sb-¹²¹Sb, Te-¹²⁵Te, I-¹²⁷I, Cs-¹³³Cs, W-¹⁸³W, Os-¹⁸⁷Os, Pt-¹⁹⁵Pt, Hg-¹⁹⁹Hg, Tl-²⁰⁵Tl, Pb-²⁰⁷Pb. All the other isotopes are described explicitly.

A special issue of *Magnetic Resonance in Chemistry* has been published on quantum-chemical computations of magnetic resonance parameters in 2010. It also includes several important papers devoted to calculations of spin-spin couplings. Among others, the calculation of *J* couplings in solids by the use of the planewave pseudopotential approach has been reviewed by Yates.³ Another paper devoted to a computational investigation of *J* couplings involving Al, O and P has been written by Bryce.⁴

Recent developments in liquid-state INADEQUATE studies have been discussed by Uhrin.⁵ The author has reviewed the methods devoted to measurements of carbon-carbon couplings and application of these couplings in structure determination of a variety of organic molecules. A separate chapter has been devoted to applications of INADEQUATE to nuclei other than carbon-13, *i.e.* silicon-29, nitrogen-15 and selenium-77.

In a review by Jankowski⁶ on application of NMR spectroscopy in isotope effects studies a short chapter has been devoted to isotope effects on chemical shifts and spin-spin couplings.

An extensive review written by Gerothanassis⁷ has been devoted to oxygen-17 spectroscopy including indirect spin-spin and quadrupole couplings.

A short review on platinum complexes of five- and six-membered P-heterocycles as potential catalysts has been written by Keglevich and Kollar.⁸ The *cis* structures of these compounds have been assigned on the basis of stereospecific ¹J_{PPt} couplings.

A review on characterization of molecular systems and monitoring of chemical reactions in ionic liquids by NMR spectroscopy has been written

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by Ananikov.⁹ It also includes some data on spin-spin couplings which have been applied, among others, in structural analysis of transition metal complexes. 1

A mini-review addressed to readers with a background in basic organic chemistry and spectroscopy, but without a specific knowledge of NMR, ECD, VCD or ORD, has been written by Petrovic *et al.*¹⁰ The authors summarize the role of quantum mechanical *ab initio* prediction of spectral properties in NMR and chiroptical spectroscopies. They have also presented examples of the application of chemical shifts and scalar couplings to the determination of chemical constitution and relative configuration of natural product. 5 10

The paper being a first-hand account of the development of the equation of motion coupled cluster (EOM-CC) methods for calculation of spin-spin couplings and their successful applications to problems of interest has been written by Perera.¹¹ 15

Radial sampling for fast NMR, concepts and practices over three decades have been reviewed by Coggins *et al.*¹² The authors covered, among others, the accordion experiments and reduced dimensionality experiments without full quadrature detection which allow effective determination of various scalar couplings. 20

An extensive review covering the literature over approximately the last ten years devoted to phosphorous NMR spectroscopy of condensed matter has been published by Potrzebowski and co-workers.¹³ It also includes some data concerning measurements of J_{PP} couplings.

In a short review written by Massiot *et al.*¹⁴ new and recently published results devoted to detection and use of small J couplings in solid state experiments have been presented. The authors discuss NMR methodologies based on or intended for measuring J couplings in solids and the novel perspectives that they open towards a better understanding of ordered and disordered materials at the subnanometric scale, a length scale that is otherwise difficult to access. 25 30

An extensive review on application of residual dipolar couplings in the configurational and conformational analysis of organic molecules has been published by Kummerlöwe and Luy.¹⁵

Prestegard and co-workers¹⁶ have published a review on solving the structures of oligomeric protein complexes using complementary structural information including residual dipolar couplings. 35

Blackledge and co-workers¹⁷ have reviewed the application of two different approaches to the quantitative description of protein motion but both using RDCs. 40

Combined methods utilizing spin-spin and residual dipolar couplings for studying the structures of polysaccharides of the glycosaminoglycan family have been discussed in a review written by Yates and co-workers.¹⁸

Wang *et al.*¹⁹ in their review have described a new method for rapid global structure determination of large RNA structures that uses RCDs together with small-angle X-ray scattering data. 45

Kwan *et al.*²⁰ have published an educational review on macromolecular NMR spectroscopy for the non-spectroscopist that covers application of residual dipolar couplings in studies of large macromolecular systems.

2 New methods

It has been demonstrated by Kazimierczuk *et al.*²¹ that the irregular (or sparse) Multidimensional Fourier Transform (MFT) method offers a convenient and highly useful approach for processing the randomly sampled NMR signals of high dimensionality, yielding spectra of excellent resolution. The authors have presented the application of high resolution 5D experiments for protein backbone assignment and measurements of couplings from the 4D E.COSY multiplets. Spectral data acquired with the use of proposed techniques allow easy assignment of protein backbone resonances and precise determination of couplings values.

New pulse sequences, BIRD-*J*-resolved HMBC and BIRD-high-resolution HMBC, have been designed by Furihata *et al.*²² for measuring heteronuclear and proton-proton long-range couplings in complicated spin systems. The practical application of these new methods has been demonstrated by the authors using portmicin, a novel polyether antibiotic, as an example.

Merlet and co-workers²³ have implemented the concept of spatial frequency encoding to a purely *J*-edited pulse sequence (G-SERF). This approach allows the selective and accurate assignment of each J_{HH} coupling in overcrowded homonuclear spectra. Farjon and Merlet²⁴ have presented ¹H SERF-filtered-SERF experiments using semi-selective pulses to assign different J_{HH} couplings to each enantiomer in their mixture dissolved in chiral oriented media. That makes possible to visualize and quantify enantiomers. The same group²⁵ have applied phaseable G-SERFph experiment to a chiral propylene oxide dissolved in a PBLG/CDCl₃ chiral solvent.

For measurement of $^1J_{HN}$ and $^1D_{HN}$ couplings in perdeuterated proteins Fitzkee and Bax²⁶ have presented the ARTSY method (method for measuring amide RDCs by TROSY Spectroscopy). For the measurement of the same couplings but in very large proteins Permi and co-workers²⁷ have described the novel pulse sequence MQ-HNCO-TROSY, a modification of HNCO-TROSY with significantly higher resolution in ¹⁵N dimension. Löhrl *et al.*²⁸ have introduced a heteronuclear DIPAP (Double-In-Phase/Anti-Phase) approach for unambiguous extraction of $^1J_{CN}$ and $^2J_{CN}$ couplings from the spectra of proteins.

Tugarinov and co-workers²⁹ have developed 3D HMCMC pulse-scheme for the measurement of methyl $^1D_{HC}$ and $^1D_{CC}$ in ILV-methyl-protonated large proteins.

A modified version of the HSQMBC pulse sequence, IPAP-HSQMBC, has been proposed by Parella and co-workers³⁰ for the easy measurement of long-range heteronuclear couplings ($^nJ_{HX}$, $n > 1$) in natural abundance molecules. Two complementary in-phase (IP) and anti-phase (AP) data sets are separately recorded from a modified HSQMBC experiment and then added/subtracted to provide spin-state-selective- α, β -HSQMBC spectra. The magnitude of $^nJ_{HX}$ ($X = C, N$) can be directly determined by simple analysis of the relative displacement between α - and β -cross-peaks. In order to show the usefulness of this new method, sets of the couplings have been measured for caffeine, 2,3-dibromopropionic acid, strychnine and cyclosporine, and compared with those published earlier.

Another modified HSQMBC pulse sequence for the measurements of long-range heteronuclear couplings has been presented by Boros and Kövér.³¹ The CPMG-HSQMBC pulse scheme implements adiabatic inversion and refocusing pulses on the heteronucleus, which yields pure absorption antiphase multiplets and allows precise and direct measurement of the ${}^nJ_{\text{HX}}$ couplings regardless of the size of the proton-proton couplings. Strychnine has been used as a model compound in order to demonstrate the usefulness of the method.

A new type of sequences, denoted as Coupling Sign Edited (CSEh and CSEc), has been designed by Blechta and Schraml³² as simple modifications of SQQh and SQQc sequences respectively. These two new sequences allow editing of heteronuclear correlation spectra according to the sign of the selected heteronuclear coupling, preserving the information about the sign and magnitude of the coupling. They are particularly useful in detection of small carbon-silicon couplings which has been shown by the authors on the example of two samples, (trimethylsiloxy)phenol and 2,3,4-tris-(trimethylsiloxy)-1,6-anhydro- β -D-glucopyranose.

A new pulse sequence, 2D INEPT-PANACEA, which allows parallel acquisition of 2D Si-Si INADEQUATE and 2D Si-H HMBC spectra and also provides the 1D Si NMR spectrum has been designed by Kupče and Wrackmeyer³³ for the use with organosilicon compounds and tested using a mixture of OH-terminated polydimethylsiloxanes. The 1D Si NMR spectrum provides accurate measurement of Si chemical shifts with a signal-to-noise ratio allowing determination of C-Si spin-spin couplings.

A new TOCSY-based decoupling difference experiment has been designed by Reith *et al.*³⁴ for the determination of ${}^3J_{\text{H3'P}}$ couplings in isotope-labelled DNA oligonucleotides and tested on a DNA octamer. The new experiment has been found to be about three times more sensitive than previously reported methods such as, for example, the already known constant-time NOESY difference method.

The pulse sequence named CESS-COSY (Carbon-13 EditSpin Selective Correlation SpectroscopY) has been reported by Nath and Suryaprakash.³⁵ The technique deciphers the severely overlapped peaks in the very intricate ${}^{13}\text{C}$ -coupled proton spectra of enantiomers and permits the determination of J_{HH} and ${}^1J_{\text{HC}}$ couplings in I_2S and I_3S groups. It requires a weakly aligning medium. Another experiment³⁶ proposed by these two authors based on a single ${}^{13}\text{C}$ spin edited selective proton-proton correlation allows one to decipher overcrowded ${}^{13}\text{C}$ coupled proton NMR spectra of weakly dipolar coupled spin systems. The experiment unravels the masked ${}^{13}\text{C}$ satellites in the proton spectrum and permits the measurement of one-bond carbon-proton residual dipolar couplings in I_3S and for each diastereotopic proton in I_2S groups. It also provides all the possible homonuclear proton-proton residual couplings, which are otherwise difficult to extract from the broad and featureless one dimensional ${}^1\text{H}$ spectrum. The same group of the authors³⁷ have designed several ω_1 -heterodecoupled- ${}^{13}\text{C}$ -filtered proton detected single and multiple quantum selective refocusing experiments that retain the difference in ${}^1\text{H}$ - ${}^1\text{H}$ couplings between the enantiomers in the indirect dimension (F_1) and both ${}^1\text{H}$ - ${}^1\text{H}$ and ${}^1\text{H}$ - ${}^{13}\text{C}$ couplings in the direct dimension (F_2). The advantages of

these experiments, which allow quantification of enantiomeric excess, are the accurate differentiation and precise determination of the homo- and hetero-nuclear RDC's, in addition to significant saving of the experimental time. The simple two dimensional ^{13}C satellite J/D resolved experiments have been proposed by Prabhu *et al.*³⁸ for the visualization of enantiomers, extraction of homo- and hetero-nuclear residual dipolar couplings and additionally determination of ^1H chemical shift differences in the anisotropic medium. The significant advantage of the techniques is the determination of scalar couplings of bigger organic molecules. The scalar couplings specific to a second abundant spin such as ^{19}F can be selectively extracted from the severely overlapped spectrum.

A new device that has capacity for RDCs and RCSA measurements has been proposed by Liu and Prestegard.³⁹

It has been shown by Filip *et al.*⁴⁰ that the use of rotor-synchronized Hahn-echo pulse train ^1H decoupling in a MAS ^{15}N spin-echo NMR experiment allows the use of longer spin-echo durations compared with the case when conventional decoupling is applied. This enables the accurate determination of very small J couplings down to a few Hz, and provides the possibility of measuring even such weak couplings as those hydrogen-mediated, which are sometimes less than 1 Hz.

A simple approach to high-resolution J -resolved heteronuclear correlation MAS NMR spectroscopy of lipid membranes has been introduced by Zorin *et al.*⁴¹ The authors have described direct observation of heteronuclear scalar J couplings from bilayer lipid membranes, and proposed J resolved heteronuclear correlation experiments. LG (Lee-Goldburg) decoupling during rare spin observation has been combined with free proton evolution in a WISE- type experiment or with LG-decoupled evolution HETCOR experiments. J_{HC} coupling values have been reported from phospholipid and resolved sterol groups within lipid membranes, and J -resolved spectra from laterally separated mixed lipid membranes have been presented.

The possibility of direct detection of hetero- and homonuclear scalar coupling in magnetic zero-field using an optical atomic magnetometer has been demonstrated by Ledbetter *et al.*⁴² The authors showed that characteristic functional groups of ethanol, which has been used as a model compound, have distinct spectra, which allows straightforward identification of molecular structure. A magnetically shielded, zero-field environment provides high absolute field homogeneity and temporal stability, allowing one to obtain 0.1 Hz linewidths without using spin echoes, and to determine scalar-coupling parameters with a statistical uncertainty of 4 mHz.

An instrumentation of the Earth's field NMR inside a laboratory has been demonstrated by Liao *et al.*⁴³ (see also ref. 44) who applied a lock-in analysis technique in order to enhance the signal-to-noise ratio. To demonstrate the usefulness of this technique the spectrum of trimethyl phosphate has been measured as a model sample for which $^3J_{\text{HP}}$ coupling of 10.99 ± 0.013 Hz has been determined. High-resolution low-field NMR signals of selected liquid samples have been recorded by Qiu *et al.*⁴⁵ by the use of a nitrogen-cooled superconducting quantum interference device (SQUID). The NMR measurements have been performed at Larmor

frequencies from 2 Hz to 40 kHz. The natural spectral linewidth of tap water could be measured in magnetic fields below 7 microtesla. To demonstrate the measurement sensitivity and resolution, J -coupling spectra of 2,2,2-trifluoroethanol have been recorded at different measurement fields, with signals separated by several hundreds of Hertz.

3 One-bond couplings to hydrogen

NMR properties of H_2 and HD molecules dissolved in toluene- d_6 and incarcerated in C_{60} have been studied by Chen *et al.*⁴⁶ in the range of 200–340 K. Among others, also $^1J_{HD}$ has been determined but not noticeable influence of temperature has been observed on this parameter.

The intact nature of the H-H bond in the dihydrogen complex *trans*-[Ru(η^2 - H_2)(P(O)(OH) $_2$)-(dppe)][OTf] complex (dppe = 1,2-bis(diphenylphosphino)ethane) has been proved by Nagaraja *et al.*⁴⁷ by the use of variable temperature 1H spin-lattice relaxation time measurements and the observation of a significant $^1J_{HD}$ coupling in its *trans*-[Ru(η^2 -HD)(P(O)(OH) $_2$)-(dppe)][OTf] isotopomer.

An interesting paper has been devoted by Wasylshen and co-workers⁴⁸ to quantitative analysis of Earth's field NMR spectra of strongly-coupled heteronuclear systems of nuclei with differing spins. The coupling $^1J_{HB} = 80.9$ Hz has been extracted from the spectrum of the tetrahydroborate anion, BH_4^- , when in the Earth's field of 53.3 μT , $\nu(^1H) = 2269$ Hz and $\nu(^{11}B) = 728$ Hz. However, for this spin system the 1H NMR spectra exhibit features that both first- and second-order perturbation theory are unable to reproduce. In the case of the ammonium anion, NH_4^- , where $^1J_{H^{14}N} = 52.75$ Hz when $\nu(^1H) = 2269$ Hz and $\nu(^{14}N) = 164$ Hz, second-order perturbation theory adequately describes 1H NMR spectrum of this anion.

