

Applications of spin-spin couplings

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DOI: 10.1039/9781849732796-00162

1 Introduction

The material in this chapter covers the period from 1 June 2009 to 31 May 2010. 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, Ni-⁶¹Ni, 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 very useful review on NMR and structural properties of iron group complexes has been written by Morris.³ The author collected data for 17 iron complexes, 98 ruthenium complexes and 70 osmium complexes that contain dihydrogen or compressed dihydride ligands, which allowed him to establish many interesting trends. For example, he observed that electronegative atoms Cl and O, when attached to the metal *trans* to the dihydrogen ligand, result in elongation of the H-H bond relative to more electropositive atoms H, C, P and N.

A review on advances in synthesis and stereochemical studies of pyrroles and vinylpyrroles has been published by Trofimov and co-workers.⁴ The conformational analysis of the compounds studied has been based mainly on experimental J_{HC} and J_{CC} couplings and their DFT calculated values.

An exhaustive review on vicinal, four- and five-bond couplings in carbohydrates and some related compounds has been written by Coxon.⁵ The author discusses all relevant types of couplings such as, for example, $^3\text{-}^5J_{\text{HH}}$, $^3J_{\text{HC}}$, $^3J_{\text{HN}}$, and $^3J_{\text{CC}}$.

A review on modern NMR techniques for the determination of spin-spin couplings and Overhauser effect as well as the use of these data in conformational analysis of oligo- and polysaccharides has been written by Grachev *et al.*⁶

Recent advances in solid-state MAS NMR methodology for probing structure and dynamics in polymeric and supramolecular systems have been reviewed by Brown.⁷ This included papers devoted to quantitative determination of J_{CC} couplings and hydrogen-bond mediated J couplings.

An exhaustive review on applications of carbon-silicon couplings has been published by Blechta.⁸

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Through-space nuclear spin-spin P-P and C-P couplings in ferrocenyl polyphosphanes and diphosphino cavitands have been reviewed by Hierso and co-workers,⁹ who discussed them in the light of recent examples found in constrained phosphorus-containing ligands such as phosphino-calixarenes, phosphinocyclodextrins and ferrocenyl phosphanes. 1

¹¹⁹Sn NMR data including J_{SnTM} couplings (TM = transition metal) has been collected and critically evaluated by Agustin and Elises¹⁰ for transition metal complexes with terminal stannylene ligands. 5

A chapter on analyses of proton NMR spectra of strongly and weakly dipolar coupled pins has been written by Baishya *et al.*¹¹ The authors have put a special emphasis on spectral simplification, chiral discrimination, and discerning degenerate transitions. 10

A review on computational solutions concerning conformational averaging of different spectroscopic parameters including vicinal 3J and dipolar couplings in biomolecules has been written by Kruschel and Zagrovic.¹² 15

Allen and Imperiali¹³ have reviewed the unique properties of inducing residual dipolar couplings lanthanide tags for investigation of protein structures.

Grzesiek and Sass¹⁴ have reviewed several NMR methods which relied, among others, on chemical shifts and dipolar couplings employed for better detection of dynamics and molecular interactions of larger proteins. 20

Reviews on the use of dipolar couplings, mainly $^1D_{\text{HN}}$ ones, for quantitative determination of the conformational properties of intrinsically disordered or partially folded proteins have been written by Blackledge and co-workers.¹⁵ 25

O'Connell and co-workers¹⁶ have reviewed NMR based methods for structural analysis of protein-protein interactions giving weight to the methods that use RCDs and paramagnetic data.

A review on theory and applications of relativistic computations of NMR parameters from first principles has been written by Autschbach and Zheng.¹⁷ 30

The scientific achievements of von Philipsborn in the field of nuclear magnetic resonance of organometallic chemistry and transition metals have been presented by a group of his former graduate students.¹⁸ It includes measurements of scalar couplings to quadrupolar nuclei via lineshape analysis. 35

The history of the development of the theoretical ideas and experimental methods of magnetic resonance as well as the applications of these methods in modern natural science, technology and medicine have been outlined by Kessenikh, a special attention being paid to Russian researchers.¹⁹ 40
A short review on achievements of one of the teams initiated by Pacault has been written by Hoarau and Rayez²⁰ Among others, the team was involved in the calculations of spin couplings.

2 New methods 45

Three important NMR pulse sequences, INADEQUATE, HSQC and three-dimensional HMBC have been combined by Kupče and Freeman²¹ to provide structural information about a small molecule in a

single experiment (HR PANACEA = *High-Resolution Parallel Acquisition NMR: an All-in-one Combination of Experimental Applications*). To prove the usefulness of the method, proton-carbon couplings across one, two, three and four bonds have been measured for methyl salicylate. 1

An experiment with selective homonuclear decoupling of multiple protons simultaneously that allows a fast and reliable determination of specific coupling values from complex spectra has been designed by Espindola *et al.*²² The authors applied a q3 shape pulse in order to obtain a multi frequency homodecoupling (MDEC) during the acquisition time. Menthol has been chosen as the model compound to prove the reliability of the method. A combination of MDEC and 1D-TOCSY-MDEC allowed the authors to extract the vicinal proton-proton couplings for much more complex spectra, such as those of cholesteryl acetate and the potent cytotoxic natural product nigricanoside A. 5 10

Luy²³ has detailed a pure phase homonuclear adiabatic z -filtered J -resolved experiment which allows the unambiguous identification of strongly coupled spins. 15

Two useful pulse sequences, selective J -resolved HMBC and high-resolution (HR-HMBC) for measuring long-range H-C couplings have been designed by Furihata *et al.*^{24,25} In these high resolution HMBC spectra, splittings of the cross peaks due to the long-range J_{HC} are realigned with separations ${}^nJ_{\text{HC}}$ along the F1 dimension, which allows to observe even the small couplings. To demonstrate the effectiveness of the proposed methods large natural products, portmicin and monazymicin, have been applied. 20

A new pulse sequence based on intermolecular single quantum coherences has been designed by Huang *et al.*²⁶ It allows to recover useful information of chemical shift, relative peak areas, J couplings, and multiplet patterns even when the field inhomogeneity is severe enough to erase all spectroscopic information. Another pulse sequence developed by this group²⁷ was devoted to acquiring high-resolution NMR spectra of liquid samples with J -scaling in inhomogeneous field via 2D intermolecular multiple-quantum coherence acquisitions. In the resulting 1D projection spectra, apparent J -couplings were obtained with a scaling factor theoretically varying from zero to infinity relative to the original J -couplings while retaining information on chemical shifts, relative peak areas, and multiplet patterns. This approach allows an accurate measurement of small J -couplings of weakly coupled spin systems. 25 30 35

A pulse sequence for the simultaneous measurement of N-H and $\text{C}\alpha$ -H α couplings in double-labelled proteins from 2D spectra has been designed by Pantoja-Uceda and Santoro.²⁸ The proposed sequence, a modification of the HN(CO)CA experiment, combines the J -modulation method and the IPAP scheme. The couplings can be readily retrieved from a series of 2D ${}^{15}\text{N}$ - ${}^1\text{H}$ correlation spectra, differing in the point at which a ${}^1\text{H}$ 180° pulse is applied. The pulse sequence has been experimentally verified with a sample of ${}^{15}\text{N}/{}^{13}\text{C}$ -enriched ubiquitin. 40 45

A useful SQ-SQ experiment has been designed by Blechta and Schraml²⁹ for the determination of carbon-silicon couplings across several bonds at natural abundance using hydrogen-silicon couplings as the sign reference. Using this new sequence the authors measured two long-range couplings in

dimethyl(phenoxy)silane, ${}^2J_{\text{CSi}} = +2.2 \text{ Hz}$ and ${}^3J_{\text{CSi}} = -1.7 \text{ Hz}$, which cannot be determined by traditional methods. Blechta and Schraml³⁰ have also proposed ${}^1\text{H}$ -detected SQ-SQ experiment (SQ-SQh) where proton detection replaces carbon detection used in the original SQ-SQ pulse sequence. The method can be applied to linear spin systems, *i.e.* systems where the silicon is coupled to the carbon in question and to any hydrogen not necessarily bonded to the carbon. In order to demonstrate the usefulness of this novel sequence long range carbon-silicon couplings have been measured for trimethylsiloxyethane and 1,2,4-tris(trimethylsiloxy)benzene.