A reasonably good agreement has been observed by Schlüter and Bernhardt between experimental and DFT calculated $^1J_{HB}$ couplings obtained for the *closo*-borates $M_2[B_7H_7]$ and $M[B_7H_8]$ ($M = PPh_4$, PNP and $N(n-Bu_4)$),⁴⁹ and 3-DBU-*closo*-2- CB_6H_6 and $[3-Cl-*closo*-2- CB_6H_6] $^-$ clusters.⁵⁰$

$^1J_{HB}$ and $^1J_{CSe}$ couplings have been extensively used by Wrackmeyer *et al.*⁵¹ in order to characterize 2-(dimethyl sulphide)-4,5-[1,2-dicarba-*closo*-dodecaborano(12)]-1,3-diselena-2-boracyclopentane, a stable source of a boron hydride, and its pyridine adduct, 2-pyridine-4,5-[1,2-dicarba-*closo*-dodecaborano(12)]-1,3-diselena-2-boracyclopentane and some related compounds.

Two-level factorial design has been used by Richter *et al.*⁵² to determine the effects of modification of the level of theory on calculated $^1J_{HC}$ couplings of norbornane derivatives. The authors analyzed the effect of four factors: the method used in geometry optimization, the functional, the basis set and the solvent in coupling calculations. The levels of theory selected were B3LYP/aug-cc-pVDZ, for geometry optimization, and B3LYP/EPR-III for $^1J_{HC}$ coupling calculations considering the molecule in gas phase. The chosen levels of theory showed good agreement with experimental data.

A set of $^1J_{\text{HC}}$ couplings has been reported by Walton *et al.*⁵³ for *E* and *Z* isomers of 2-ethyl-1-methyl-7-oximino-dipyrrolo-pyrimidine-3,5-dione, their *O*-methyloxoimino derivatives and *Z* isomer of 2-ethyl-1-methyl-7-(*N*-methylnitron)-dipyrrolo-pyrimidine-3,5-dione. Interestingly, $^1J_{\text{HC}}$ coupling of *ca.* 175 Hz has been measured for *E* isomers and 180 Hz for *Z* ones. The difference has been interpreted by the authors in terms of intramolecular hydrogen bonding interaction. A similar interaction has been reported recently by Afonin *et al.*⁵⁴ for a pyrrole ring system.

The complete NMR assignments of *N,N'*-methylenodidemnin A isolated from the ascidian *Trididemnum solidum* has been performed by Molinski and co-workers⁵⁵ who also applied $^1J_{\text{HC}}$ couplings in order to confirm the presence of the imidazolidinone ring in this compound.

The structures of three saponins from *Blighia sapida* have been elucidated by Mazzola *et al.*⁵⁶ to a high degree with the aid of $^1J_{\text{HC}}$ couplings. Schmidt and co-workers⁵⁷ have measured six types of heteronuclear couplings, namely, $^1J_{\text{HC}}$, $^1J_{\text{HN}}$, $^1J_{\text{CC}}$, $^1J_{\text{CN}}$, $^2J_{\text{HC}}$ and $^2J_{\text{CN}}$ for ERp18, human endoplasmic reticulum protein. They have measured in total 1268 couplings, which allowed to annotate the secondary-structure of this 157-residue long macromolecule.

Schwalbe and co-workers⁵⁸ have suggested a general method for the determination of conformations of ribose, nucleobase and the 2'OH group in RNA based on interpretation of $^1J_{\text{H}1'/\text{C}1'}$ and $^1J_{\text{H}2'/\text{C}2'}$ couplings.

Relatively large $^1J_{\text{HC}}$ couplings of 114 and 118 Hz have been observed by Calladine *et al.*⁵⁹ for two organometallic alkane complexes, *i.e.* CpRe(CO)₂(cyclopentane) and CpRe(CO)₂(2,2-dimethylbutane- η^2 -C¹,H¹), respectively. This result and large negative $\delta(^{13}\text{C})$ values observed for the co-ordinated hydrogen allowed the authors to conclude that no agostic interactions take place in these two compounds. Another paper published by this group⁶⁰ has been devoted to two manganese alkane complexes, CpMn(CO)₂(propane) and CpMn(CO)₂(butane) generated photochemically from CpMn(CO)₃ at 130–136 K with the alkane as a solvent. Also in these compounds only a small decrease of one-bond proton-carbon couplings upon complexation has been observed, and $^1J_{\text{HC}}$ of *ca.* 120 Hz has been found.

Experimental and calculated $^1J_{\text{HC}}$ couplings have been reported by Buczek *et al.*⁶¹ for *E* and *Z* isomers of *N*-acetyl-dehydrophenylalanine *N',N'*-dimethylamide, a member of α , β -dehydroamino acids, and by Alver and Parlak⁶² for 1-phenylpiperazine. The calculated $^1J_{\text{HC}}$ and $^1J_{\text{CC}}$ couplings for 1,3-phenylenediacetic acid have been published by Gökce and Bahçeli.⁶³

It has been indicated by Howe⁶⁴ that the $^1J_{\text{HC}}$ couplings in many popular molecules vary over wide range of $^1J_{\text{HC}}$ values which differ quite strongly from those estimated by the use of widely applied relationship between $^1J_{\text{HC}}$ and ^{13}C chemical shift of the carbon atom involved. Generally, the predicted coupling values are too low. As a result the standard HSQC sequences which can be optimised for one coupling value only fail for a significant subset of functional groups. Quite often even incorporation of adiabatic pulses into the INEPT elements is not sufficient. The author has demonstrated that this imperfectness of the method can be reduced by avoiding refocusing delays and by using a *J*-compensated excitation element.

$^1J_{\text{HN14}}$ coupling of a typical value 51.1 Hz has been observed by Wang *et al.*⁶⁵ in the proton spectra of doped polyaniline (PANI). The determined integral area ratio of the triplet peak is dependent on the effective doping of the PANI backbone and has a clear relationship with the conductivity of this polymer.

The influence of conformation and hydrogen bonds in the pyrrole-2-carbaldehyde on $^1J_{\text{HN}}$ coupling has been studied by Afonin *et al.*⁶⁶ Another paper published by this group⁶⁷ has been devoted to the influence of $\text{NH}\cdots\text{O}$ intramolecular hydrogen bond on the $^1J_{\text{HN}}$ coupling in push-pull diaminoenones. $^1J_{\text{HN}}$ couplings determined by Ullah *et al.*⁶⁸ for intramolecularly hydrogen-bonded enamino-carbonyl derivatives of Meldrum's and tetric acids indicate that these compounds exist in the NH form.

$^1J_{\text{HGe}}$ coupling of 191 Hz has been measured by Samanamu *et al.*⁶⁹ for $(\text{Ph}_3\text{Ge})_3\text{GeH}$, one of the studied by them branched oligogermanes. This coupling is nearly twice as large as those observed for several monomeric arylgermanium hydrides for which typically couplings of *ca.* 100 Hz have been observed; for example, $^1J_{\text{HGe}} = 98$ Hz has been reported for Ph_3GeH and PhGeH_3 .

4 One-bond couplings not involving hydrogen

$^1J_{\text{BC}}$ of *ca.* 110 Hz and $^2J_{\text{BC}}$ of *ca.* 20 Hz couplings have been determined by Himmelsbach and Finze⁷⁰ for a series of dicarba-*closo*-dodecaboranes with one and two ethynyl groups bonded to boron. Good agreement has been observed between the experimental and calculated J_{BC} values. ^{11}B chemical shift tensors and $^1J_{\text{BC}}$ couplings have been calculated by Wrackmeyer *et al.*⁷¹ for a series of 9-borafluorene derivatives and some doubly hydrogen-bridged 1,2-diphenylenediboranes, and compared with experimental data.

Ab initio EOM-CCSD/(qzp/qz2p) calculations have been carried out by Del Bene *et al.*⁷² in order to investigate structural and electronic effects on $^1J_{\text{BN}}$, $^1J_{\text{HB}}$ and $^1J_{\text{BF}}$ couplings in complexes $\text{X}:\text{BH}_n\text{F}_{3-n}$ where $\text{X} = \text{N}_2$, NCH , NCLi , H_2CNH , NF_3 and NH_3 , with $n = 1-3$. $^1J_{\text{BN}}$ couplings vary from -19 Hz to 9 Hz for complexes classified as covalent and do not exceed the absolute value of 2 Hz for van der Waals complexes. Also two remaining couplings, *i.e.* $^1J_{\text{HB}}$ and $^1J_{\text{BF}}$ have been found to be sensitive towards the nature of the B-N bond. Another paper has been devoted by this group of authors⁷³ to an *ab initio* study of a set of 15 fluoro-substituted 1,3-diborata-2,4-diphosphonicyclobutanes $\text{B}_2\text{P}_2\text{F}_n\text{H}_{8-n}$ for $n = 0, 1, 2, 4$, with four member B-P-B-P rings. Couplings involving ^{31}P , *i.e.* $^1J_{\text{BP}}$, $^1J_{\text{FP}}$, $^2J_{\text{FP}}$, $^3J_{\text{FP}}$ and $^2J_{\text{PP}}$ are large and sensitive to the number of fluorines present, and can discriminate between axial, equatorial, and geminal B-F and P-F bonds, although not all do this to the same extent.

The optimized aug-cc-pVTZ-J basis sets have been extended by Provasi and Sauer⁷⁴ to the calculation of indirect nuclear spin-spin couplings involving the atoms B, Al, Si, P, and Cl. As a first illustration, the one-bond indirect spin-spin couplings have been calculated in BF, BH_4 , AlH, AlF, SiH_4 , SiF_4 , PH_3 , PF_3 , H_2S , SF, HCl and ClF at the level of density functional theory using the Becke three parameter Lee-Yang-Parr and the

second order polarization propagator approximation with coupled cluster singles and doubles amplitudes. 1

$^1J_{\text{BSe}}$ couplings of *ca.* 60 Hz have been determined by Wrackmeyer *et al.*⁷⁵ for lithium and tetrabutylammonium salts of bis(1,2-dicarba-*closo*-dodecaborane-1,2-diselena)borate and $^1J_{\text{BSe}}$ of 35 Hz in lithium salt of 5
1,2-dicarba-*closo*-dodecaborane-1,2-diselenadihydroborate. For all these compounds also $^1J_{\text{CSe}}$ couplings of *ca.* 158 Hz have been measured. The calculated $^1J_{\text{BSe}}$ and $^1J_{\text{CSe}}$ couplings are numerically larger than the experimental values. In both cases the calculations predict a negative sign which in the case of $^1J_{\text{CSe}}$ couplings has been confirmed by experiment. 10

Reasonably good agreement has been observed by Dodziuk *et al.*⁷⁶ between the experimental and DFT-computed $^1J_{\text{CC}}$ couplings derived for *trans* and *cis* isomers of [3.3]paracyclophane. The coupling values are typical of unstrained aromatic and aliphatic hydrocarbons, despite the significant nonplanarity of the benzene rings and strain in the aliphatic bridges in the studied compound. 15

An extensive study on theoretical modelling of molecular spectra parameters of a large series of variously substituted diacetylenes has been performed by Roman *et al.*⁷⁷ This also included the DFT calculations of carbon-carbon couplings at the B3LYP level of theory, the aug-cc-pVDZ-20
sul basis set for the C atoms and the aug-cc-pVDZ basis set for other elements. However, comparison with experimental $^1J_{\text{CC}}$ data, if available, shows that the calculations generally overestimate their values by *ca.* 15 Hz. The calculated by Haque *et al.*⁷⁸ $^1J_{\text{CC}}$ couplings in C_8H_2 polyyne at a similar level of theory are also obviously overestimated quite significantly. 25
The reported DFT J values across the triple CC bonds attain *ca.* 250 Hz, whereas the corresponding experimental value for diacetylene is of 194 Hz.⁷⁹ Isomerization effects on chemical shifts, and $^1J_{\text{C-C}}$ and $^1J_{\text{C=C}}$ couplings in polyacetylene chains have been estimated by Colherinhas *et al.*⁸⁰ by the use GIAO-DFT calculations and some regularities have been established. 30

$^nJ_{\text{CC}}$ ($n = 1-4$) couplings have been measured by Kamounah *et al.*⁸¹ for the partially ^{13}C labelled minor product of acetylation of cedarwood oil (Virginia), 1,7,7-trimethyl-2,3-(3',4'-dimethylbenzobicyclo)-bicyclo[3.2.1]octane. The analysis of $^1J_{\text{CC}}$ couplings in the fusaric acid 35
isolated from the cultures fed with different ^{13}C -labelled substrates allowed Stipanovic *et al.*⁸² to confirm the biosynthesis of this compound.

The method based on 1,1-ADEQUATE technique which allows to determine unambiguously substitution sites in monosubstituted five-membered aromatic heterocycles has been proposed by Schraml *et al.*⁸³ The authors indicate that it is rather difficult to establish correctly the structure 40
of these seemingly simple compounds using other correlation methods such as COSY, HETCOR etc. due to the fact that long-range proton-proton as well as proton-carbon couplings are of similar values.

An analysis of sometimes complex NMR spectra of a series of novel fluoro-substituted benzo- and benzothienofused pyrano[2,3-*c*]pyrazol-4(1*H*)-ones synthesized by Holzer *et al.*⁸⁴ yielded a full set of ^1H , ^{13}C and ^{19}F NMR data including one-bond and long range C-F couplings, which were particularly useful in assignment of ^{13}C NMR resonances and corroboration of the structure of the obtained compounds. 45

The effect of the influence of hyperconjugation, inductive, steric and hydrogen-bond interactions on $^1J_{CF}$ and $^2J_{CF}$ couplings in *cis*- and *trans*-4-*t*-butyl-2-fluorocyclohexanones and their alcohol derivatives has been studied by Anizelli *et al.*⁸⁵ Among others, the authors indicate that the FC term of $^2J_{CF}$ coupling in *cis*-4-*t*-butyl-2-fluorocyclohexanone is transmitted in part by the superposition of the F and O electronic clouds.

Experimental, SOPPA(CCSD) and DFT analysis of substituent effects on $^1J_{CF}$ couplings in fluorobenzene derivatives has been carried out by Vilcagagua *et al.*⁸⁶ A correlation observed between substituent effect on the PSO contribution to $^1J_{CF}$ and the substituent effect on the corresponding fluorine CSs has been interpreted by the authors in terms of the close resemblance between the operators of the paramagnetic part of the fluorine nuclear magnetic shielding tensor and the part of the PSO operator centred at the F atom. This provides for the first time a possible method to estimate experimentally a PSO contribution magnitude to spin-spin coupling.

The influences of cation- π and anion- π interactions on NMR data have been studied theoretically by Ebrahimi *et al.*⁸⁷ in complexes of cations and anions with 1,3,5-trifluorobenzene. An increase in $^1J_{CF}$ and $^1J_{HC}$ couplings and in the chemical shifts of hydrogen and fluorine accompanied by a decrease in $^1J_{CC}$ has been observed upon cation- π interaction. The changes are in reverse direction in the presence of anion- π interaction.

$^{1,2}J_{CF}$ couplings have been of some help in elucidation of the structure of 1,2-dialkoxy-1,2-difluorinated carbo- and heterocyclic compounds synthesized by Surmont *et al.*⁸⁸ in the reaction of the deoxofluorination of cyclic α,α -dialkoxyketones with morpholinosulfur trifluoride.

The combined analysis of gas-phase electron-diffraction scattering data, rotation constants and dipolar couplings from NMR experiments in liquid crystal solvents has allowed Rankin and co-workers⁸⁹ not only to estimate molecular structures of 1,2- and 1,3-difluorobenzenes with high accuracy, but also the anisotropy components of some of the one-bond C-F and long-range F-F indirect couplings could be deduced directly from the experimental data.

Two papers have been devoted by Yoshifuji *et al.*^{90,91} to NMR studies of 1-*t*-butyl-3-methyl-2,4-bis(2,4,6-tri-*t*-butylphenyl)-1,3-diphosphacyclobutane-2,4-diyl. The authors indicate that the observed couplings between the carbon atom involved in the 1,3-diphosphacyclobutane ring and the adjacent phosphorus atoms, $^1J_{CP}$, are unusually small (3.5 and 11.0 Hz only), which suggests a small s-character contribution in such bonds.

It has been observed by Wróblewski and Drozd⁹² that the spatial arrangement of the nitrogen lone pair and the phosphorous atom has a strong influence on the $^1J_{CP}$ coupling values in *N*-(1-phenylethyl)aziridine-2-phosphonates; for *syn*-periplanar $^1J_{CP} = -215$ Hz, and for *peri*-planar $^1J_{CP} = -182$ Hz have been determined (see Fig. 1).

$^1J_{CRh}$ couplings have been measured by Poulain *et al.*⁹³ for two series of rhodium complexes of 1,3-disubstituted 1,2,3-triazolylidene and their values analysed from the point of view of substituent influence on the metal electronic properties. A small increase of $^1J_{CRh}$ coupling value was observed when the alkyl substituents were replaced by the aryls.

The first observation of $^1J_{CSn}$ coupling across tin-carbon double bond has been reported by Mizuhata and Tokitoh.⁹⁴ $^1J_{CSn}$ of 624 Hz has been found

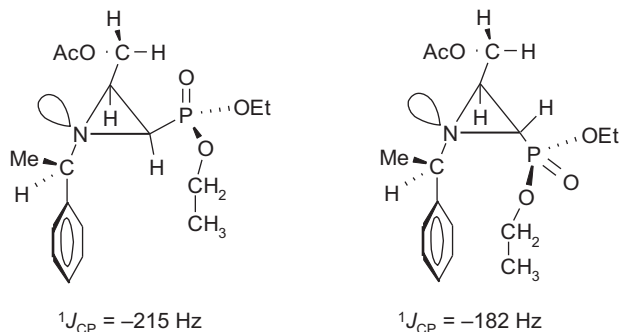


Fig. 1

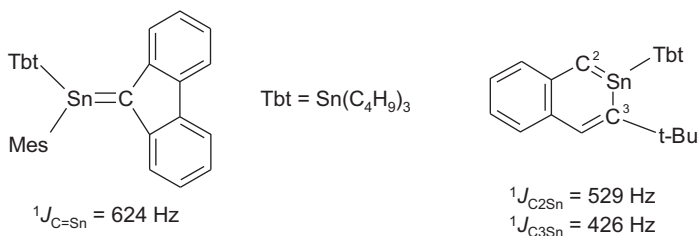


Fig. 2

for 6-stannapentafulvene and ${}^1J_{\text{CSn}}$ of 529 Hz (C2)/426 Hz (C3) for 2-stannanaphthalene (see also Fig. 2).

Ab initio molecular dynamics and relativistic density functional methods have been applied by Zheng and Autschbach⁹⁵ to calculate the one-bond C-Hg couplings for $[\text{Hg}(\text{CN})_2]$ and $[\text{CH}_3\text{HgCl}]$ in solution. The MD average calculated ${}^1J_{\text{CHg}}$ values are 3200 and 1575 Hz, respectively. The experimental coupling values of $[\text{Hg}(\text{CN})_2]$ (in methanol) and $[\text{CH}_3\text{HgCl}]$ (in DMSO) are 3143 Hz and 1674 Hz, respectively.

Himmel *et al.*⁹⁶ have described the strong dependence of ${}^1J_{\text{NP}}$ couplings on the pH value in monophosphorylated histidine.

Solvent effects on ${}^1J_{\text{NPt}}$ coupling in *cis*-diamminedichloroplatinum (II), so-called cisplatin, and its three derivatives have been investigated by Sutter *et al.*,⁹⁷ who used combination of density functional theory, based on *ab initio* molecular dynamics and all-electron relativistic DFT NMR calculations employing the two component relativistic zeroth-order regular approximation. Good agreement with experiment was obtained by the authors when explicit solvent molecules were taken into account.

One-bond heteronuclear spin-spin couplings ${}^1J_{\text{PX}}$ (X = H, O, S, Se, C and N) between the phosphorus atom and axial and equatorial substituents in dioxaphosporinanes have been DFT computed by Pecul *et al.*⁹⁸ at different levels of theory. The experimental values of these couplings for a variety of substituents can be applied to identify different distereoisomers. The DFT calculations confirm the systematic trend observed in experiment, although in almost all cases the theoretical data considerably overestimate the experimentally observed $|{}^1J_{\text{P}_{\text{Xax}}} - {}^1J_{\text{P}_{\text{Xeq}}}|$ difference.

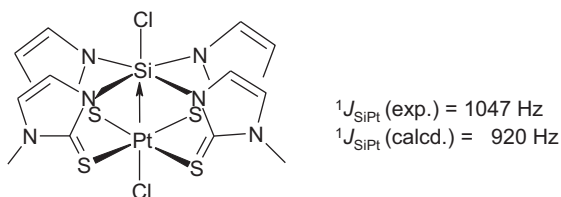


Fig. 3

Two papers have been devoted to inhomogeneous state of the electron system in superconducting oxides $\text{BaPb}_{1-x}\text{Bi}_x\text{O}_3$ ($x \leq 0.21$)⁹⁹ and perovskites $\text{BaPb}_{1-x}\text{Sb}_x\text{O}_3$ ($x \leq 0.33$).¹⁰⁰ The direct estimations of the constants of indirect interaction between the nuclei of nearest neighbours (O-Pb and Pb-Pb atoms) give convincing evidence in favour of the development of a microscopically inhomogeneous state of the electron system in the metallic phase of the oxides.

The origin of metal-induced relativistic effects on three NMR parameters: isotopic chemical shift, chemical shift anisotropy (CSA) parameters and spin-spin couplings in three metallasilatranes (Pt, Pd and Ni) has been studied by Truflandier *et al.*¹⁰¹ (see Fig. 3). In the case of the Pt silatrane reasonable agreement has been observed between the calculated and experimental ${}^1J_{\text{SiPt}}$ coupling values, 1047 and 920 Hz, respectively. The authors indicate that this coupling hints at notable covalent contributions to the Pt-Si bonding, thus raising the question as to the applicability of the 'metallasilatrane' (metalla to sila site trans annular dative bond) model Pt \rightarrow Si.

${}^1J_{\text{PP}}$ couplings of *ca.* 100 Hz have been applied by Dillon *et al.*¹⁰² for identification of a series of some new mixed-valence phosphorus thiohalides obtained from the reaction of phosphorus trihalide PX_3 ($X = \text{Cl}, \text{Br}$ or I) with a thiophosphorus halide $\text{P}(\text{S})\text{Y}_3$ ($Y = \text{Cl}$ or Br) in the presence of zinc powder.

The solid-state ${}^{31}\text{P}$ MAS NMR spectra with ${}^1J_{\text{PCu}}$ couplings of 1330 and 1600 Hz have been measured by Yuan *et al.*¹⁰³ for a novel neutral mixed-valence Cu(I) Cu(II)Cu(I) linear trinuclear copper metallomacrocyclic $[(\text{PPh}_3)_2\text{Cu}]_2[\mu\text{-}o\text{-C}_6\text{H}_4\text{COO}]_2\text{Cu}$. This compound consists of two Cu(I) ions and one Cu(II) ion which are bridged by two salicylate (2^-) ligands, and the external copper (I) atoms are coordinated by four terminal triphenylphosphines.

The donor properties of the pentacyclic phosphane (1*S*,4*R*,4*aS*-, 5*aR*,6*R*,9*S*,9*aS*,10*aR*)-4,6,11,11,12,12-hexamethyl-10-phenyldodecahydro-1,4:6,9-dimethanophenoxaphosphinine (phenop) have been estimated by Edwards *et al.*¹⁰⁴ by the use of ${}^1J_{\text{PSe}}$ and ${}^1J_{\text{PRh}}$ couplings measured for phenopSe and *trans*-[Rh(κ^1 -phenop)] derivatives, respectively. A combined analysis of these absolute J values and the relevant (CO) stretching frequencies in the IR spectra of the series of phenop derivatives allowed the authors to conclude that there is a close electronic analogy between κ^1 -phenop and triphenylphosphane.

${}^1J_{\text{PSe}}$ couplings of *ca.* 710 Hz have been measured by Starosta *et al.*¹⁰⁵ for three aliphatic selenides, $\text{SeP}(\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{NCH}_3)_3$, $\text{SeP}(\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{NCH}_2\text{CH}_3)_3$, and $\text{SeP}(\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{O})_3$, but no correlation has been observed between these couplings and Tolman's electronic parameters.

$^1J_{\text{PRh}}$ couplings of *ca.* 145 Hz have been found by Fabrello *et al.*¹⁰⁶ for a series of rhodium complexes of the type $[\text{Rh}(\text{COD})(\text{ligand})]\text{PF}_6$ where a variety of diphosphines were used as ligands. 1

The one-bond P-Pt couplings have been applied by Rigamonti *et al.*¹⁰⁷ for elucidation of *cis* and *trans* influence in $[\text{PtX}(\text{PPh}_3)_3]^+$ complexes. From the $^1J_{\text{PPt}}$ values of the studied compounds the following series have been established by the authors: $\text{I} > \text{Br} > \text{Cl} > \text{NO}_3 > \text{ONO} > \text{F} > \text{AcO} > \text{NO}_2 > \text{H} > \text{Me}$ (*cis* influence) and $\text{Me} > \text{H} > \text{NO}_2 > \text{AcO} > \text{I} > \text{ONO} > \text{Br} > \text{Cl} > \text{F} > \text{NO}_3$ (*trans* influence). The weights of both influences, relative to those of $\text{X} = \text{Cl}$, were found to be dependent on the charge and nature of the complex. 5 10

It has been suggested by Waddell *et al.*^{108,109} that the variation in the determined crystallographically Pt-P bond lengths observed in synthesized by them complexes, $[\text{Pt}(\text{S}_2\text{N}_2)\{\text{P}(\text{OR})_n\text{R}'_{3-n}\}_2]$ and $[\text{Pt}(\text{SeSN}_2)\{\text{P}(\text{OMe})_n\text{Ph}_{3-n}\}_2]$ ($n = 0-3$),¹⁰⁸ and *cis*- $\text{PtX}_2(\text{P}(\text{OMe})_n\text{Ph}_{3-n})_2$ ($\text{X} = \text{Br}$ or I ; $n = 0-3$)¹⁰⁹ correlates linearly with the decreasing magnitude of $^1J_{\text{PPt}}$ measured for these compounds, and two equations have been proposed, $r_{\text{PPt}} = 2.421 - J/24255$ and $r_{\text{PPt}} = 2.422 - J/21827$.¹⁰⁹ However, no correlation between $^1J_{\text{PPt}}$ couplings and P-Pt bond length has been observed by Mandell *et al.*¹¹⁰ in a series of studied by them $[\text{PtCl}_2(\text{bis}(\text{phosphino})\text{metallocene})]$ complexes. 15 20

$^1J_{\text{Sn}117\text{Sn}119}$ of 9221 Hz has been recorded by Turek *et al.*¹¹¹ for bis- $\{2-(N,N\text{-dimethylaminomethyl})\text{phenyl}\}n\text{-butylchloro}\}$ distannane, $\text{L}^{\text{CN}}n\text{-Bu}(\text{Cl})\text{-Sn-Sn}(\text{Cl})n\text{-BuL}^{\text{CN}}$, which is typical for pentacoordinated tin(IV) compounds containing *n*-Bu and L^{CN} groups (L^{CN} is 2-(*N,N*-dimethylaminomethyl)-phenyl- as chelating ligand). The coupling value is one of the highest values determined up to now; for example, $^1J_{\text{Sn}117\text{Sn}119}$ of 6814 Hz has been reported for the intramolecularly coordinated distannane, $[\text{MeN}(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{-SnCl}]_2$. 25

The magnitude of finite-nucleus-size effects in relativistic density functional computations of indirect NMR nuclear spin-spin couplings such as, for example, $^1J_{\text{HgHg}}$ in the Hg_2^{2+} complex with 15-crown-5 and 18-crown-6 has been estimated by Autschbach.¹¹² The author indicates that finite-nucleus-size effects on couplings involving elements as heavy as Pt, Pb, Hg and most probably also W and 5d elements are by no means negligible. 30 35

5 Two-bond couplings to hydrogen

Using advanced methods of spectral analysis, total quantitative interpretation of the proton spectra of [3.3]paracyclophane has been performed by Szymański and co-workers⁷⁶ in both the static and dynamic regimes yielding all geminal and vicinal couplings for bridge protons of this compound. Moreover, for the first time, complete Arrhenius data has been obtained for the *cis-trans* inter-conversion process in this strained molecule. 40

Comparison of the experimental $^{2,3,4}J_{\text{HH}}$ couplings of 1,6-epoxycarvone and α -epoxypinene with J_{HH} 's calculated for their *cis* and *trans* isomers allowed Queiroz Jr. *et al.*¹¹³ to conclude that both these compounds exist in the *trans* form. Tayler and Levitt¹¹⁴ have measured $^2J_{\text{HH}}$ geminal coupling between almost magnetically equivalent protons of the terminal glycine in 45

the AGG tripeptide. It was possible by applying a new method in which the long living singlet state of these spins is accessed.

The determined by the use of 2D ^1H , ^1H -COSY experiments $^2J_{\text{HH}}$ couplings of 4.5 and 5.2 Hz have been used by Harder *et al.*¹¹⁵ as convincing evidence for the existence of [(para)₃Mg₈H₁₀] in solution (para = *para*-phenylene bridged bis(β -diketiminate). The experimental $^2J_{\text{HH}}$ values strongly disagree with theoretical predictions of Alkorta *et al.*,¹¹⁶ 55–80 Hz in linear MgH₂, but they are only slightly lower than the coupling of 7.45 Hz between bridging and terminal hydrides in the somewhat more covalent B₂H₆.¹¹⁷ However, it is currently unclear whether the hydride-hydride coupling detected by NMR spectroscopy is due to a through-bond or a through-space mechanism. It is also worth mentioning that these are the first experimental observations of $^2J_{\text{HH}}$ couplings in a magnesium hydride.

Geminal and vicinal proton-proton couplings have been reported by Yu *et al.*¹¹⁸ for two guaiane-type sesquiterpenoid glucosides isolated from *Gardenia jasminoides* Ellis, (1*R*,7*R*,10*S*)-11-*O*- β -D-glucopyranosyl-4-guaien-3-one and (1*R*,7*R*,10*S*)-7-hydroxy-11-*O*- β -D-glucopyranosyl-4-guaien-3-one. However, the observed by the authors coupling of 11.5 Hz has been described most obviously erroneously as allylic coupling. A typical value for this type of coupling is of *ca.* 3 Hz, whereas the reported 11.5 Hz value is typical of the geminal couplings, which are additionally of a negative sign.