Several papers have been published by Suryaprakash and co-workers^{31–33} on the application of different variants of COSY experiment for accurate chiral discrimination by ${}^1\text{H}$ NMR. The experiments are designed for detection of the enantiomer spectrum of chiral molecules aligned in the polypeptide liquid crystalline solvent. The authors emphasize that the advantages of their techniques are in their pure phase spectra which enable the measurement of couplings of negligible strengths, precise measurement of enantiomeric excess and also considerable reduction in the instrument time.

Problems, artifacts and solutions in the INADEQUATE NMR experiment have been thoroughly analysed by Bain and co-workers.³⁴

Otten *et al.*³⁵ have demonstrated a pair of 2D ${}^{13}\text{C}'$ -resolved spin-echo difference experiments to measure with superior resolution ${}^3J_{\text{H}\text{NH}\alpha}$ couplings of unfolded proteins. Schwalbe and co-workers³⁶ have reported a novel HN(COCA)HAHB experiment for the determination of ${}^3J_{\text{H}\text{NH}\alpha}$ couplings in non-native states of proteins.

Clare and co-workers³⁷ have presented the 3D TROSY HNC0 pulse scheme with very good resolution in the ${}^{15}\text{N}$ dimension, suitable for accurate measurements of ${}^1D_{\text{HN}}$ couplings in proteins. Bax and co-workers³⁸ have developed 2D BSD-IPAP HSQC experiment to improve the accuracy of ${}^1J_{\text{HN}}$ and ${}^1D_{\text{HN}}$ couplings measured in protonated proteins. Also Arbogast *et al.*³⁹ have introduced a pair of 3D HNC0-based experiments for measurements of one-bond amide H-N couplings with optimized precision.

Golovanov and co-workers⁴⁰ have proposed an isotopically discriminated IDI-RDC-TROSY experiment for simultaneous measurement of ${}^1D_{\text{HN}}$ residual dipolar couplings for both proteins in protein heterodimers in which one protein is labelled with ${}^{15}\text{N}$ and the other with ${}^{13}\text{C}$ and ${}^{15}\text{N}$. Veglia and co-workers⁴¹ have reported a gradient-selected TROSY-based experiment that, combined with an asymmetric isotopic labelling scheme, enables simultaneous measurement of RDCs from subunits of binary and ternary complexes.

A TROSY-based J -modulated approach for the measurement of small ${}^{13}\text{C}$ - ${}^{15}\text{N}$ couplings (scalar couplings ${}^1J_{\text{C}'\text{N}}$, ${}^1J_{\text{C}\alpha\text{N}}$, ${}^2J_{\text{C}\alpha\text{N}}$ and ${}^1D_{\text{C}'\text{N}}$, ${}^1D_{\text{C}\alpha\text{N}}$ residual dipolar couplings) in large proteins has been described by Liu and Prestegard.⁴² Zuiderweg and co-workers⁴³ have discussed in details utility and limitations of a RDC-TROSY method for measurement of ${}^1D_{\text{HN}}$ couplings in large proteins.

The 2D exclusively heteronuclear experiments based on the CON scheme with ${}^{13}\text{C}$ direct detection for determination of several one-bond scalar and residual dipolar couplings have been proposed by Pieratelli and co-workers.⁴⁴

An experimental strategy for observing the anisymmetric portion of J_{AB} coupling in powdered samples of tightly coupled homonuclear spin pairs based on ideas originally described by Andrew and Farnell⁴⁵ has been presented by Wasylishen and co-workers.⁴⁶ It has been found by the authors that in certain rare cases J^{anti} has the potential to affect the NMR line shapes from AB spin systems, but even in these cases the most intense features of the spectra are not affected and may be analyzed independently of J^{anti} .

3 One-bond couplings to hydrogen

Metal-hydride bonding in higher alkali metal boron hydrides has been studied by Haywood and Wheatley⁴⁷ by the use of ^1H and ^{11}B NMR spectroscopies.

$^1J_{\text{HB}}$ couplings of ca. 74.6, 70.6 and 73.8 Hz have been observed for $\text{Et}_3\text{BHLi} \cdot 2(\text{TMEDA})$, $\text{Et}_3\text{BHNa} \cdot \text{TMEDA}$ and $\text{Et}_3\text{BHK} \cdot \text{TMEDA}$ complexes in DMSO solution. The coupling values decreased considerably in a hydrocarbon solution to 52.0 Hz in $\text{Et}_3\text{BHNa} \cdot \text{TMEDA}$ and 62.4 Hz in $\text{Et}_3\text{BHK} \cdot \text{TMEDA}$, which has been invoked by the authors as indication that a dimeric structure of these complexes has been retained in non-polar solvents.

The electronic structure of the benzenium cation, $[\text{C}_6\text{H}_7]^+$, the simplest intermediate of electrophilic aromatic substitution reactions, has been analysed by García-Revilla and Hernández-Trujillo⁴⁸ in terms of the properties of electron densities obtained from multiconfigurational quantum theoretical methods. The indirect H-C couplings and the physical contributions to their values have been calculated by the authors and rationalized in terms of the electron delocalization between the quantum topological atoms in the molecule. The estimated theoretical $^1J_{\text{HC}}$ of 30 Hz agrees reasonably well with the experimental value reported by Olah *et al.*,⁴⁹ $^1J_{\text{HC}}$ of 26 Hz.

Spin-spin coupling, $^1J_{\text{HC}}$ of 141.148 Hz and $^3J_{\text{HH}}$ coupling of 5.353 Hz in methanol has been re-measured by Kupka⁵⁰ in diluted CDCl_3 solution and compared with the coupling values calculated using B3LYP and BHandH density functionals and various basis sets. Similar studies have been performed by the author for $^1J_{\text{HO}}$ in water and $^1J_{\text{HD}}$ in HD.⁵¹ A theoretical study of stationary structures of the methane surface with special emphasis on NMR parameters including $^1J_{\text{HC}}$ and $^2J_{\text{HH}}$ couplings has been performed by Alkorta and Elguero.⁵² The reasons for the unexpected differential sensitivity and associated anomalous isotope effects in the one-bond indirect nuclear spin-spin couplings in CH_4 , SiH_4 , BH_4^- and NH_4^+ and their absence in NH_3 and H_2O have been studied by Provasi and Sauer⁵³ by an analysis in terms of contributions from localized occupied molecular orbitals. Theoretical studies which included calculations of $^1J_{\text{HC}}$ couplings have been performed by Li *et al.*⁵⁴ on size-expansion effect on the C8-site activity in the modified guanine-cytosine analogues.