$^2J_{\text{HH}}$ and $^3J_{\text{HH}}$ couplings have been also found to be a useful tool in characterization of poly(vinyl acetate)-block-poly(methyl acrylate-*co*-methyl methacrylate) block terpolymers.¹¹⁹

An NMR approach based on comparison of experimental and calculated $^3J_{\text{HH}}$ and $^{2,3}J_{\text{HC}}$ couplings which allows to determine the relative configuration of all the possible chiral centres in oxolane rings, has been presented by Napolitano *et al.*¹²⁰ The authors emphasize that the designed methodology can be easily extended to cover other five-membered rings such as cyclopentanes, furanosides and pyrrolidines either directly or with minor modifications.

The difference between $^2J_{\text{H}_3\text{C}_2}$ and $^2J_{\text{H}_2\text{C}_3}$ spin-spin couplings in heterocyclic five- and six-membered rings has been used by Contreras *et al.*¹²¹ as a probe for studying σ -ring currents. The compounds studied were thiophene, selenophene, pyrrole, furan, benzene, pyridine, protonated pyridine and pyridine *N*-oxide.

A very successful method to study the configurational stereochemistry of large acyclic compounds, mostly of natural origin, based on $^2J_{\text{HC}}$, $^3J_{\text{HC}}$ and $^3J_{\text{HH}}$ couplings and therefore called *J*-based configurational analysis (JBCA) was developed by Murata and co-workers¹²² in 1999. An improvement of this method based on DFT calculation of the couplings and comparison of the computed *J* values with the experimental ones has been introduced by Bifulco *et al.*¹²³ Recently, the JBCA approach has been applied by Sugahara *et al.*¹²⁴ to elucidate the structure of a polyoxy linear carbon chain compound, prorocentrol, which was isolated from cultured cells of the dinoflagellate *Prorocentrum hoffmannianum*. The compound possesses 30 hydroxy groups, 1 ketone, and 8 double bonds on the C₆₅-linear carbon chain. The same approach has been applied by Napolitano *et al.*¹²⁵ in their studies on corozalic acid, a new serine/threonine

phosphatase inhibitor structurally related to okadaic acid, obtained from cultures of *Prorocentrum belizeanum*. Also the structure including partial relative configuration of a super-carbon-chain compound, symbiopolyol, isolated from a symbiotic dinoflagellate of the jellyfish *Mastigias papua*, has been established by Hanif *et al.*¹²⁶ mainly on the basis of $^3J_{\text{HH}}$ and $^2J_{\text{HC}}$ couplings and ROESY data. Although a direct comparison between symbiopolyol and lingshuiol B has not been yet completed, the authors suggest that this new compound is the enantiomer of lingshuiol B. Further examples of application of the JBCA method include studies carried out by Pereira *et al.*¹²⁷ on two molluscicidal metabolites, thiopalmyrone and palmyrrolinone, isolated from extracts of Palmyra Atoll environmental assemblages of two cyanobacteria, cf. *Oscillatoria* and *Hormoscilla* spp., which represent new and potent molluscicidal chemotypes against *Biomphalaria glabrata*. Hetero- and homonuclear J-based analysis combined with molecular modelling has been applied by Paterson *et al.*¹²⁸ in order to determine the structure of leiodermatolide, a structurally unique polyketide-derived macrolide of potentially antimetabolic properties, isolated from the deep water marine sponge *Leiodermatium* sp. (see Fig. 4)

Murata's approach has been extensively applied by Igarashi *et al.*¹²⁹ in order to establish the structure of a new spirotetronate-class polyketide, maklamicin, comprising a *trans*-decalin unit and a tetrone acid moiety spiro-linked with a cyclohexane ring which was isolated from the culture extract of an endophytic actinomycete of the genus *Micromonospora*. The $^{2,3}J_{\text{HC}}$ and $^3J_{\text{HH}}$ couplings have been used in elucidation of the structure of gephyronic acid from *Archangium gephyra* by Nicoals *et al.*¹³⁰

An interesting paper demonstrating that computational chemistry can provide a great help in the structure elucidation of natural products has been published by Bagno.¹³¹ The compound studied was the sponge metabolite arsenicin A, whose NMR spectrum is very simple and provides little information on the structure of this compound. It is enough to mention that only two proton signals at 1.37 and 2.42 ppm with coupling of 13.8 Hz has been observed in it. In spite of some difficulties the author was able to prove that out of 12 possible structures the correct one is that shown in Fig. 5.

Two- and three-bond H-C couplings have been applied by Ai *et al.*¹³² to establish the structures of five new pyrimido[5,4-*c*]quinoline-4(3*H*)-one derivatives.

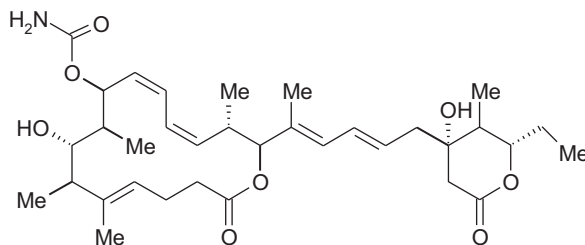


Fig. 4

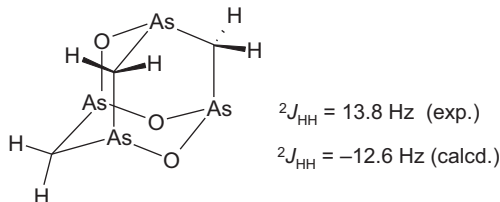


Fig. 5

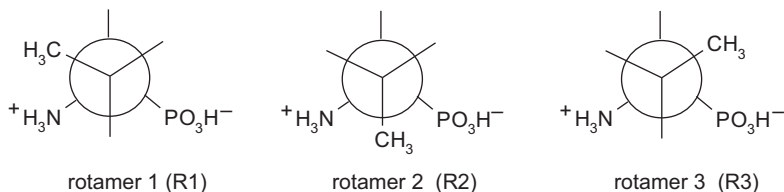


Fig. 6

$^2J_{\text{HSi}}$ couplings of *ca.* 35 Hz have been observed by Calimano and Don Tilley¹³³ in three new rhodium complexes of general formula, (PNP^{Ph})RhH(SiR₃) where R₃ denotes Ph₃, Et₃ or Ph₂Cl, and PNP^{Ph} = [N(2-PPh₂-4-Me-C₆H₃)₂]⁻, whereas the analogous iridium complexes exhibit couplings less than 10 Hz.

Conformational analysis of α -aminopropanephosphonic acid by the use of ^1H chemical shifts and long-range couplings in solution and by X-ray analysis in the solid state has been carried out by Bashall *et al.*¹³⁴ Especially useful information has been derived from $^2J_{\text{HH}}$ and $^2J_{\text{CP}}$ couplings measured at different pD. The authors also performed a detailed analysis of vicinal proton-proton and proton-phosphorous couplings combined with theoretical calculations. The results obtained allowed the conclusion that the staggered anticonformation R1 (see Fig. 6) is the dominant rotational isomer in the studied betaine, H₃N⁺CH₂EtPO₃H⁻.

A significant increase has been observed by Gholivand *et al.*¹³⁵ for $^2J_{\text{HP}}$, $^3J_{\text{HP}}$ and $^6J_{\text{HP}}$ couplings in the spectra of the monodentate *O*-donor P(O)(PhNH)(NC₄H₈)₂ ligand upon formation of its high-coordinated lanthanum(III) complexes. Two different couplings, $^2J_{\text{HN}}$ of 7.3 and 4.4 Hz, have been found by the same group of authors¹³⁶ for two samples of a novel phosphoramidate 3-C₅H₄C(O)NHP(O)(N(C₄H₉)₂)₂ prepared from two polymorphic forms of the compound. This difference, quite strikingly but obviously erroneously, has been assigned to the fact that the two samples of the compound for which the spectra have been measured, have been obtained from two polymorphic forms of the compound. However, contrary to the authors opinion, polymorphism cannot be a likely cause for the difference between the spectra recorded in solution.

A combined experimental and theoretical approach has been presented by K  v  r *et al.*¹³⁷ to measure and evaluate geminal and vicinal H-Se couplings in the parent methyl β -D-selenoglucoside and its tetramethyl and tetraacetyl derivatives for their use in conformational analysis of selenoglycosides. Good agreement has been observed between the experimental

and calculated ${}^2J_{\text{HSe}}$ and ${}^3J_{\text{HSe}}$ coupling values. Furthermore the calculations performed at the SOPPA level indicate that ${}^2J_{\text{HSe}}$ coupling can be very useful in conformational studies, being very sensitive to the torsion angle around the C1-Se bond in a H1-C1-Se-CH₃ moiety. Interestingly, the dependence has been found to be much higher for the two-bond couplings than for the three-bonds ones.

${}^2J_{\text{HSe}}$ and ${}^1J_{\text{CSe}}$ couplings have been determined by Wrackmeyer and co-workers¹³⁸ to characterize 4,5-[1,2-dicarba-*closo*-dodecaborano(12)]-1,3-diselenacyclopentane and some products of its rearrangement.

6 Two-bond couplings not involving hydrogen

An increase with the increasing B-O-B bond angle and B-B distance has been observed for two-bond boron-boron couplings, ${}^2J_{\text{BB}}$, calculated by Barrow *et al.*¹³⁹ by the use of the GIPAW approach for lithium diborate, metaborate and triborate. The calculated ${}^2J_{\text{BB}}$ values are rather small (0.95, 1.20 and 2.65 Hz in lithium diborate), which provided explanation why zero crossing due to J modulation has not been observed by the authors in their J solid state NMR correlation experiments carried out for half-integer quadrupolar nuclei.

It has been demonstrated by Deev *et al.*¹⁴⁰ that selective ${}^{15}\text{N}$ -labelling and analysis of the long-range C-N couplings, mostly those across two, ${}^2J_{\text{CN}}$, and three bonds, ${}^3J_{\text{CN}}$, provide an effective tool for studying the structure and azide-tetrazole equilibrium in a series of tetrazolo[1,5-*b*][1,2,4]triazines and tetrazolo[1,5-*a*]pyrimidines. The authors stressed that the selective labelling can be particularly useful in those cases in which conventional methods based on H-C and C-C couplings are ineffective due to low proton and carbon densities. ${}^2J_{\text{CN}}$ couplings have been used by Lyčka *et al.*¹⁴¹ to assign Z and E isomers in ${}^{15}\text{N}$ -labelled 5-oxo-2-phenyl-4-(2-phenylhydrazono)-4,5-dihydro-1*H*-pyrrole-3-carboxylate.

A full set of ${}^1J_{\text{CF}}$ and ${}^2J_{\text{CF}}$ couplings has been determined by Baker *et al.*¹⁴² for 2H,2H,3H,3H-perfluoronanoic acid, $\text{CF}_3(\text{CF}_2)_5\text{CH}_2\text{CH}_2\text{COOH}$. The couplings across one bond are of *ca.* 270 Hz and those across two bonds of *ca.* 30 Hz.

Good agreement has been observed by Wrackmeyer *et al.*¹⁴³ between determined and DFT calculated for 2,2-dimethyl-5-ethyl-3-(1-ethylpropylidenyl)-1-oxa-2-sila-5-boracyclopentane long-range C-Si couplings, while the calculated ${}^1J_{\text{CSi}}$ values are by *ca.* 15% smaller than the experimental data.

A cationic gold carbonyl complex, $[(\text{Mes}_3\text{P})\text{Au}(\text{CO})][\text{SbF}_6]$, has been synthesized and characterized by Dias *et al.*¹⁴⁴ by the use of various techniques including NMR spectroscopy. The ${}^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of this complex in CD_2Cl_2 collected at room temperature or at -10°C showed a doublet centred at 128.6 ppm with ${}^2J_{\text{CP}} = 115$ Hz, which can be assigned to the ${}^{31}\text{P}$ -coupled carbon resonance of the gold(I)-bound CO moiety.

A study on the dependence of NMR ${}^{31}\text{P}$ shielding tensor and ${}^2J_{\text{CP}}$ coupling on the solvation of nucleic acid phosphate by Mg^{2+} and water has been conducted by Benda *et al.*¹⁴⁵ by the use of methods of bioinformatic structural analyses of crystallographic data and DFT B3LYP calculations

of NMR parameters. The calculations showed that the dynamically averaged ^{31}P chemical shift and $^2J_{\text{C}5'\text{P}}$ coupling magnitude decrease by 2–9.5 ppm and by 0.2–1.8 Hz, respectively, upon Mg^{2+} coordination.

Ab initio EOM CCSD calculations have been performed by Del Bene *et al.*¹⁴⁶ to study N-F couplings in mono-, di- and trifluoroazines. They have found that $^2J_{\text{NF}}$ and $^4J_{\text{NF}}$ couplings (with one exception) are negative, whereas those across three bonds are in most cases positive. The calculated couplings are in good agreement with the experimental values, if available.

A systematic study utilizing homonuclear (^{27}Al , ^{31}P) and heteronuclear ($\{^{31}\text{P}\}^{27}\text{Al}$ and $\{^{27}\text{Al}\}^{31}\text{P}$) spin echo as well as $\{^{27}\text{Al}\}^{31}\text{P}$ refocused INEPT experiments have been performed by Xue¹⁴⁷ on AlPO_4 berlinite in order to gain a better understanding of the J modulation behaviour involving half-integer quadrupolar nuclei for solid materials with framework structure. In general, all experiments yielded consistently $^2J_{\text{AlP}} = 25$ Hz, but more accurate values have been obtained from analysis of the J modulation on the coherence of ^{27}Al (spins coupled to spin-1/2 nuclei).

New perspectives for application of the recently developed by Picard and Mauri PAW/GIPAW approach for first-principles calculations of NMR parameters using periodic boundary conditions have been considered by Bonhomme *et al.*¹⁴⁸ (GIPAW denotes the gauge including projected augmented wave protocol). It included, among others, the calculation of J coupling tensors of $^2J_{\text{SiOP}}$ couplings in inorganic solid performed for some selected samples, *i.e.* $\text{Si}_5\text{O}(\text{PO}_4)_6$ and SiP_2O_7 polymorphs. The authors conclude that in the near future the PAW approach for J coupling tensors including the J_{aniso} and J_{anti} parts will be used as a routine method for accurate calculations. The antisymmetric components of σ and J tensors can be considered as new spectroscopic data for chemists, although measuring these antisymmetric components remains an open question.

The analysis of complexation process of Be^{2+} with *cyclo*-tri- μ -imido-triphosphate, $c\text{-P}_3\text{O}_6(\text{NH}_3)_2$, performed by Maki *et al.*¹⁴⁹ excluded the possibility of direct coordination of Be^{2+} to the imino nitrogen atoms of the ligand molecule. Instead, simultaneous formation of M_2L and ML_2 type complexes, in addition to ML type complexes have been revealed, for which $^2J_{\text{PP}}$ couplings of *ca.* 10 Hz and typical splitting patterns of the ^{31}P signals have been observed.

$^2J_{\text{PP}}$ coupling of 292 Hz has been observed by Ainscough *et al.*¹⁵⁰ in the CP MAS spectra of the dihydrate $[\text{Au}(\text{PBN}_3)_2]\text{Cl} \cdot 2\text{H}_2\text{O}$, which indicates that the cations in this complex are noncentrosymmetric with two inequivalent phosphorus atoms. The coupling value is similar to that observed in other analogous systems. A considerable $^2J_{\text{PP}}$ coupling has been observed by Grünberg *et al.*¹⁵¹ in the 2D MAS NMR spectrum of the Wilkinson catalyst $[\text{RhCl}(\text{PPh}_3)_3]$. This coupling disappears upon immobilization of the catalyst inside the pores of ammine functionalized mesoporous silica material SBA-3, and has been observed neither in off-magic-angle-spinning experiments nor in slow-spinning MAS experiments. This led the authors to the conclusion that two triphenylphosphine ligands are replaced and the catalyst is bonded to the silica surface through two linker molecules.