Two examples have been provided by Contreras *et al.*⁵⁵ to illustrate the potential of NMR spin-spin couplings as probes to study fine details of electronic molecular structures and effects such as, for example,

hyperconjugation. One example has been devoted to a qualitative analysis of the polarization propagator expression for the Fermi contact term, which has been applied for predicting factors affecting $^1J_{\text{HC}}$ coupling constants, the other to the electronic factors defining a Karplus relationship $^3J_{\text{HH}}$.

An anomalously large blue shift of the C-H stretching frequency in syn rotamers of 2-vinyloxypyridine and -quinoline has been predicted theoretically by Afonin and Vaschenko⁵⁶ and interpreted in terms of the intramolecular C-H...N bonding. The authors have recalled that this strong blue shift effect is accompanied by a dramatic decrease of the chemical shift of the corresponding proton and increase of $^1J_{\text{HC}}$ coupling.

A facile method for distinguishing between imidazoles and oxazoles based on a combination of NMR spectroscopy and quantum mechanical calculations has been proposed by Weitman *et al.*⁵⁷ In the NMR data the oxazole C-2 has a chemical shift of ca. 150 ppm, whereas in oxazoles it is found at ca. 135 ppm, with a $^1J_{\text{HC}}$ of ca. 250 Hz for the oxazoles and ca. 210 Hz for the imidazoles.

$^1J_{\text{HC}}$ couplings have been used in compositional and structural analysis of xylomannan antifreeze in the freeze-tolerant Alaskan beetle *Upis ceramoides* by Walters *et al.*,⁵⁸ and in elucidation of the structure of bionectriol A, a polyketide glycoside from the fungus *Bionectria sp.* by Clardy and co-workers.⁵⁹

Leśniak *et al.*⁶⁰ have confirmed the structures of synthesised by them series of aryliminoacetonitriles with $^1J_{\text{HC}}$ and $^3J_{\text{HH}}$ couplings.

Conformational analysis of allyl acrylate by the use of vibrational and NMR spectroscopies combined with theoretical calculations has been undertaken by Jamróz *et al.*⁶¹ The experimental vibrational spectra have been found to be in good agreement with the theoretical spectra of two out of ten most stable conformers with *cis* arrangement of the acrylic moiety. The room temperature NMR spectra which also include $^1J_{\text{HC}}$, $^2J_{\text{HC}}$ and $^3J_{\text{HH}}$ couplings suggest that a dominating form in an inert solvent exhibits the *cis* conformation of the acrylic moiety and extended allyl group.

An extensive study on computational analysis of solvent effects on chemical shifts and spin-spin couplings in two model compounds, chloroform and three alanine forms has been carried out by Dračinský and Bouř.⁶² They have found that chemical shifts and $^1J_{\text{HC}}$ coupling in chloroform are particularly sensitive to the molecular dynamics model used to generate the cluster geometries. The results show that computationally efficient solvent modelling is possible and can reveal fine details of molecular structure, solvation and dynamics. Another theoretical study has been performed the same group of authors⁶³ in order to get insight into the structure of the alanine hydration shell by the aid of NMR chemical shifts and spin-spin couplings including those across one H-C and C-C bonds. The attempt has been made to explain subtle differences observed for these parameters in the three forms, *i.e.* neutral (zwitterionic), cationic and anionic of this aminoacid.

Proton-carbon couplings across one and more bonds and proton-proton couplings across three, four and five bonds have been reported by Holzer and co-workers⁶⁴ for a series of 14 heterocyclic analogues of xanthonines, 5,6-fused 3-methyl-1-phenylpyrano[2,3-*c*]pyrazol-4(1*H*) thiones.

The experimental and calculated using B3LYP method $^1J_{\text{HC}}$ 1
couplings have been reported by Alver *et al.* for 1,9-diaminononane,⁶⁵
1,7-diaminoheptane⁶⁶ and 3-phenylpropylamine.⁶⁷

Two complexes, $[\text{IrRu}(\text{CO})_4(\mu\text{-CH}_3)(\text{dppm})_2][\text{CF}_3\text{SO}_3]_2$ and $[\text{IrRu}(\text{CO})_3$ 5
 $(\text{PMe}_3)(\mu\text{-}\eta^1\text{:}\eta^2\text{-CH}_3)(\text{dppm})_2][\text{CF}_3\text{SO}_3]_2$, containing bridging methyl
groups have been studied by Samant *et al.*⁶⁸ In both compounds very slow
on the NMR time scale exchange between the terminal and agostic methyl
hydrogens at low temperatures has occurred allowing the two different H-C
couplings to be measured. The $^1J_{\text{HC}}$ couplings of 65 and 72 Hz have been 10
found for the agostic interactions and those for the terminal hydrogens are
146 and 146 Hz, respectively. A similarly small $^1J_{\text{HC}}$ coupling of 81 Hz only
has been observed by Siebert⁶⁹ in the spectrum of the $\text{CpCo}(\text{C}_3\text{B}_2\text{HMeEt}_4)$
complex having an endo C-H bond, which indicates the reduced bond
strength of the bond under consideration.

$^1J_{\text{H14N}}$ and $^2J_{\text{HH}}$ couplings in liquid NH_3 have been calculated by Gester 15
*et al.*⁷⁰ using the sequential QM/MM method. The calculated $^1J_{\text{H14N}}$ values
vary between -67.8 and -63.9 Hz depending on the theoretical model used in
comparison with the experimental value of -61.5 Hz. The calculated for the
 $^1J_{\text{H14N}}$ parameter vapour to liquid shift is about 0.5 Hz only in agreement
with that observed experimentally, 0.8 Hz. 20

Perturbations in $^1J_{\text{HN}}$ couplings have been proposed by Tjandra and
co-workers⁷¹ as an additional probe for measuring structural changes in
proteins upon ligand binding.

$^1J_{\text{HSi}}$ couplings have been applied by Calimano and Don Tilley⁷² to
characterize $[(\text{PNP})(\text{SiH}(\text{Mes})(\text{Hex}))\text{IrH}(\text{SiH}_2\text{Mes})][\text{B}(\text{C}_6\text{H}_5)_4]$ complex 25
obtained by addition of H_3SiMes to $[(\text{PNP})(\text{H})\text{Ir} = \text{Si}(\text{Mes})\text{Hex}][\text{B}(\text{C}_6\text{H}_5)_4]$.
 $^1J_{\text{HSi}}$ of 180 Hz has been found for resonances assigned to diastereotopic
Si-H hydrogens of an Ir-SiH₂Mes group and $^1J_{\text{HSi}}$ of 102 Hz has been found
for a β -agostic Si-H group. The resonance identified as an iridium hydride
ligand has revealed a small $^2J_{\text{HSi}}$ coupling of 8 Hz, indicating little to no 30
interaction between this hydride and silicon atom.

$^1J_{\text{HSi}}$ coupling of 191.6 Hz has been measured by Grellier *et al.*⁷³ for the
novel disilazane compound, 2-pyridinetetramethyldisilazane; the coupling
value increases upon complexation of the compound and $^1J_{\text{HSi}}$'s of ca.
204 Hz have been found in $\text{RuH}_2(\eta^2\text{-HSiMe}_2)(\text{N}-[(\text{C}_6\text{H}_4\text{N})(\text{SiMe}_2\text{H}))]$ 35
 $(\text{PCy}_3)_2$ and $\text{RuH}(\eta^2\text{-HSiMe}_2)(\text{N}-[(\kappa\text{N-C}_6\text{H}_4\text{N})(\text{SiMe}_2\text{H}))](\text{PCy}_3)_2$ complexes.

Germa-closo-dodecaborate, a new ligand in transition-metal chemistry
has been synthesized by Dimmer *et al.*⁷⁴ with a strong *trans* influence
confirmed by IR spectroscopy and NMR coupling; for example, $^1J_{\text{HPt}}$ of
1096 and $^2J_{\text{HP}}$ of 12.9 Hz have been determined for the $[\text{Bu}_3\text{MeN}][\text{trans-}$ 40
 $\{(\text{PEt}_3)_2\text{PtH}(\text{GeB}_{11}\text{H}_{11})\}]$ complex (see Fig. 1).

4 One-bond couplings not involving hydrogen

Ab initio calculations have been carried out by Del Bene *et al.*⁷⁵ to determine 45
the structures, binding energies and spin-spin couplings of complexes
stabilized by X-Li...N bonds with F-Li, H-Li and CH_3Li as the Lewis acids.
The one-bond coupling $^1J_{\text{LiF}}$ may increase or decrease upon complexation,
whereas $^1J_{\text{LiC}}$ and $^1J_{\text{HLi}}$ couplings decrease significantly. No correlation has

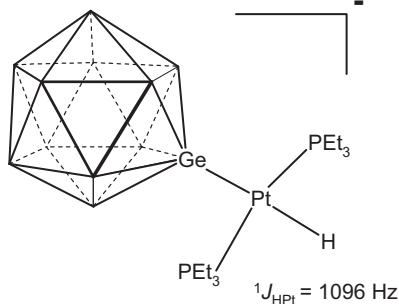


Fig. 1

been found between $^1J_{\text{LiX}}$ and the Li-X distance or $^{11\text{Li}}J_{\text{LiN}}$ and the Li-N distance.

$^1J_{\text{BB}}$ and $^1J_{\text{HB}}$ couplings have been calculated by Alkorta *et al.*⁷⁶ for *trans* and *cis* diborenes, $\text{HLB} = \text{BLH}$ where $\text{L} = \text{CO}, \text{NH}_3, \text{OH}_2, \text{PH}_3, \text{SH}_2, \text{ClH}$. Inverse correlations have been found between these couplings and the corresponding BB and BH distances. Unfortunately, no experimental J values are available. NMR parameters, including $^1J_{\text{BN}}, ^1J_{\text{HB}}$ and $^1J_{\text{HN}}$ couplings have been calculated by the same group of authors⁷⁷ for 1,2-dihydro-1,2-diazaborine and some related compounds, *i.e.* a set of diazaborines, borazine and pseudoborazine. Changes in the coupling values are caused by the changes in bonding patterns of these compounds; when N1 and B2 are bonded to the less electronegative atoms C and B, $^1J_{\text{B}_2\text{N}_1}$ increases relative to borazine, but when either N1 or B2 is bonded to N $^1J_{\text{B}_2\text{N}_1}$ decreases. The calculated coupling values are in agreement with the experimental ones published in the literature, if available. *Ab initio* calculations have been carried out by Del Bene *et al.*⁷⁸ to investigate bonding patterns and B-N couplings in five-membered rings $\text{N}_3\text{B}_2\text{H}_4\text{X}$ and $\text{N}_2\text{B}_3\text{H}_4\text{X}$ for $\text{X} = \text{H}, \text{Li}$ and F with substitution occurring only at the nitrogen atoms. The F substituent exerts only localized effect on $^1J_{\text{BN}}$ couplings whereas the effect of Li substituent is more delocalized.

A modified $^{11\text{B}}$ NMR pulse sequence has been applied by Oliveira *et al.*⁷⁹ to determine $^1J_{\text{BF}}$ couplings in a series of potassium organotrifluoroborates such as, for example, potassium ethynyltrifluoroborate, potassium vinyltrifluoroborate, potassium ethynyltrifluoroborate, potassium phenylethynyltrifluoroborate, potassium *o*-tolyltrifluoroborate and some others. The measurements performed for ethynyltrifluoroborate in a variety of solvents have shown a strong solvent dependence of this coupling. The smallest value of ca. 11 Hz has been observed in CD_3OD , the largest one of 36.6 Hz in aprotic $\text{DMSO-}d_6$.

$^{1-3}J_{\text{CC}}$ and $^{1-4}J_{\text{HC}}$ couplings including their signs have been determined by Tiainen *et al.*⁸⁰ for $^{13\text{C}}$ -labelled α and β -D-glucose.

Ab initio one-, two-, and three-bond C-C, C-N and N-H couplings have been calculated by del Bene *et al.*⁸¹ using second-order polarization propagator approximation and equation-of-motion coupled cluster singles and doubles for a large series of small basic molecules such as acetylene, benzene and pyrrole. Both methods overestimate $^1J_{\text{CC}}$ couplings but those EOM-CSSD calculated are in better agreement with experiment.

$^1J_{CC}$, $^1J_{CF}$, $^2J_{CF}$, $^2J_{FF}$ and $^3J_{FF}$ couplings have been calculated by Del Bene *et al.*⁸² for tetrafluoroethene C₂F₄ in ternary π complexes. The largest $^1J_{CC}$ coupling of 212.9 Hz has been calculated for the C₂F₄. Cl⁻ complex, the smallest one, $^1J_{CC}$ of 195.3 Hz, for the HF:C₂F₄ moiety. ¹³C nuclear shielding and one-, two- and three-bond carbon-carbon spin-spin coupling tensors have been calculated by Vaara and co-workers⁸³ for a series of planar hydrocarbons of increasing size, *i.e.* benzene, coronene, circumcoronene and circumcircumcoronene using density functional theory linear response methods.

J couplings including $^1J_{CC}$ and $^1J_{OO}$ have been calculated for a series of closed H-bonded molecules, *i.e.* malonaldehyde, nitromalonaldehyde and nitromalonamide, by Zarycz *et al.*⁸⁴ and analyzed from the point of view of the resonance-assisted hydrogen bond mechanism.

The origin of significant solvent effects on $^1J_{CC}$ couplings in acetylene and its derivatives has been studied by Biedrzycka *et al.*⁸⁵ They have demonstrated that $^1J_{CC}$'s in acetylenes of the R-C \equiv CH structure display high sensitivity to solvent effects, while those in R-C \equiv CR' fail to show it (see Table 1).

These results have been explained in terms of two effects of prime importance, solvent polarity and the solute to solvent hydrogen bonds where the CH moiety in R-C \equiv CH acetylenes acts as a donor of hydrogen bonds to acceptor sites in the solvent concerned.