A family of capped hexatomic copper clusters of general structure, $[\text{Cu}_6\text{L}_2\text{X}_2]$ ($\text{L} = \text{C}(\text{Ph}_2\text{P} = \text{NSiMe}_3)_2^{2-}$; $\text{X} = \text{CH}_3, \text{Cl}, \text{Br}, \text{I}, \text{O}-t\text{-Bu}$) with a

unique nonsymmetric boat-type geometry supported by a pair of pincer methane-diide ligands which geminally bind to two copper atoms has been synthesized by Ma *et al.*¹⁵² Phosphorus NMR spectra of all these copper clusters in solution show an AB coupling pattern with slightly different ³¹P chemical shifts and ²J_{PP} of *ca.* 60 Hz indicating nearly chemically identical but magnetically inequivalent P atoms within the pincer ligand.

Seleno-aunofin, (1-seleno-β-D-glucopyranose-2,3,4,6-tetraacetato-Se)-(triethylphosphine)gold(I), the orally active antiarthritic gold drug in clinical use has been synthesized and characterized spectroscopically by Hill *et al.*¹⁵³ including NMR. According to the authors, the absence of ²J_{PSe} coupling in the ³¹P and ⁷⁷Se spectra of this compound may be due to dynamic processes occurring in solution or because the ²J_{PSe} couplings are smaller than the observed bandwidths. They also indicate that coupling across gold has been observed in only three cases, (2,4,6-tri-*t*-butylphenylselenide)-(triphenylphosphine)gold (I), ²J_{PSe} = 41 Hz; [Ph₃PAu{SeC(NH₂)₂}]Cl, ²J_{PSe} = -13 Hz and [(μ-dppm)(AuSeC(NH₂)₂)₂]Cl₂ ²J_{PSe} = -13 Hz.

²J_{PY} couplings of *ca.* 10 Hz have been determined by Fernández *et al.*¹⁵⁴ for four yttrium complexes obtained in the reaction of hydrated yttrium (III) nitrate with triphenylphosphine oxide. It is worth noting that in order to identify these compounds, correlation experiments between Y and P nuclei through scalar coupling using ³¹P detection have been applied by the authors.

7 Three-bond hydrogen-hydrogen couplings

Castillo *et al.*¹⁵⁵ have proposed a fast algorithm for the simulation of NMR spectra of large spin systems. The algorithm contains a procedure that efficiently splits the spin system. The performance of 250 different computational protocols, which included combinations of density functional, basis sets and methods, has been evaluated by Bally and Rablen¹⁵⁶ on a set of 165 well-established experimental proton-proton couplings *J*_{HH} from 65 molecules. The authors came to the conclusion that calculations of only Fermi contact term actually yield more accurate predictions than calculations which include all four terms that contribute to *J*_{HH}. Most probably the sum of these other terms cannot be calculated with sufficient accuracy to improve the overall result.

Biased molecular dynamics has been used by van Gunsteren and co-workers¹⁵⁷ to satisfy ³*J*_{HH} NMR structural constraints measured for the peptide, GCN4(1-16). Hegefelfd *et al.*¹⁵⁸ have used experimentally measured ³*J*_{HαHN} couplings to validate the calculated helical population in Ac-(Ala)₅-NH₂. The ³*J*_{HαHN} couplings monitoring has been used by Mitternacht *et al.*¹⁵⁹ in Monte Carlo simulations of conformations of Aβ42, and by Sgourakis *et al.*¹⁶⁰ in unbiased molecular dynamics simulations of this peptide in water. In the latter case the ¹*D*_{HN} couplings were also used.

The consistency of the calculated and measured values of different ³*J*_{HH} couplings has been checked by Zhu *et al.*¹⁶¹ in their studies on the molecular mechanical model for acyclic β-amino acids.

³*J*_{HαHN} couplings have been applied by Grdadolnik *et al.*¹⁶² to assign β and P_{II} bands in the amide III region in Raman and IR spectra of 19

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

Name	<i>a</i>	<i>b</i>	Reference
β -azidoalanine and its dipeptide	2, 3	1, 3	166
Ac-Nle-c[DHfRWK], with <i>N</i> -methylated H, R,W, and K	7	14	167
four Igl ² -vasopressin analogues	9	4 to 6	168
four Dpa ² -vasopressin analogues	9	6	169
Dpg-14, a designed tetrapeptide containing two Dpg residues	14	12	170
GCN4p ₁₆₋₃₁	16	15	157, 171
BTK-2 from <i>Mesobuthus tamulus</i>	32	ca. 40	172

^a the number of amino acid residues.
^b the total number of vicinal backbone and side chain proton-proton couplings measured.

dipeptides. Oh *et al.*¹⁶³ have used reference β and P_{II} $^3J_{\text{H}\alpha\text{H}\text{N}}$ couplings in the studies of conformers of trialanine in water.

Tripathi *et al.*¹⁶⁴ have assigned the structures of cyclodepsipeptides, lagunamides A and B from *Lyngbya majuscula*, with the aid of $^3J_{\text{HH}}$. Wüthrich and co-workers¹⁶⁵ have applied $^3J_{\text{H}\alpha\text{H}\text{N}}$ couplings in detailed comparison of the NMR and X-ray structures of the protein NP_247299.1.

In Table 1 are listed polypeptide chains for which vicinal proton-proton couplings have been used in their structure calculations.

A torsion angle-based Monte Carlo searching routine for carbohydrates which contains a module to calculate proton-proton couplings has been developed by Dowd *et al.*¹⁷³

The structures of a series of 20-keto pregnane glucosides have been determined by García¹⁷⁴ with the help of vicinal proton-proton couplings. Vicinal and geminal proton-proton couplings have been applied by Ghiasi *et al.*¹⁷⁵ in conformational studies on the exocyclic hydroxymethyl group in the disaccharide rutinose in rutin (vitamin P) in solution. The effect of solvent and counterions on the structure and $^3J_{\text{HH}}$ couplings in heparin disaccharide has been studied by Hricovíni.¹⁷⁶ DFT computed couplings agree well with the experimental ones published in the literature and indicate that the population of the $^1\text{C}_4$ chair form of the 2-O-sulfated iduronic acid residue increases in the presence of Ca^{2+} ions compared to the presence of Na^+ ions. Sattelle *et al.*¹⁷⁷ have used proton-proton vicinal couplings to validate the results of molecular dynamic calculations carried out for idourenic acid and a series of related monosaccharides.

The DFT computed by Hricovíniová¹⁷⁸ proton-proton couplings for the Amadori ketose 1-deoxy-1-amino-D-gluco-heptulose were found to be comparable with the experimentally obtained couplings and were in agreement with the $^4\text{C}_1$ pyranose form in aqueous solution at room temperature. Lowary and co-workers¹⁷⁹ have developed a new Karplus-type relationship for $^3J_{\text{H4H5R}}$ and $^3J_{\text{H4H5S}}$ in β -D-arabinofuranoside ring and applied it to di- and trisaccharide fragments of mycolyl-arabinogalactan.¹⁸⁰

The complete assignment of ^1H , ^{13}C and ^{15}N NMR spectra including proton-proton couplings has been reported by Casati *et al.*¹⁸¹ for a large set of adenosine derivatives with different amino substituents at C^6 -position.

In Table 2 are given several examples of nucleosides and carbohydrates whose structures have been obtained with the help of $^3J_{\text{HH}}$ couplings.

Table 2 Nucleosides and carbohydrates for which $^3J_{\text{HH}}$ couplings have been used as a structural parameter.

Name	Reference
a series of adducts to 2'-deoxyguanosine	182
2'-spiroisoxazolidine thymidine analog	183
series of eight bioactive derivatives of NAD	184
a series of <i>aep</i> -PNA monomers	185
carbohydrates:	
a series of 2-naphthyl β -D-xylopyranosides	186
a series of idourenic acid related monosaccharides	177
carbasugar bioisosteres of α -L-iduronic acid and its methyl glycoside	187
a series of glycolipids	180
glucosyl- and maltosyl- cellobiose	188
Trimannoside	189
LNF-1, the pentasaccharide	190
a series of acylated pentasaccharides from mycobacterial arabinogalactan	191

$^3J_{\text{HH}}$ couplings and interring ROESY cross-peaks have been used by Gaggelli *et al.*¹⁹² to derive dihedral angles in the unusual aminoglycoside antibiotic hygromycin B and subsequently to define its overall average structure using a conformational search routine in Hyperchem. It is worth noting that hygromycin B presents a peculiar chemical structure, characterized by two sugar rings joined *via* a spiro connection.

An analysis of vicinal proton-proton couplings has been carried out by Jabrane *et al.*¹⁹³ for glaucosides A-C, three saikosaponins isolated from *Atriplex glauca* L.var.*ifiniensis* (Caball) Maire, and by Noté *et al.*¹⁹⁴ for three new acacic acid-type saponins, coriariosides C, D and E isolated from the roots of *Albizia coriaria*.

A strong dependence of the NMR spectrum of 1,4-dideoxy-1,4-imino-4-C-methyl-D-arabinitol on the pH of solution has been observed by da Cruz *et al.*;¹⁹⁵ vicinal proton-proton couplings found for the free base are considerably smaller than those determined for its salt.

The conformational landscape of dictyostatin, a complex, flexible polyketide macrolide that reveals potent microtubule-polymerization activity has been explored by Jogalekar *et al.*¹⁹⁶ by the use of extensive force-field-based conformational searches combined with geometric parameters derived from solution NMR data including $^3J_{\text{HH}}$ couplings. The results illustrate the molecule's flexibility and exclude the previously suggested in the literature¹⁹⁷ dominant solution conformation.

^1H and ^{13}C NMR data including $^3J_{\text{HH}}$ couplings have been applied by Wang *et al.*¹⁹⁸ in structure elucidation of seven protolimonoids isolated from the stem barks of *Aphanamixis grandifolia*, by Hostettmann and co-workers¹⁹⁹ to characterize two new triterpenoids, $3\beta,19\beta$ -dihydroxylup-12,20(29)-diene-28-oic acid and $3\beta,19\beta$ -dihydroxylup-12-en-28-oic acid, isolated from the stems of *Paragonia pyramidata* (Bignoniaceae) and by Kildahl-Andersen *et al.*²⁰⁰ in order to get evidence for boat conformation in D ring of a series of 2α - and 3β -methyl substituted $17\alpha(H),21\alpha(H)$ -hopanes.

An analysis of vicinal proton-proton couplings has been performed by Hussiain *et al.*²⁰¹ to establish the relative configuration of asymmetric centres of cichorin A isolated from *Cichorium intybus* and by Molina *et al.*²⁰² in conformational studies on a sesquiterpene lactone, 1 β -hydroxy-4-oxo-11 β H-4-noreudesman-6,12-olide. 1

Proton-proton couplings have been extensively applied by Cardoso *et al.*²⁰³ in the conformational studies on an unprecedented neolignan chimarrchinin isolated from the leaves of *Chimarrhis turbinata*, a Rubiaceae plant species. The relative configuration of neolignan skeleton and its conformation have been evaluated by the authors using RM1 semiempirical calculations and proton-proton couplings. 5

One unusual aromatic monacolin analogue, monacophenyl, has been isolated by Liu *et al.*²⁰⁴ from *Monascus purpureus*-fermented rice and its structure unambiguously established by 1D and 2D NMR techniques as (4 β ,6 α)-6-((2 α -2,6-dimethyl-5,6,7,8-tetrahydronaphtalen-1-yl)ethyl)-4-hydroxytetrahydro-2H-pyran-2-one. The stereochemistry of the 4-hydroxytetrahydro-2H-pyran-2-one moiety in this compound, which has two chiral centres, has been determined by the analysis of ³J_{HH} and ⁴J_{HH} couplings and NOESY data. 10

Jiang *et al.*²⁰⁵ have elucidated the structure of nine speciosins, isoprenylated cyclohexanoids from the basidiomycete *Hexagonia specia*. Configurational and conformational analysis of a series of palmarumycins BG1-BG7 and of preussomerin BG1 has been carried out by Cai *et al.*²⁰⁶ on the basis of ³J_{HH} couplings. 15

The conformational properties of epothilone A, antimitotic polyketid produced from the myxobacterium *Sorangium cellulosum*, have been analyzed in detail by Rusińska-Rozzak *et al.*²⁰⁷ by the use of electronic structure calculations to better understand the effect of intramolecular hydrogen bonding on the conformational energies of this highly potent anticancer molecule. The authors conclude that the general trend of the conformer populations of epothilone A obtained from conformational energies resembles those derived from experiments and can be used to interpret the values of vicinal proton-proton couplings determined for this compound. 20

Enigmazole A and its two congeners representing a new structural family of marine phosphomacrolides with an unusual array of structural motifs and functional groups have been isolated by Oku *et al.*²⁰⁸ from the Papua New Guinea collection of the marine sponge *Cinachyrella enigmatica*. The structure of these compounds has been determined by a combination of spectroscopic analyses including proton-proton and proton-carbon couplings, and a series of microscale chemical derivatization studies. The compounds are comprised of an 18-membered phosphamacrolide that contains an embedded exomethylene-substituted tetrahydropyran ring and an acyclic portion that spans an embedded oxazole moiety. Additionally, ²J_{CP} coupling of 4.7 Hz observed on the C5 carbon signal in the spectrum of enigmazole A has been useful in deducing of a phosphate group attachment to this carbon. 25

An analysis of ³J_{HH} couplings between allylic proton and adjacent protons performed by Roshan and Rashidi-Ranjbar²⁰⁹ has confirmed that there is a marked difference in conformational behaviour of the two 30

diastereomers of 1,1-dichloro-7b-((Z)-8-chloro-6,7-dihydro-7-alkoxy-5H-benzo[7]annulen-9-yl)-1a,2,3,7b-tetrahydro-1H-cyclopropa[a]naphthalene. It has been found that the substituent in position 7 in isomer 1aR*/S*,7bR*/S* adopts only position *exo*(e'), while in isomer 1aS*/R*,7bS*/R* both *exo*(e') and *endo*(a') forms are present.

Vicinal couplings $^3J_{\text{HH}}$ have been applied by Ramachandran *et al.*²¹⁰ to prove that synthesised by them variously substituted 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one semicarbazones and corresponding to them thiosemicarbazones adopt a twin-chain conformation with equatorial orientation of the aryl groups.

A set of vicinal proton-proton couplings has been measured by Dobado *et al.*²¹¹ for a large series of regioisomeric pairs of tricyclic hydroquinones, analogues of antitumor 9,10-dihydroxy-4,4-dimethyl-5,8-dihydroanthracen-1(4H)-one. The presence of a seven membered intramolecular hydrogen bond ring has been suggested for 5-hydroxymethyl derivatives for which $^3J_{\text{HH}}$ coupling of the methylene protons has been observed. This coupling does not appear in the spectra of the 8-hydroxymethyl isomers.

Vicinal and geminal proton-proton couplings have been measured and analyzed by Manimekalai and Balamurugan²¹² for some monocyclic and bicyclic aryloacetonitriles which, in combination with DFT optimized geometries, allowed the authors to elucidate the conformations of these compounds. Thus, for example, it has been established that (*cis*-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-ylidene)(phenyl)acetonitrile and (*cis*-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-ylidene)(*p*-chlorophenyl)acetonitrile adopt twin chair conformations in solution. Vicinal proton-proton couplings have been also applied by Joseph *et al.*²¹³ to establish the stereochemistry of some novel heterocyclic *endo*-7-halo-3-oxo-2-azabicyclo[4.1.0]heptanes obtained by the reduction of 7-gem-dihalo-3-oxo-2-azabicyclo[4.1.0]heptanes.