Very small, $^1J_{CC}$ = 9.3 Hz only, carbon-carbon coupling has been determined by Wrackmeyer *et al.*⁸⁶ for 1-diphenylsilyl-1,2-dicarba-*closo*-dodecaborane. It is of interest to notice that the calculations performed for this compound and several other similar structures predict a negative sign for this coupling providing a new example of very rare negative couplings across one CC bond.

NMR parameters including $^1J_{CC}$ and $^3J_{HC}$ couplings have been calculated by Dodziuk *et al.*⁸⁷ for two tricyclododecadienes - strained hydrocarbons with close distance between perpendicularly or parallelly arranged double bonds.

Kamieńska-Trela and co-workers have continued their studies on carbon-carbon couplings in enaminketones.⁸⁸ The recent paper has been devoted to experimental and DFT calculated $^nJ_{CC}$'s couplings (n = 1, 2, 3) in aryl-substituted enaminketones and their thio analogues.⁸⁹

Krivdin and co-workers have continued their studies on the application of carbon-carbon couplings in structural studies. The recent paper⁹⁰ published by this group has been devoted to the theoretical studies of a dependence of $^1J_{CC}$ couplings upon internal rotation in carbonyl-containing oximes.

Table 1 Influence of solvents on $^1J_{C\equiv C}$ [Hz] in acetylenes

compound	in C ₆ D ₁₂	in DMSO _d ₆	ΔJ
H-C \equiv C-H	173.5	160.6	12.9
Ph-C \equiv C-H	178.2	170.2	8.0
Ph-C \equiv C-Me	182.0	179.3	2.7

A comparison of the experimental $^1J_{CC}$ and $^1J_{HC}$ couplings performed for 2-vinyloxymethylfuran and 2-vinyloxymethyltetrahydrofuran allowed Rusakov *et al.*⁹¹ to draw a conclusion on the existence of both compounds in solution in the form of *s-cis* conformers with respect to the C α -O bond, which agrees with the results of theoretical conformational analysis.

A full set of experimental couplings taken from the literature for *o*-, *m*- and *p*-difluorobenzenes has been collected by Alkorta *et al.*⁹² and compared with the SOPPA calculated *J* values. This included carbon-carbon and carbon-fluorine couplings across one and more bonds. Another paper has been devoted to all fluorobenzenes, but the authors⁹³ emphasized that the SOPPA calculations are not always able to reproduce the experimental results. This concerns $^1J_{HC}$, $^1J_{CF}$, $^3J_{HF}$ and $^3J_{FF}$ couplings. *Ab initio* EOM-CCDS calculations have been performed by the same group of authors⁹⁴ to evaluate one-bond C-F couplings, $^1J_{CF}$, and three-, four-, and five-bond F-F couplings, $^nJ_{FF}$, in a series of mono-, di-, and trifluoroazines. 1H and ^{13}C NMR assignments of all three isomeric *o*-fluoronaphthaldehydes and three *o*-fluorophenanthrene aldehydes have been performed by Busacca *et al.*⁹⁵ This also included determination of one-bond carbon-fluorine couplings as well as long-range ones.

Oriental order properties of two fluorinated liquid crystals containing the 1,3,2-dioxaborinane ring has been studied by Borsacchi *et al.*⁹⁶ by means of ^{13}C and ^{19}F NMR spectroscopy. A large set of data has been obtained by the authors including ^{13}C and ^{19}F chemical shift anisotropies and C-F and H-F couplings relative to nuclei on the aromatic rings. An analysis of the obtained results allowed determination of local order parameters for different rigid fragments of the mesogen aromatic core using advanced DFT methods for the calculation of geometrical parameters and chemical shift tensors.

Multinuclear magnetic resonance and DFT studies which also included analysis $^{1-3}J_{CF}$ couplings have been performed Wormald and co-workers⁹⁷ for the poly(chlorotrifluoroethylene-*alt*-ethyl vinyl ether)copolymers.

Dynamic solution behaviour of chloro(diene)rhodium(I) phosphine complexes with a pendant unsaturated heterocycle at phosphorus (2-pyridyl, 2-imidazolyl; diene = COD, NBD) has been studied by Brück and Ruhland⁹⁸ by the VT 1D NMR studies. This included measurements of $^1J_{CRh}$ and $^1J_{PRh}$ couplings for the complex chlorocycloocta-1,5-diene (diisopropyl-2-pyridylphosphine)rhodium.

$^1J_{CSn}$ couplings of the range 320–360 Hz have been observed for organotin(IV) derivatives of 4-[(2,4-dinitrophenyl)amino]-4-oxo-2-butenic acid and 2-[[[(2,4-dinitrophenyl)amino]carbonyl]benzoic acid,⁹⁹ which supports the tetrahedral coordination geometry of these compounds in non-coordinating solvents.

$^1J_{NP}$ couplings of ca. 10 Hz have been found by Gordillo and co-workers¹⁰⁰ for *cis-ax* 2-*p*-X-anilino-2-thio-4,6-dimethyl-1,3,2 λ^5 -dioxaphosphinanes, and of ca. 25 Hz for their *cis-eq* counterparts.

$^1J_{SiSe}$ couplings of ca. 120 Hz have been measured by Wrackmeyer *et al.*¹⁰¹ for some diselenasilacycles containing an annelated dicarba-closo-dodecaborane(12) unit. The observed coupling values are in agreement with the data set already published for numerous other cyclic selenium-silicon compounds.

$^1J_{PP}$ couplings in the solution and in solid state have been measured by Burck *et al.*¹⁰² for a series of *P*-phospholyl-substituted *N*-heterocyclic phosphines. Analysis of trends in these couplings indicated that an inverse relation exists between the magnitude of $^1J_{PP}$ (solid) and the P-P distance. The large discrepancies between $^1J_{PP}$ (solid) and $^1J_{PP}$ (solution) as well as the temperature dependence of the latter have been interpreted by the authors in terms of an equilibrium between *trans* and *gauche* rotamers in solution combined with solvation-induced relaxation of bond length.

Significant differences of the magnitudes of $^1J_{PP}$ couplings in a series of phosphine-stabilized phosphoranimine cations 13–25 Hz vs. 276–324 Hz have been assigned by Manners and co-workers¹⁰³ rather to the differences in the electronegativity of substituents than to the strength of the donor-acceptor P-P bond.

The literature data on substituent influence on the ^{51}V , ^{55}Mn , ^{57}Fe , ^{59}Co , ^{61}Ni , ^{95}Mo , ^{103}Rh , ^{183}W , ^{187}Os and ^{195}Pt NMR chemical shifts δ and on $^1J_{PM}$ ($M = \text{Mn, Fe, Mo, Rh, W, Os}$) couplings has been analyzed by Egorochkin *et al.*¹⁰⁴ for 30 series of the organometallic compounds in terms of the inductive, resonance and polarizability effects of substituents.

$^1J_{PCu}$ couplings of ca. 1400–1500 Hz have been determined by Lucier *et al.*¹⁰⁵ for a large series of bis(triphenylphosphine) copper species by the use of ^1H - ^{31}P PCP/MAS NMR spectroscopy.