An assignment of the relative configurations of 3-alkoxy-6,7-epoxy-2-oxabicyclo[3.3.0]octane has been made by Aav *et al.*²¹⁴ on the basis of 75 vicinal $^3J_{\text{HH}}$ couplings. The authors have also proposed a procedure for testing the prediction capability of the applied methods for distinguishing the related diastereomers.

The stereochemistry and relative configurations of (1*R*,2*S*,6*R*)-2-amino-6-hydroxycyclooctanecarboxylic and (1*R*,2*S*,3*R*,4*S*)-2-amino-5,6-dihydroxycyclooctanecarboxylic acids have been established by Palkó *et al.*²¹⁵ by 1D and 2D NMR spectroscopy based on 2D NOE cross-peaks, $^3J_{\text{HH}}$ couplings and X-ray crystallography.

An analysis of the ^1H and ^{13}C NMR data which included $^3J_{\text{HH}}$ couplings performed by Pihlaja *et al.*²¹⁶ for 1-oxo-1,3-dithiolane and its six monomethylsubstituted derivatives has allowed the authors to conclude that most of these compounds adopt two $\text{S}^1=\text{O}$ type envelopes, the $\text{S}=\text{O}_{\text{ax}}$ envelope greatly prevailing. *Cis*-4-methyl-1-oxo-1,3-dithiolane represents a special case exhibiting four almost evenly populated forms, *i.e.* both two closely related $\text{S}=\text{O}_{\text{ax}}$ as well as $\text{S}=\text{O}_{\text{eq}}$ forms [$\text{S}^1=\text{O}$ and C^4 envelopes, respectively]. For all these compounds also $^2J_{\text{HH}}$ couplings have been reported. $^3J_{\text{HH}}$ couplings have been also of some help in the conformational analysis of cyclic six-membered ring sulfoxides and sulfones performed by Dračinský *et al.*^{217,218}

The Gibbs conformational energies ΔG° of substituents at C⁵ in the 1,3-dioxane ring have been determined by Kuramshina and Kuznetsov²¹⁹ on the basis of experimental and theoretical vicinal couplings. Three other papers published by this group have been devoted to conformational analysis of 2-methyl-5-nitro-1,3,2-dioxaborinane,²²⁰ 2-methyl-5-alkyl- and 5-aryl-1,3,2-dioxaborinanes,²²¹ and 2,4-dialkyl-1,3,2-dioxaborinanes.²²²

It has been indicated by Liu *et al.*²²³ that there is the need for caution when ³*J*_{HH} couplings are used for estimation of the relative configuration in bicyclic triazole and related systems such as studied by them (4*S*,5*R*,6*R*)-6-[(4'-methoxyphenoxy)methyl]-3-dodecyl-5,6-dihydro-4*H*-pyrrolo[1,2-*c*]-[1,2,3]triazol-4,5-diyl acetate. In this compound two very close ³*J*_{HH} couplings have been found for *cis*(H4H5) and *trans*(H5H6) arranged hydrogen atoms, 5.8 and 4.4 Hz, respectively while in its 4*S*,5*S*,6*S* isomer where both hydrogen pairs are *trans* arranged ³*J*_{HH} couplings of *ca.* 1.5 Hz have been found (Fig. 7). This apparent discrepancy has been explained by the authors in terms of the two different conformations adopted by these compounds.

A set of ¹H and ¹³C NMR data including vicinal H-H couplings have been reported by Besada *et al.*²²⁴ for a series of pyridazin-3(2*H*)-one derivatives, and by Franco *et al.*²²⁵ for a series of new 2-aminocarbohydrate-1,4-naphthoquinone derivatives synthesized under influence of ultrasonic irradiation. ³*J*_{HH} couplings have been applied by Montalvo-González *et al.*²²⁶ in their studies on the conformations and relative configurations of 20 exocyclic amines derived from *N*-(1-phenylethyl)cyclohexanamine, *N*-[1-(naphthalen-2-yl)ethyl]cyclohexanamine, *N*-(diphenylmethyl)cyclohexanamine and *N*-(propan-2-yl)cyclohexanamine. On the basis of vicinal proton-proton couplings, the chair conformation with equatorial orientation of the substituents at C-2, C-3, C-6 and N has been proposed by Dindulkar *et al.*²²⁷ for a series of thirteen 1-benzyl-3-alkyl-2,6-diarylpiperidin-4-ones. The influence of the structure of phenyl acridine-9-carboxylates and 10-methyl-9-(phenoxy-carbonyl)acridinium trifluoromethanesulphonates on chemical shifts and proton-proton couplings has been studied by Krzymiński *et al.*²²⁸ The influence of solvent polarity on ¹H NMR parameters including proton-proton couplings of strychnine has been analysed by Pan *et al.*²²⁹

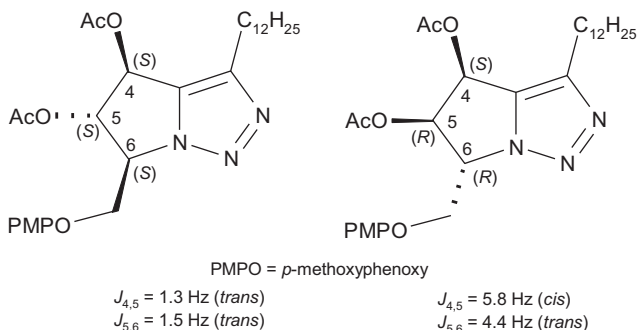


Fig. 7

A complete set of NMR data including proton-proton couplings has been reported by Jo *et al.*²³⁰ for a series of methoxylated *cis* and *trans*-stilbenes as well as 1,2-diphenylethanes as the model compounds for interpretation of the spectra of naturally occurring polyphenols such as, for example, resveratrol isolated from many natural sources including grapes, mulberries, eucalyptus or lilies.

An interesting paper by Stevenson²³¹ has been devoted to proton NMR spectra of 1,2-disubstituted ethanes bearing commonly encountered organic functional groups such as sulfones, phosphonium salts and some large protecting groups. It has been shown by the author that due to magnetic non-equivalence of chemically equivalent nuclei and due to preference for the particular conformer these spectra are essentially second-order even in such cases when higher magnetic fields are used to record them. Thus, for example, aryl *n*-propyl sulfones and *n*-propyl triphenylphosphonium bromide adopt an *anti*-conformation, which extenuates the difference in vicinal couplings, and additionally the substituents cause diminishing in the geminal couplings. As a result, the proton spectra of these compounds are perpetually second-order and should be analysed as such.

Proton-proton couplings and chemical shifts have been calculated by Atieh *et al.*²³² for three prostate polyamines, putrescine, spermidine and spermine, and the Boltzmann weighted averages of chemical shifts and spin-spin couplings over a large number of stable conformers have been evaluated for each molecule.

De Graaf *et al.*²³³ have published a procedure that allows quantification of 29 compounds in the rat brain extracts. The procedure requires complete prior knowledge of chemical shifts and scalar couplings of these compounds.

Vicinal proton-proton couplings have been calculated by Sánchez-Mendoza and Hernández-Trujillo²³⁴ for pyrrole, furan, thiophene and 15 related heteroaromatic compounds by the use of Khon-Sham approximation. Comparison of the calculated couplings with their available experimental values has shown that this approach is appropriate for obtaining reliable couplings for this type of molecules.

³*J*_{HH} couplings have been applied by Mamo *et al.*²³⁵ to characterize a series of Ru(II) and Os(II) complexes with new bidentate 2-pyridylquinoline ligands, 4-*p*-methoxyphenyl-6-bromo-2-(2'-pyridyl)quinoline and 4-*p*-hydroxyphenyl-6-bromo-2-(2'-pyridyl)-quinoline.

³*J*_{HH} couplings have been applied by Chevry *et al.*²³⁶ to study conformational behaviour of Pt and Pd complexes with the triazole chelators in the presence of guanosine. The authors conclude that the changes observed for these new complexes are very similar to those already observed for *cis*-platin.

A simple experiment suited for the undergraduated organic laboratory in which a Fisher esterification reaction product has been identified, among others via 2D NMR techniques, has been described by Clausen.²³⁷ It also incorporates molecular modelling arguments and the Karplus relationship between torsional angles and vicinal couplings in the assignment of ¹H NMR signals to specific diastereotopic hydrogens.

Effects of scalar spin-spin interactions on the nuclear magnetic relaxation dispersion (NMRD) of coupled multispin systems have been analysed by

Korchak *et al.*²³⁸ The authors have emphasised that with the increasing complexity of spin systems the intramolecular spin-spin couplings reveal pronounced influence on the NMRD of protons, and neglecting these effects may lead to misinterpretation of the NMRD curves and significant errors in determining the correlation times of molecular motion. As examples the proton-proton coupling systems in imidazole-5-carboxylic acid, aspartic acid and N-acetylhistidine have been analysed as representing two-, three and five-spin models, respectively.

8 Three-bond couplings to hydrogen

Aliev and Courtier-Murias²³⁹ have verified 12 different force fields against $^3J_{\text{HC}}$ and $^3J_{\text{HH}}$ couplings measured for flexible tetrapeptide, GPGG. The structures of tumescenamides A and B, two cyclic depsipeptides from *Streptomyces tumescens* YM23-260, have been solved by Motohashi *et al.*²⁴⁰ using $^3J_{\text{HC}}$ and $^3J_{\text{HH}}$ couplings.

Malkina and co-workers²⁴¹ have measured $^{1,3}J_{\text{HC}}$ and $^2J_{\text{CN}}$ couplings for *N*-methylated adenine isomers and calculated the couplings values at various levels of theory. They found the predominance of the FC contributions to the values of all these heteronuclear long-range couplings.

Conformations of spermine in ATP complexes have been traced with $^3J_{\text{HC}}$ and $^3J_{\text{HH}}$ couplings by Maruyoshi *et al.*²⁴²

The nonplanarity of nucleic acid bases and its effect on the phase shift of the Karplus equations for $^3J_{\text{H1}'\text{-C8}/6}$ and $^3J_{\text{H1}'\text{-C4}/2}$ couplings across the glycosidic bond have been discussed in details by Vokáčová *et al.*²⁴³

An extension of the CHARMM force field to enable the modelling of glycosidic linkages in polysaccharides containing furanose sugars has been presented by Raman *et al.*²⁴⁴ The force-field validation included comparison with experimental $^3J_{\text{HC}}$ and $^3J_{\text{HH}}$ couplings.

Other examples of carbohydrates whose structures were solved with the aid of 3J heteronuclear couplings are listed in Table 3.

$^3J_{\text{HC}}$ and $^3J_{\text{HH}}$ couplings have been extensively used by Gening *et al.*²⁴⁹ in conformational studies of a series of homologous cyclic oligo-(1 → 6)-β-D-glucosamines consisting of two to seven residues and representing a new type of functionalized cyclic oligosaccharides.

Table 3 Carbohydrates for which heteronuclear vicinal couplings have been used as a structural parameter.

Name	^a	Reference
carbasugar bioisosteres of α-L-iduronic acid and its methyl glycoside	$^{2,3}J_{\text{HC}}$	187
methyl β-maltoside and methyl α- and β-cellobioside	$^3J_{\text{HC}}, ^3J_{\text{CC}}$	245
Trimannoside	$^3J_{\text{HC}}$	189
α-L-Rhap-(1 → 2)[α-L-Rhap-(1 → 3)]-α-L-Rhap-Ome	$^{2,3}J_{\text{HC}}, ^{1,3}J_{\text{CC}}$	246
fragments of O-antigen of <i>Shigella boydii</i> type 6	$^{1,3}J_{\text{HC}}$	247
LNF-1, the pentasaccharide	$^3J_{\text{HC}}$	190
a series of four S ₂ βCD	$^{1,3}J_{\text{HC}}$	248

^a type of vicinal heteronuclear couplings measured.

A simple methodology based on analysis of experimental long-range proton-carbon couplings and DFT predicted product formation has been devised by Leutbecher *et al.*²⁵⁰ for rapid assignment of ring-proton deficient polycyclic benzofuran regioisomers. The compounds studied are the products of laccase-catalyzed oxidation of substituted catechols followed by reaction with 4-hydroxy-pyrone/benzopyrone.

Ardá *et al.*²⁵¹ have described a strategy called by them temperature-dependent *J*-based configurational analysis, which allows to solve *gauche*(+)/*gauche*(−) equilibria from a *threo* or *erythro* configuration in flexible acyclic systems by observing the temperature tendency toward a unique rotamer. The analysis rests on the changes in corresponding $^3J_{\text{HC}}$ and $^3J_{\text{HH}}$ couplings.

$^3J_{\text{HC}}$ couplings provided crucial information on the configuration of a series of highly functionalized 1-heteroaryl-1,3-butadienes, *i.e.* (2*E*,3*E*)-dimethyl-2-[(dimethylamino)methylene]-3-(2-substituted)succinates, synthesized by Bezenšek *et al.*²⁵² via cycloaddition of dimethyl acetylenedicarboxylate to (*E*)-3-dimethylamino-1-heteroaryl-prop-2-en-1-ones. ^1H , ^{13}C and ^{15}N NMR chemical shifts have been measured by Petrova *et al.*²⁵³ in compounds with a strong intramolecular $\text{NH}\cdots\text{O}=\text{C}$ hydrogen bond. The positive values of isotope effects on carbons forming H-chelate cycle together with the values of the couplings $^3J_{\text{HNCH}}$ and $^1J_{\text{HN}}$ and quantum chemical calculation data indicate that the proton transfer does not occur in these *trans* fixed CHNH enaminones, and the position of the equilibrium does not change upon the deuteration of NH hydrogen.

It is known that ^{14}N in choline is coupled to all three groups of protons: to the CH_2O methylene protons with $^3J_{\text{H}14\text{N}}=2.7$ Hz, to the methyl protons with $^2J_{\text{H}14\text{N}}=0.6$ Hz and to the NH_2 methylene protons with $^2J_{\text{H}14\text{N}}=0.2$ Hz.^{254,255} Based on these properties ^1H - ^{14}N HSQC technique has been introduced by Mao *et al.*²⁵⁶ which allows the detection of choline and its derivatives in solutions.

^{14}N and ^{15}N NMR data has been reported by Klenov *et al.*²⁵⁷ for *E* and *Z* isomers of 1-methoxy-2-(4-nitrophenyl)diazene[1- ^{15}N] 1-oxide and for *N*-methyl-*N*-[nitro- ^{15}N]-*O*-(4-nitrophenyl)hydroksylamine; for all three compounds $^3J_{\text{HN}}$ of ca. 4 Hz has been observed.

Vicinal $^3J_{\text{HF}}$ couplings which follow a Karplus-like relationship have been applied by Ampt *et al.*²⁵⁸ to support the investigation of the stereochemistry of substituents with respect to the main steroid scaffold in several fluorine substituted steroids.

All regioisomeric and diastereomeric methyl *anti*- and *syn*-2,3-fluorohydroxyalkanoates with C_{16} , C_{18} and C_{20} chains have been synthesized in distereomerically and enatiomerically pure form by Husstedt *et al.*²⁵⁹ The stereochemical analysis of these compounds has been performed mainly by the use of experimental and DFT/B3LYP calculated $^3J_{\text{HF}}$ couplings. For two of these compounds, methyl (2*S*,3*R*)-3-fluoro-2-hydroxyhexadecanoate and methyl (2*S*,3*S*)-3-fluoro-2-hydroxyoctadecanoate, the temperature dependence of $^3J_{\text{HF}}$ couplings has been measured. Comparison of the experimental $^3J_{\text{HF}}$ values with those calculated for the relevant model compounds indicated that the first of these compounds has the *anti*-configuration while the other is *syn* arranged.

$^2J_{\text{HSi}}$ and $^3J_{\text{HSi}}$ couplings have been collected by Ambati and Rankin²⁶⁰ for some bridged silanes. Analysing the variation of $^3J_{\text{HSi}}$ and $^3J_{\text{HH}}$ couplings in the bridging group of bis(trihydroxysilalyethane) with the corresponding Si-C-C-H and H-C-C-H dihedral angles, respectively, the authors derived the Karplus equations for both these couplings:

$$^3J_{\text{HSi}} = -14.95 \cos^2 \varphi + 3.1 \cos \varphi - 0.4 \text{ where } \varphi \text{ represents Si-C-C-Si dihedral angle}$$

and

$$^3J_{\text{HH}} = 14.9 \cos^2 \varphi + 0.8 \cos \varphi + 0.5 \text{ where } \varphi \text{ represents the H-C-C-H angle}$$

Dihedral dependence of $^2J_{\text{HP}}$ and $^3J_{\text{HP}}$ couplings in trivinylphosphine and three trivinylphosphine chalcogenides has been studied by Fedorov *et al.*²⁶¹ Satisfactory agreement has been observed between the experimental J values and the data calculated at the second-order polarization propagator approach/aug-cc-pVTZ-J level of theory.

$^3J_{\text{HP}} = 7$ Hz has been detected by Bogado *et al.*²⁶² in the spectrum of a neutral carbene complex observed *in situ* in a methylene chloride solution during the reaction between $[\{\text{RuCl}(\text{dppb})_2\}-(\mu\text{-Cl})_2]$ (dppb = 1,4-bis(diphenylphosphine)butane) and ethyldiazoacetate, confirming its structure (see Fig. 8).

A combined theoretical and experimental study on conformational analysis and diastereotopic assignments in a series of selenium-containing heterocycles by the use of geminal and vicinal H-Se couplings has been performed by Rusakov *et al.*²⁶³ The authors draw attention to the fact that $^3J_{\text{HSe}}$'s should be applied with proper caution since in some cases the values of *cisoidal* couplings are close or even greater than those of *transoidal* ones. Typical ranges covered by these couplings are 4–11 Hz (*cis*) and 6–17 Hz (*trans*). It means that conclusive assignment at the double bond can be made only through a combination of experimental and theoretical data.

Very large $^3J_{\text{HSn}}$ couplings have been observed by Kuate *et al.*²⁶⁴ in the spectra of the first examples of structurally characterised cationic organotin(IV)-substituted crown ether complexes; $^3J_{\text{HSn}} = 377$ Hz in $[\text{PhSnCH}_2([16]\text{crown-5})][\text{ClO}_4]_2$ has been found and $^3J_{\text{HSn}} = 470$ Hz in $[\text{HOSnCH}_2([16]\text{crown-5})][\text{ClO}_4]_2$ and $[\text{HOSnCH}_2([16]\text{crown-5})][\text{CF}_3\text{SO}_3]_2$.

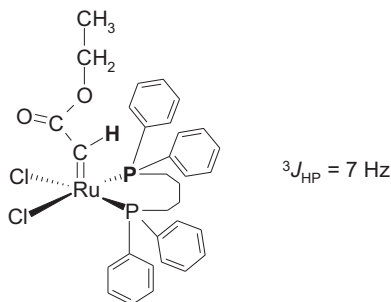


Fig. 8

9 Three-bond couplings not involving hydrogen

Kay and co-workers²⁶⁵ have correlated the value of $^{13}\text{C}(\delta_1)$ chemical shift of isoleucines with the value of the corresponding $^3J_{\text{C}\alpha\text{C}\delta_1}$ coupling. This allows to obtain conformation of Ile side chain χ_2 angle directly from the Ile $^{13}\text{C}(\delta_1)$ chemical shift. The same group²⁶⁶ has expanded this approach to valine side chains in proteins and calibrated methyl $^{13}\text{C}(\gamma_1/\gamma_2)$ chemical shifts against a set of four corresponding $^3J_{\text{CC}}$ and $^3J_{\text{CN}}$ couplings. This allows to obtain conformation of Val side chain χ_1 angle directly from the Val $^{13}\text{C}(\gamma_1/\gamma_2)$ chemical shift. An analogous idea has been applied for methionine by Butterfoss *et al.*²⁶⁷ where methyl $^{13}\text{C}(\epsilon)$ chemical shifts have been related to χ_3 angle *via* correlation with $^3J_{\text{CSCC}}$ couplings.

Såwén *et al.*²⁶⁸ have proposed reparametrization of $^3J_{\text{CC}}$ and $^3J_{\text{HC}}$ Karplus type relationships for the glycosidic angles. This new parametrization called JCX/SU09 allows to obtain better conformation population distributions of flexible sugars.

Serianni and co-workers²⁶⁹ have continued their conformational studies of saccharides. Recently, eight Karplus relationships have been determined by them for the use in conformational analysis of saccharide *N*-acetyl side-chains in solution by NMR spectroscopy. Six vicinal *J* couplings sensitive to the C2-N2 torsion angle were parametrized: $^3J_{\text{H}_2,\text{NH}}$, $^3J_{\text{H}_2,\text{CO}}$, $^3J_{\text{C}_1,\text{NH}}$, $^3J_{\text{C}_3,\text{NH}}$, $^3J_{\text{H}_2,\text{NH}}$, $^3J_{\text{C}_1,\text{CO}}$, and $^3J_{\text{C}_3,\text{CO}}$. Two vicinal couplings, $^3J_{\text{NH},\text{CH}_3}$ and $^3J_{\text{C}_2,\text{CH}_3}$, sensitive to amide bond conformation (*cis* and *trans* amide) were also investigated. The usefulness of these equations has been illustrated in an analysis of experimental *J*-couplings measured within the *N*-acetyl side chain of a ^{13}C -labelled methyl *N*-acetyl- α -D-glucosamide.

$^{1-3}J_{\text{CF}}$ couplings have been reported by Casano *et al.*²⁷⁰ for some new acetamido and aminoflavonoid derivatives.

NMR conformational analysis by the use of $^3J_{\text{CF}}$, $^3J_{\text{HF}}$ and $^3J_{\text{HC}}$ couplings has been performed by Paul *et al.*²⁷¹ in order to establish which conformation of a novel fluorinated gold(I) *N*-heterocyclic carbene complex prevails in solution. The results obtained have clearly indicated that rotamer I (see Fig. 9) is the dominant one ($\varphi_{\text{NCCF}} = 60^\circ$).

The vicinal $^3J_{\text{CCCP}}$, $^3J_{\text{HCCP}}$, $^3J_{\text{H}_2\text{H}_3\text{eq}}$ and $^3J_{\text{H}_1'\text{H}_2}$ couplings of 12.6–14.3, 4.7–5.1, 3.3–3.4 and 3.0–3.9 Hz, respectively, have been measured by Piotrowska *et al.*²⁷² for 2*R*,5*R*,6*R*,1'*R* diastereomer of dialkyl(*R*)- and (*S*)-hydroxy-[(2*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl]methylphosphonates; $^3J_{\text{CCCP}}$ smaller than 10 Hz and $^3J_{\text{H}_1'\text{H}_2}$ of *ca.* 6 Hz have been

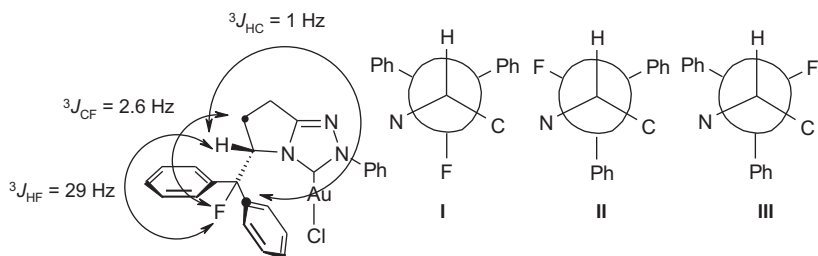


Fig. 9

found for their 2*R*,5*R*,6*R*,1'*S* counterparts. These results led the authors to the conclusion that the 2*R*,5*R*,6*R*,1'*R* diastereomers exist in the form of almost one rotamer only, while in the other group of the compounds the 1-hydroxymethylphosphonate fragment freely rotates around the C'-C2 bond.

Two series of phosphoric triamides^{273,274} have been obtained by Gholivand and co-workers and characterized by the use of NMR parameters including $^3J_{CP}$ and $^3J_{HP}$ couplings. For *N*-2,4-dichlorobenzoyl-dihydroxy phosphoramidate $^6J_{HP}$ coupling of 1.3 Hz has been observed.²⁷³

Conformational dependence of $^3J_{C-X-C-Sn}$ (where X = N, O, S) vicinal couplings has been studied theoretically in details by Casella *et al.*²⁷⁵ The Karplus type behaviour has been confirmed for the couplings with the use of ZORA relativistic and non-relativistic DFT protocols.

$^1J_{PPt} = 1910$ Hz, $^3J_{PPt} = 33$ Hz and $^2J_{PP} = 51$ Hz couplings have been measured by Rashidi *et al.*²⁷⁶ for $[Me_2Pt(\mu-SMe_2)(\mu-dppm)PtMe_2]$ complex and $^1J_{PPt} = 1928$ Hz, $^3J_{PPt} = 14$ Hz and $^2J_{PP} = 62$ Hz for the synthesized from it phthalazine derivative, $[Me_2Pt(\mu-phthalazine)(\mu-dppm)PtMe_2]$ (dppm = bis(diphenylphosphino)methane). These results have been used as a proof that the structures established crystallographically for these complexes are maintained in solution and that potential isomers with metal-metal complexes are not present.

10 Couplings over more than three bonds and through space

The 'W' type $^4J_{HH}$ couplings have been used by Nicolaou *et al.*²⁷⁷ as key spectroscopic evidence in solving the configuration of synthetic and natural vannusal B. This type of couplings has been also applied by Molinski *et al.*⁵⁵ in confirmation of the structures of a series of didemnins.

It has been shown by Kleinmeier and Gschwind²⁷⁸ that $^4J_{HH}$ couplings between individual acylguanidinium NH resonances observed in the spectra of monoalkylated acylguanidines allow the unequivocal chemical shift and conformational analysis of protonated monoalkylated acylguanidinium moieties. The observation of these long-range couplings is limited to an all-*trans* pathway for the magnetisation transfer, and they do not appear in the spectrum if at least one fragment is *cis* arranged. In order to obtain a genuine assignment of conformations in solution the measurements should be carried out in temperatures in which slow conformational exchange prevails.

An extensive use of $^2J_{HH}$, $^3J_{HH}$ and $^4J_{HH}$ couplings has been made by Dastgir *et al.*²⁷⁹ to characterize two imidazolium salts, 7,9-bis(2,4,6-trimethylphenyl)-6b,9a-dihydroacenaphtho[1,2-*d*]-imidazolium tetrafluorobate and 7,9-bis(2,6-diisopropylphenyl)-6b,9a-dihydroacenaphtho[1,2-*d*]-imidazolium tetrafluorobate, and the Pd(II) complexes synthesized from the corresponding free carbenes. For one of these complexes also variable-temperature measurements have been performed. It is worth noting that in 7,9-bis(2,4,6-trimethylphenyl)-6b,9a-dihydroacenaphtho[1,2-*d*]-imidazolium tetrafluorobate compound a bifurcate hydrogen bond has been observed between tetrafluorobate anions and the central imidazolium proton (N-CH-N).

A set of proton-proton couplings has been reported by Yuvaraj and Pandiarajan²⁸⁰ for a series of 3-aryl-5*r*-aryl-6*t*-carbethoxycyclohex-2-enones. This included allylic couplings across four bonds, which have been observed between H-2 protons and H-4*t* only. Another paper published by these authors has been devoted to some 3,5-[bis(*E*)-thienylmethylene]piperidin-4-ones.²⁸¹

ⁿJ_{HN} (n = 2, 3, 4) couplings including their signs have been collected for a series of typical molecules by Klika²⁸² in his paper devoted to direct detection of non-proton-bearing ¹⁵N nuclei by long-range couplings using polarization transfer.

The experimentally measured remote ⁴J_{HF} couplings have been used by Jaune *et al.*²⁸³ as arguments in discussion on the secondary structure of β -peptides containing β^3 hAla(α F) and β^3 hAla(α F₂).

The analysis of the second-order AA'BB'X spectra of the aromatic protons in 4-fluoroaniline and its two derivatives *N*⁴-(4'-fluorophenyl)succinamic acid and *N*⁴-(4'-fluorophenyl)-3,3-difluorosuccinamic acid has been carried out by Risley *et al.*²⁸⁴ by the use of WINDNMR-Pro, yielding new full sets of *J*_{HH} and *J*_{HF} couplings including those across three, four and five bonds. The authors emphasize that their results confirm that second-order analyses of an AA'BB'X system are required for derivatives of 4-fluoroaniline, rather than first order analyses that were used in previous reports.

Two papers devoted to application of through space proton-fluorine couplings, ^{5,6}J_{HF}, in comparative analysis of conformational equilibrium in fluorine-substituted aryl vinyl sulphides²⁸⁵ and selenides²⁸⁶ have been published by Afonin.

A set of eight couplings including those across four and more bonds between the amine (or aromatic) protons and the phosphorus atoms have been extracted by Dastychova *et al.*²⁸⁷ from the higher order spectra of *gem*-2,2-diamino-4,4,6,6-tetraphenoxy-1,3,5-*cyclo*-triaz- λ^5 -phosphorine, *gem*-P₃N₃(OC₆H₅)₄(NH₂)₂. Petrová *et al.*²⁸⁸ have assigned the configuration of individual epimers in the mixtures of 5'-C-phosphonates by measurement of ⁴J_{HP} and ³J_{HH} couplings in the corresponding 3'-deoxy derivatives.

It has been shown by Alemany *et al.*²⁸⁹ that the ¹³C and ¹⁹F NMR spectra of rather simple compounds such as 1,1,1,3,3,3-hexafluoropropyl alcohol, (CF₃)₂CHOH and its triflate, (CF₃)₂CHOSO₂CF₃, due to the presence of a relatively large four-bond F-F coupling, ⁴J_{FF} = 9.2 Hz, in the (¹³CF₃)-¹²CH-(¹²CF₃)-containing isotopomer are much more complex than expected and reveal higher order effects even at very high magnetic field strengths. The spectrum of triflate exhibits further complexity because of the presence of two different types of CF₃ groups exhibiting ⁶J_{FF} in any of the isotopomers and the chemical shift differences in hertz between the various ¹⁹F signals in the two different ¹³CF₃-containing isotopomers.

A detailed analysis of long-range F-F couplings across four and five bonds carried out by Ghiviriga *et al.*²⁹⁰ for a series of monosubstituted perfluoroparacyclophanes provided very important structural information and conformational preferences in these compounds. The authors also indicate that the couplings across four bonds are transmitted to a great extent through space.

Unusual J_{FF} couplings of -11.2 and -3.6 Hz have been DFT calculated by Griffin *et al.*²⁹¹ for a fluorinated hydroxyl-silicate, clinohumite $4\text{Mg}_2\text{SiO}_4 \cdot \text{Mg}(\text{OD}_{1-x}\text{F}_x)_2$ ($x = 0.5$). The calculated J values are in reasonable agreement with the splitting observed in the MAS NMR spectra of this silicate, 18.5 and 3.2 Hz, respectively. This is a rather unusual observation since the fluorines in the structure are connected by F-Mg-F or F-Mg-O-Mg-F linkages, and the Mg-F interaction is expected to be primarily ionic in character. Therefore the authors suggest that the through space mechanism should be invoked to explain the couplings observed and calculated.