$^1J_{PSe}$ couplings of 787 and 792 Hz have been measured for *N,N*-bis(diphenylselenophosphino)-2-isopropylaniline and *N,N*-bis(diphenylselenophosphino)-4-isopropylaniline, respectively, two new ligands synthesized by Aydemir *et al.*¹⁰⁶

$^1J_{PAg}$ couplings have been determined by Wasylishen and co-workers¹⁰⁷ for a series of 1:1 silver-triphenylphosphine complexes, $[\text{Ph}_3\text{P}Ag\text{X}]_n$ ($X = \text{anion}$ and $n = 1, 2, 3$ or ∞), by the use of high-resolution, solid-state ^{31}P NMR spectroscopy. The absolute coupling values ranged from 401 ± 10 Hz for $X = \text{N}_3^-$ to 869 ± 10 Hz for $X = \text{SO}_3\text{CF}_3^-$ and decreased as Ag-P lengths increased. Another paper has been devoted by these authors¹⁰⁸ to structural characterization of silver dialkylphosphite salts, $\text{Ag}(\text{O})\text{P}(\text{OR})_2$ ($R = \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_4\text{H}_9$ and C_8H_{17}) using solid-state Ag and P NMR, IR as well as DFT calculations. The magnitudes of $^1J_{PAg}$ couplings vary from 1250 ± 10 to 1318 ± 10 Hz and are the largest reported so far. It is worth noting that according to NMR and IR data the salts studied exist most probably in the form of dimer.

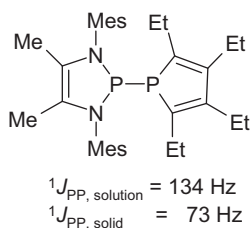


Fig. 2

$^1J_{\text{PIn}}$ couplings ranging from 550 ± 20 to 2500 ± 20 Hz, and their anisotropies Δ^1J_{PIn} , have been determined by Wasylshen and co-workers¹⁰⁹ for a series of triarylphosphine indium trihalide adducts, $\text{X}_3\text{In}(\text{PR}_3)$ and $\text{X}_3\text{In}(\text{PR}_3)_2$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) from their CP MAS spectra. The $^1J_{\text{PIn}}$ and Δ^1J_{PIn} values have been found to be comparable in magnitude and positive. The former generally increase with increasing basicity of the triarylphosphine ligands. The calculated $^1J_{\text{PIn}}$ and Δ^1J_{PIn} values have been found to be significantly lower than the experimental values, but they correctly reproduce experimental trends and indicate that both the Fermi contact and spin-dipolar Fermi contact mechanisms are important contributions to the $^1J_{\text{PIn}}$ tensors.

Berke and co-workers¹¹⁰ have measured $^1J_{\text{PW}}$ couplings of the range 30–40 Hz in a series of dinuclear tungsten carbene complexes.

$^1J_{\text{PPt}}$ coupling of 1518 Hz observed in the spectrum of Pt(II) complex of *trans*-chelating bis(diisopropylphosphino)triptycene has been used by Azerraf and Gelman¹¹¹ as evidence of the presence of the $\text{C}(\text{sp}^3)\text{-Pt}$ bond. The magnitude of the coupling implies the *trans*-located phosphine donors.

The $^1J_{\text{PPt}}$ couplings have been collected by Bennett *et al.*¹¹² for about fifty *ortho*-metallated triarylphosphane complexes of platinum(II) of general structures, *cis*- $[\text{PtX}(\kappa^2\text{-C}_6\text{H}_3\text{-5-Me-2-PPh}_2)(\text{PPh}_2\text{-4-tol})]$, $\text{X} = \text{amionic ligand}$, and *cis*- $[\text{PtL}(\kappa^2\text{-C}_6\text{H}_3\text{-5-Me-2-PPh}_2)(\text{PPh}_2\text{-4-tol})]$, $\text{L} = \text{neutral ligand}$. The magnitude of $^1J_{\text{P(A)Pt}}$ spans a fairly narrow range (1930–2100 Hz), whereas $^1J_{\text{P(B)Pt}}$ varies over quite a large range (1040–3200 Hz) as X and L are varied reflecting, at least to a first approximation, changes in the electronic nature of X and L .

Three heteroleptic Pt(II) complexes of the general formula $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{PPh}_2)_2]\text{Pt}(\text{benzenethiolate})$ with 1,1'-bis(diphenylphosphino)ferrocene, and benzenemonothiolate ligands such as benzenethiolate, (TB) 2,3,5,6-tetrafluorobenzenethiolate (TFBT) and 3,5-dimethylbenzenethiolate (DMBT) have been synthesized by Lee *et al.*¹¹³ and characterized by NMR spectroscopy. The P-Pt coupling of the TFBT complex ($^1J_{\text{PPt}} = 3171$ Hz) is much larger than that of DMBT and BT complexes, 3000 and 3001 Hz, respectively, which has been interpreted by the authors in terms of the electron-withdrawing strength of the TFBT ligand.

Cooperation between *cis* and *trans* influences on the P-Pt bond length and the couplings across this bond, $^1J_{\text{PPt}}$, has been studied by Rigamonti *et al.*¹¹⁴ on the basis of the data collected for a series of Pt(II) complexes of the general formula, *cis*- $[\text{PtX}_2(\text{PPh}_3)_2]$ and *cis*- $[\text{PtXY}(\text{PPh}_3)_2]$. It has been found that the *cis* influence cannot be neglected and has to be taken into account in establishing the *trans* influence scale.

An inverse correlation of Tolmans electronic parameter ν with the $^1J_{\text{PPt}}$ and $^1J_{\text{PtPt}}$ couplings has been observed by Albrecht *et al.*¹¹⁵ for a series of $\{[\text{Pt}(\text{PR}_3)]_2(\mu\text{-SMe})(\mu\text{-dppm})\}$ Cl complexes.

$^1J_{\text{YbYb}}$ coupling of 76.1 Hz has been found by Dietel *et al.*¹¹⁶ for a bimetallic complex of ytterbium stabilized by sterically demanding dipyr-idylamides, $\text{Yb}_2\text{I}(\text{Ap}^*\text{py})(\text{THF})$, where Ap^*py is a deprotonated (6-methylpyridin-2-yl)-[6-(2,4,6-triisopropylphenyl)-pyridin-2-yl]-amine.

A benchmark study for relativistic DFT calculations of NMR spin-spin couplings has been performed by Moncho and Autschbach.¹¹⁷ The test set

contained 47 complexes with heavy metal atoms (W, Pt, Hg, Tl, Pb) with a total of 88 couplings involving one or two heavy metal atoms. One-, two-, three- and four-bond spin-spin couplings have been computed at different levels of theory and compared with the experimental available values.

The data obtained by Sadykov *et al.*¹¹⁸ on the Pb spin echo decay and the relevant estimates of the indirect couplings of the nuclei of the nearest neighbour Pb atoms, J_{PbPb} , in $\text{BaPb}_{1-x}\text{Sb}_x\text{O}_3$ superconducting perovskites, has clearly demonstrated the development of the electron system state in the oxide metal phase, which is microscopically inhomogenous over the crystal.

5 Two-bond couplings to hydrogen

Geminal proton-proton couplings have been reported by Kruger and co-workers¹¹⁹ for a series of pentacycloundecane precursors of potential pharmaceutical agents and for some novel pentacycloundecane-based peptides,¹²⁰ by Potmischil *et al.*¹²¹ for a series of 9-substituted 1,2,3,4,5,6,7,8-octahydroacridines and their *N*-oxides, and two- and three-bond proton-proton couplings have been measured by Przybylski *et al.*¹²² for four new hydroxyl-aminoalkyl- α,β -unsaturated derivatives of the macrolide antibiotic josamycin (see Fig. 3).