Unusually large through-space phosphorous-phosphorous couplings of 223 – 244 Hz have been observed by Maji *et al.*²⁹² in the spectra of three unsymmetrical $25,26;27,28$ -dibridged *para-tert*-butylcalix[4]arene bisphosphites obtained by the reaction of $25,26$ -bridged *para-tert*-butylcalix[4]arene bisphosphite with $(\text{R}'\text{O})\text{PCl}_2$ where $\text{R}' = 2,4$ -*t*-Bu₂-C₆H₃, $2,6$ -*i*-Pr₂-C₆H₃ or $(1R,2S,5R)$ -(-)-menthyl.

A weak long-range homonuclear ${}^4J_{\text{PP}}$ (P-O-P-O-P) coupling has been observed by Xue¹⁴⁷ for AlPO_4 berlinite from ${}^{31}\text{P}$ homonuclear spin echo and INADEQUATE experiments.

New examples of long-range couplings between two phosphorus atoms have been reported by Doskocz *et al.*²⁹³: ${}^7J_{\text{PP}}$ coupling of *ca.* 6 Hz, has been found in the spectra of 1-[(diethoxyphosphoryl)butyryloxymethyl]-4-[(diethoxyphosphoryl)hydroxymethyl]benzene and 1,4-bis[phosphorylhydroxymethyl]benzene, and ${}^6J_{\text{PP}}$ of *ca.* 3 Hz in the spectrum of tetraethyl phenylene-1,3-bis(hydroxymethylphosphonate).

${}^4J_{\text{SeSe}}$ coupling of 329.7 Hz has been determined by Guzyr *et al.*²⁹⁴ for 1-(phenylselenyl)-8-(2-methyl-1,2-dicarba-*closo*-carboranyl-selenyl)naphthalene. The reported coupling is in agreement with the already published data for 1-methylselenyl-8-arylselenyl-naphthalene derivatives.

11 Couplings through hydrogen bonds

A paper by Siuda and Sadlej²⁹⁵ has been devoted to DFT calculations of NMR parameters for methane molecule trapped in clathrate hydrates including calculations of the intermolecular hydrogen-bond transmitted ${}^1J_{\text{HO}}$ couplings which are substantial. The increase of their values is connected with the elongation of the intramolecular H-O bond and the shortening of the intermolecular O \cdots H distance.

${}^1J_{\text{HH}}$ and ${}^2J_{\text{HN}}$ couplings transmitted through Ir-H_b \cdots H_a-N dihydrogen bonds have been calculated by Olejniczak and Pecul²⁹⁶ for three six-coordinated complexes of iridium selected as models of heavy metal complexes. The calculated ${}^1J_{\text{HH}}$ value is of the range 1.6 – 2.9 Hz, depending on the model but with $r_{\text{HH}} < 2.0$ Å, while the experimental values are 2 – 5 Hz for similar distances. The calculated ${}^2J_{\text{HN}}$ coupling ranges from approximately -5.1 Hz for dihydrogen bonds of 2 Å up to -7.1 Hz for very short ones, *i.e.* 1.6 Å. The authors conclude that the dihydrogen-bond transmitted couplings and the shielding tensor of the H_a atom are the most sensitive probes of the H_a-H_b distance.

Experimentally measured $^3\text{h}J_{\text{C}'\text{N}}$ couplings and RDCs have been applied to cross-validate calculated structural data by Lange *et al.*²⁹⁷ in their studies on MM force fields in the submicrosecond timescale.

The $^2\text{h}J_{\text{NN}}$ coupling of 10.2 Hz has been measured by Claramunt *et al.*²⁹⁸ in powdered tetrachlorogallate salt of pyridinium solvated by pyridine. This is the first example of an intermolecular $^2\text{h}J_{\text{NN}}$ coupling for a cationic species measured in the solid state.

Very interesting results concerning spin-spin coupling across the hydrogen bond have been published by Reddy *et al.*,²⁹⁹ who investigated weak molecular interactions in three isomeric fluorinated benzanilides using ^{19}F and ^1H NMR (with ^{14}N decoupling) spectroscopic techniques in combination with DFT calculations. Simultaneous presence of through space nuclear spin-spin couplings $^1\text{h}J_{\text{N-H}\cdots\text{F}}$ of diverse strengths has been detected as a function of site specific substitution of fluorine atoms within the basic identical molecular framework. Thus $^1\text{h}J_{\text{N-H}\cdots\text{F}}$ of 3.6 Hz has been measured in isomer **1**, $^1\text{h}J_{\text{N-H}\cdots\text{F}}$ of 16.0 Hz in isomer **2**, and two couplings of 3.7 and 17.7 Hz have been determined for isomer **3** (see Fig. 10).

Compounds for which couplings through hydrogen bonds were used in structural analysis are listed in Table 4.

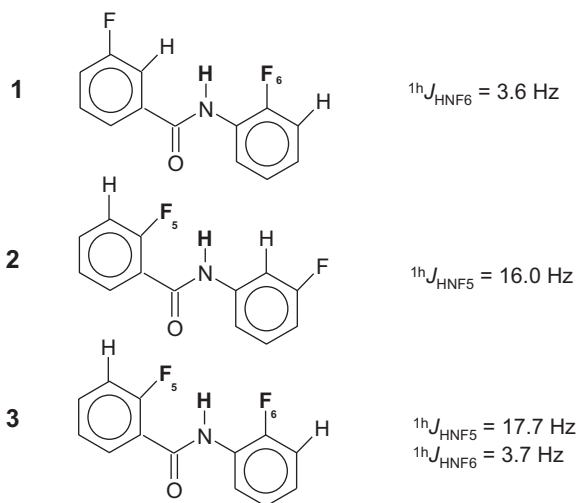


Fig. 10

Table 4 Compounds for which scalar couplings have been measured through the hydrogen bond.

Name	<i>a</i>	<i>b</i>	<i>c</i>	Reference
ubiquitin, lysine side chains	$\text{N-H}\cdots\text{O}=\text{C}$	$^3\text{h}J_{\text{CN}}$	2	300
E4B U-box	$\text{N-H}\cdots\text{O}=\text{C}$	$^3\text{h}J_{\text{CN}}$	19	301
the A730 loop of the <i>Neurospora</i> VS ribozyme	$\text{N-H}\cdots\text{N}$	$^2\text{h}J_{\text{NN}}$	10	302

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

12 Residual dipolar couplings

It has been shown on numerous examples that residual dipolar couplings have already become an invaluable tool in determination of the conformation and the configuration of small to medium-sized organic molecules. An elegant example of a new application of this parameter for structure identification of unknown small molecules has been published by Kummerlöwe *et al.*³⁰³ The molecule studied by them was one of the products obtained by reacting the azide containing 1,5-enyne in the presence of electrophilic iodine sources. Using classic methods the authors were able to identify solely some fragments of the unknown compound and only measurement of RDC's and their analysis allowed them to establish the structure of a previously unidentified tricyclic aziridine shown in Fig. 11.

An improved approach has been presented by Chassé *et al.*³⁰⁴ for the analysis of ¹H double-quantum NMR build-up data, mainly for the determination of residual dipolar couplings and distributions thereof in polymer gels and elastomers, yielding information on crosslink density and potential spatial inhomogeneities. The authors introduced a new generic build-up function, for use as component fitting function in linear superpositions, or as kernel function in fast Tikhonov regularization. This method yields faithful coupling distributions, as limitations on the fitting limit are in this case lifted.

A combined experimental and theoretical approach to establish the absolute configuration of (–)-dibromopalau' amine, the most prominent member of a whole family of marine natural products, the pyrrole-imidazole alkaloids, has been presented by Reinscheid *et al.*³⁰⁵ At first, the authors determined conformational ensembles and the relative configuration of palau'amine by the use of ³J_{HH} and ³J_{HC} couplings, ROE's and residual dipolar couplings which furthermore allowed them to calculate, using DFT method, electronic circular dichroism (ECD) and optical rotator dispersion (ORD) spectra and compare them to experimental. As a result, the absolute configuration of natural (–)-dibromopalau' amine was determined as 6*S*, 10*R*, 11*S*, 12*S*, 16*R*, 17*S*, 18*S*, 20*S*.

A general strategy has been designed by Emsley and co-workers³⁰⁶ for obtaining F-F and C-F residual dipolar couplings in perfluorocarbons from the NMR spectroscopy in liquid crystalline samples. A two-dimensional Fluorine Detected Local Field(FDLF) NMR experiment has been demonstrated on a sample of perfluoropropyl iodide dissolved in the nematic solvent ZLI1132. A simple map of the heteronuclear coupling network has been obtained by the authors in the indirect dimension for each resolved site of the carbon spectrum.

Kummerlöwe *et al.*³⁰⁷ have introduced variable angle NMR spectroscopy (VA NMR). In this approach the scaling of alignment for mechanically

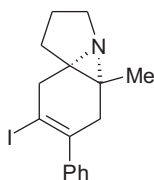


Fig. 11

stretched polymer gels is produced by varying the angle of the director of alignment relative to the static magnetic field. This allows measuring RDCs and RCSA with a single sample. 1

The properties of a new alignment medium, cellulose nanocrystals, have been tested by Denisov *et al.*³⁰⁸ who have shown that the medium permits measurements of RDCs of proteins in different conditions. Using hen egg-white lysozyme Higman *et al.*³⁰⁹ have shown that the charge and shape of the protein molecule may limit the number of independent alignments of a protein, which makes measurement of eight independent sets of RDCs impossible. 5 10

A new approach based on the best global agreement between experimental and calculated RDCs from a structural template has been introduced by Wang *et al.*³¹⁰ for protein backbone resonance assignment.

Salmon *et al.*³¹¹ have proposed a description of a molecular representation of intrinsically disordered proteins using $^1D_{\text{HN}}$ and $^1D_{\text{H}\alpha\text{C}\alpha}$ couplings combined with paramagnetic relaxation enhancements and with an efficient ensemble selection algorithm (ASTEROIDS). A method that includes the Bayesian weighting formalism has been presented by Fisher *et al.*³¹² for modelling the conformational properties of IDPs. Subsequently this approach has been validated against RDCs and SAXS data. Rao *et al.*³¹³ have proposed a combinatorial approach for characterization of partially folded proteins with the use of RDCs and pulsed EPR data. Bertini and co-workers³¹⁴ have introduced the concept of *maximum occurrence*, *i.e.* the maximum percent of time that flexible proteins can spend in any given conformation and tested it using RDCs and other data measured for the flexible two-domain calmodulin. 15 20 25

Berlin *et al.*³¹⁵ have presented PATIDOCK, a molecular RDCs guided docking method that relies on the experimentally derived RDCs. Residual dipolar couplings have been helpful in the studies of ‘substrate-induced’ motions in *Limulus* arginine kinase carried out by Niu *et al.*³¹⁶ 30

Robustelli *et al.*³¹⁷ have introduced a procedure to determine the structures of proteins by incorporating RDCs (or other NMR data) as structural restraints in MD simulations. RDCs have been imposed by using a flat-bottom harmonic potential with a width determined by the magnitude of the experimental error. 35

It has been shown by Godoy-Ruiz *et al.*³¹⁸ that $^1D_{\text{HC}}$ ’s measured for the alanine methyl groups in $\{\text{U-}^2\text{H; Ala}^\beta\text{-}^{13}\text{CHD}_2\}$ -labelled malate synthase G (73 Ala in ca. 700 residues) are good probes of molecular structure and dynamics in such a large system.

$^1D_{\text{HN}}$ ’s have been employed by Shealy *et al.*³¹⁹ and by Park *et al.*³²⁰ in the simultaneous structure and dynamics studies of membrane-bound Pfl coat protein; by Walther *et al.*³²¹ in the studies of membrane alignment of the pore-forming component TatA_d; by Zhang *et al.*³²² in the studies of the impact of peptide binding to the second PDZ domain of PTP1E; by Lim *et al.*³²³ for characterization of amyloidogenic unfolded states of proteins; 40 45
by Ascitutto *et al.*³²⁴ for characterization of the open states of cytochrome P450_{cam} and by Kim *et al.*³²⁵ to study the solution structure of the Z β domain of human DAI and its binding to B- and Z-DNAs. In the latter case $^1D_{\text{CC}}$ couplings have been also used.

Further examples of proteins whose structures were solved or refined using RDCs have been collected in Table 5.

The magnitude of internal motions in LNDFH I, the complex human milk hexasaccharide lacto-N-di-fuco hexose-I has been estimated by Ganguly *et al.*³⁴⁰ using $^nD_{HH}$ and $^1D_{HC}$ couplings.

Nucleic acids and carbohydrates for which RDCs have been measured and applied in structural analysis are listed in Table 6.

Table 5 Proteins for which the solution structure has been calculated with RDCs.

Name	<i>a</i>	<i>b</i>	<i>c</i>	Reference
a rigid peptidic scaffold	2	11	$^1D_{HC}$	326
PLN, monomeric phospholamban	52	101	$^1D_{HN}$, $^1D_{CC}$, $^1D_{CN}$	327
p7, a membrane protein	63	56	$^1D_{HN}$	328
holo-GmACP3 from <i>Geobacter metallireducens</i>	86	113	$^1D_{HN}$	329
E4B U-box	100	63	$^1D_{HN}$	301
the Zif268(335-432)/DNA complex	98 + 12bp	ca. 70	$^1D_{HN}$	330
the AML1-ETO NHR3/PKA(RII α) complex	38 + 2x50	76	$^1D_{HN}$, $^1D_{CC}$, $^1D_{CN}$, $^2D_{HC}$	331
POTRA4-5 tandem	161	132	$^1D_{HN}$	332
the CaM(Ca ²⁺)/CaMKIp complex	148 + 22	115	$^1D_{HN}$	333
the SCaM4/BCA1(19-47) complex	149 + 25	124	$^1D_{HN}$	334
the Oct1/DNA complex	163 + 24bp	85	$^1D_{HN}$	335
the yeast myr-Arf1/GTP complex	181 + 1nt	219	$^1D_{HC}$, $^1D_{HN}$, $^1D_{CN}$	336
the Rna15/Hrp1/RNA complex	84 + 167 + 13nt	201	$^1D_{HC}$, $^1D_{HN}$	337
H189Q EI, the non-phosphorylatable mutant	575x2	40x2	$^1D_{HN}$	338
EI, free enzyme I from <i>E. coli</i>	573x2	58	$^1D_{HN}$	339
the EI-HPr complex	573x2 + 88	43	$^1D_{HN}$	339

a number of residues.
b the total number of residual dipolar couplings measured.
c types of residual dipolar couplings measured.

Table 6 Oligonucleotides and carbohydrates for which the solution structure has been calculated with RDCs.

Name	<i>a</i>	<i>b</i>	<i>c</i>	Reference
R _p and S _p borano phosphonate DNA/RNA hybrids	9x2	45	$^1D_{HC}$	341
the A730 loop of the Neurospora VS ribozyme	26	30	$^1D_{HC}$, $^1D_{HN}$	302
the K-turn U4 snRNA	33	79	$^1D_{HC}$	342
(DIS) ₂	30x2	42	$^1D_{HC}$	343
LCS1co, a construct mimicing <i>let-7</i> miRNA/LCS1 interaction	34	52	$^1D_{HC}$, $^1D_{HN}$	344
2'-F/2'-OMe modified dimeric siRNA construct	42	42	$^{2,3}D_{HF}$	345
carbohydrates:				
LNF-1	5	44	$^1D_{HC}$, $^nD_{HH}$	190
enzymatically depolymerized hyaluronic acid	10	40	$^1D_{HC}$	346

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

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