$^2J_{\text{HH}}$ and $^3J_{\text{HH}}$ couplings have been applied by Parthiban *et al.*¹²³ in their structural studies of variously substituted *N*-methylpiperidin-4-one-*O*-benzyloximes, and by Manimekalai and Sivakuramar,¹²⁴ who studied some *N*-acyl-*t*(3)-isopropyl-*r*(2),*c*(6)-2'-furylpiperidin-4-one oximes. The majority of proton-proton couplings have been assigned by Salles *et al.*¹²⁵ in a series of bioactive cage-like polycyclic compounds prepared via the Diels-Alder reaction between cyclopentadiene and *p*-benzoquinone.

The *J*-based configuration analysis method has been applied by Nilewski *et al.*¹²⁶ to establish the conformation and configuration of a series of chlorinated natural products, which included 1,2-dichlorinated systems and chlorohydrins. In order to obtain the reliable *J* reference data the $^2J_{\text{HC}}$, $^3J_{\text{HC}}$ and $^3J_{\text{HH}}$ couplings have been determined for a simple conformationally rigid model system, *i.e.* *cis*-1,2-dichloro-4-*tert*-butylcyclohexane.

The unambiguous and complete structure elucidation of all products of the laccase-catalyzed reaction between catechols and heterocyclic 1,3-dicarbonyls (pyridinones, quinolinones and thiocoumarins) has been achieved by Hajdok *et al.*¹²⁷ by means of NMR spectroscopic methods

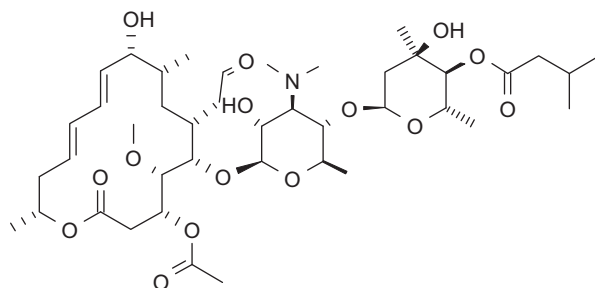


Fig. 3

which included measurement and analysis of $^2J_{\text{HC}}$ and $^3J_{\text{HC}}$ couplings. This approach has been applied by Rota *et al.*¹²⁸ to confirm the configuration around the anomeric centre of some derivatives of sialic acid obtained by chemoselective *N*-transacylation of secondary amines by means of perfluorinated anhydrides.

Structure and absolute configuration of karlotoxin-2, an ichthyotoxin from the marine doflagellate *Karlodinium veneficum* causing repeated ocean fish kills has been established by Place and co-workers¹²⁹ by the extensive use of $^2,3J_{\text{HC}}$ and $^3J_{\text{HH}}$ couplings. The carbon backbone connections in this compound have been established from the 2D INADEQUATE spectrum of the uniformly (10%) ^{13}C -enriched sample. The *J*-based configuration analysis has been also applied by Izumikawa *et al.*¹³⁰ to determine the relative configuration of the chain structure connected to the tetramic acid moiety of a methylated derivative of JBIR-22, an inhibitor for protein-protein interaction of the homodimer of proteasome assembly factor 3 (see Fig. 4).

A combination of *J*-based configurational and Mosher's analyses allowed Gerwick and co-workers¹³¹ to assign the correct configuration of a chlorosulfolipid malhamensilipin A isolated from the freshwater chrysophyte *Poterioochromonas malhamensis*. With the aid of $^3J_{\text{HH}}$ couplings the relative stereochemistry has been determined for the major chlorosulfolipid from *Ochromonas danica* by Bedek *et al.*,¹³² and for seven chlorosulfolipids by Kawahara *et al.*¹³³

$^2J_{\text{HN}}$ couplings have been calculated by Aidas *et al.*¹³⁴ for H9 and H7 tautomers of adenine in aqueous solution and compared with the experimental values published in the literature, and determined by Vicha *et al.*¹³⁵ for a series of glucosids and ribosides of aromatic cytokinins.

Don Tilley and co-workers¹³⁶ have designed a general route to neutral ruthenium silylene and germylene complexes, including rare hydrogen

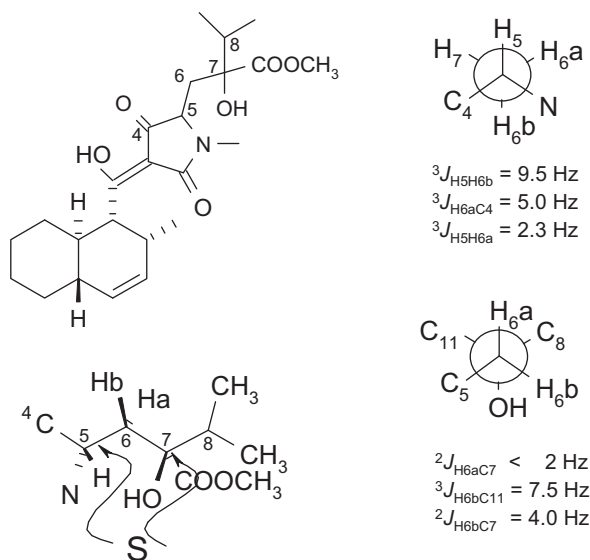


Fig. 4

substituted silylenes and germylene compounds; three of them have exhibited characteristic SiH ^1H NMR resonances downfield of 8 ppm and very small $^2J_{\text{HSi}}$ couplings of 8–10 Hz. These were $\text{Cp}^*(\text{iso-Pr}_2\text{MeP})(\text{H})\text{Ru} = \text{SiHR}$, where $\text{R} = 2,4,6\text{-iso-Pr}_3\text{-C}_6\text{H}_2$, $2,6\text{-Mes}_2\text{-C}_6\text{H}_3$ and $2,4,6\text{-(CF}_3)_3\text{-C}_6\text{H}_2$.

It is already well established that the *trans* influence of a ligand correlates well with metal-ligand couplings. This correlation has been successfully applied by Butsch *et al.*¹³⁷ in their studies on organoplatinum complexes of nucleobases and their derivatives, [(1,5-cyclooctadiene)PtMe(or neopentyl)(bioligand)], by using $^2J_{\text{HPt}}$ coupling as a measure for the bond strength of the corresponding *trans*-oriented alkyl ligand or (bio)ligand; as bioligands cytosine or uracil, their methyl derivatives and caffeine have been applied. Almost uniform $^2J_{\text{HPt}}$ values of ca. 30 Hz have been found for the olefinic protons *trans* to the strong σ -donor alkyl co-ligands, whereas the corresponding couplings of the olefinic protons *trans* to the (bio)ligands varied from 67 to 78 Hz. It has been concluded by the authors that all (bio)ligands are medium strong ligands such as Cl^- (74.3 Hz), OH^- (73.7 Hz) and pyridine (72.1 Hz) and that they are considerably stronger ligands than H_2O (89.3 Hz).

$^2J_{\text{HPt}}$ couplings between platinum and terminal acetylenic proton ranging from 65 to 70 Hz have been observed by Engelman *et al.*¹³⁸ for a series of η^2 -terminal acetylene adducts of Pt(II) providing unequivocal evidence of their structure; $^1J_{\text{CPt}}$ couplings between platinum and the acetylenic carbons ranged between 350 and 408 Hz. The general structure of the complexes studied was $\text{Tp}'\text{PtMe}(\eta^2\text{-HC}\equiv\text{CAlk})$ where $\text{Tp}' = \text{hydridotris}(3,5\text{-dimethylpyrazolyl})\text{borate}$.

6 Two-bond couplings not involving hydrogen

Schmidt *et al.*¹³⁹ have analyzed total ca. 4000 different 2J couplings measured for 969 amino acid residues in six proteins in terms of correlation with protein secondary structure. The authors have found the most pronounced conformational dependence on the backbone torsions ϕ and ψ for two of these couplings, $^2J_{\text{C}\alpha(i)\text{N}(i+1)}$ and $^2J_{\text{HNC}\alpha}$.

Novák *et al.*¹⁴⁰ have written S3EPY, a Phytos extension to the program Sparky for routine assessment and use of small scalar couplings: $^1J_{\text{CN}}$, $^2J_{\text{HN}}$ and other 2J couplings comparable to the resonance linewidth from in-phase/antiphase and spin-state-selective excitation experiments.

The C-N couplings across one, two and three bonds have been determined by Lyčka *et al.*¹⁴¹ for *E* and *Z* isomers of ^{15}N -labelled ethyl 5-oxo-2-phenyl-4-(2-phenylhydrazono)-4,5-dihydro-1*H*-pyrrole-3-carboxylate. Among them the $^2J_{\text{CN}}$ couplings are the most sensitive towards the orientation of the carbon atoms with respect to the nitrogen atom electron lone pair as has been shown in Fig. 5. This observation is in agreement with the results already published by Lyčka and co-workers.^{142,143}

$^2J_{\text{CP}}$ ranging from ca. 10 to about 90 Hz have been observed by Nomura *et al.*¹⁴⁴ for the thiolene carbons of several platinum dithiolene complexes of π -coordinating and π -interacting η^4 -cyclobutadiene ligands. J_{CPt} of ca. 100 Hz and $J_{\text{HPt}} = 13\text{--}15$ Hz have been found for the C_4Me_4 fragment of these compounds.

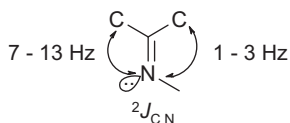


Fig. 5

A large series of new heterocyclic compounds, diazaphosphorinanes, diazaphospholes and oxazaphospholes has been synthesized by Gholivand *et al.*¹⁴⁵ and characterized by the use of NMR including $^2J_{\text{HN}}$ and $^{2,3}J_{\text{CP}}$ couplings. For all diazaphospholes $^2J_{\text{HendocyclicP}}$ couplings of *ca.* 18 Hz and $^{2,3}J_{\text{CP}}$ couplings of *ca.* 14.5 and 13.5 Hz, respectively, for the aromatic carbon atoms connected to the five-membered ring have been measured. Replacement of one NH group in a diazaphosphole ring by an oxygen atom resulted in a considerable decrease of $^2J_{\text{HendocyclicP}}$ coupling.

$^2J_{\text{NF}}$ and $^2J_{\text{FaxFeq}}$ couplings *ca.* 20 Hz and 134 Hz, respectively, have been determined by Schrobilgen *et al.*¹⁴⁶ for *mer*- and *fac*-OsO₃F₂(^{14/15}NCCH₃).

$^2J_{\text{PP}}$ couplings of 160 and 148 Hz have been found by Morris and co-workers¹⁴⁷ for [Fe{(C₆H₅)PCH₂CH = NCH₂H₄P(C₆H₅)₂}(CH₃CN)₃]²⁺ and [Fe{(C₆H₅)PCH₂CH = NCH₂H₄P(C₆H₅)₂}(CH₃CN)₃]²⁺ complexes, respectively. These large coupling values and the planar geometry of imine bonds strongly support a *mer* arrangement of the P-N-P ligand instead of a *fac* arrangement about the iron(II) centre.

Two dimensional variations in $^2J_{\text{P1P1}}$ couplings of the range 13.4 to 14.8 Hz, $^2J_{\text{P2P2}}$ of the range 5.9 to 9.1 Hz and $^2J_{\text{P1P2}}$ of the range 15.0 to 18.2 Hz (where P1 = PO₄²⁻ and P2 = PO₄¹⁻) have been measured by Guerry *et al.*¹⁴⁸ for a cadmium phosphate glass by the use of ³¹P MAS refocused INADEQUATE spin-echo (REINE) NMR pulse sequence, originally designed by Cadars *et al.*¹⁴⁹ Separate variations obtained by the authors for each 2D ³¹P REINE peak revealed correlations between the *J* couplings and the ³¹P chemical shifts.

$^2J_{\text{P117/119Ag}}$ coupling of 15.3 Hz has been observed by Petz *et al.*¹⁵⁰ in a linear coordinated complex, [(Ph₃P)₂C]Ag(C{PPh₃}₂)Cl, which provided the authors with an unambiguous proof of its structure.

7 Three-bond hydrogen-hydrogen couplings

The performance of the ff99SB force field has been evaluated by Simmerling and co-workers¹⁵¹ against experimental values of $^3J_{\text{HNH}\alpha}$ couplings using replica-exchange molecular dynamics simulations of Ala₃ and Ala₅ in explicit water models.

Bui *et al.*¹⁵² have investigated the multiple timescale motions of the small protein Gβ1 and have found in these simulations large variations of $^3J_{\text{HNH}\alpha}$ couplings for residues that exhibit slow timescale motions.

Marckwick *et al.*¹⁵³ have checked the ability of AMD and standard MD trajectories to reproduce the experimental values of three types of protein scalar couplings, namely $^3J_{\text{HNH}\alpha}$, $^3J_{\text{HNC}'}$ and $^3J_{\text{HNC}\beta}$. Sinnavee *et al.*¹⁵⁴ have applied $^3J_{\text{HH}}$ couplings to show that the conformation of the backbone of the cyclic lipodepsipeptide Pseudodesmin A does not change between two

solvents chloroform and acetonitrile. A complete NMR analysis which also included determination of proton-proton spin-spin couplings has been performed by Ohno *et al.*¹⁵⁵ for oxytocin, neurohypophyseal peptide hormone, in phosphate buffer.

In Table 2 are listed structured and partially structured polypeptide chains for which vicinal proton-proton couplings were used in their structure calculations.

Hendrickx *et al.*¹⁷¹ have presented the results of their studies on the use of time-averaged $^3J_{\text{HH}}$ restrained molecular dynamics simulations for the conformational analysis of five-membered ring systems. A set of six ribose-based molecules has been applied as model compounds.

Lowary and his group¹⁷² have continued their studies on the furanoside-containing polysaccharides that are found in the cell wall structure of mycobacteria, including the pathogenic species *Mycobacterium tuberculosis* and *Mycobacterium leprosus*, which cause tuberculosis and leprosy, respectively. In the published paper they applied the combined use of AMBER/GLCYCAM MD simulations and calculation of a variety of $^3J_{\text{HH}}$ couplings to probe from the resulting conformer distribution the conformation of oligosaccharides consisting of two to four arabinofuranosyl residues. $^3J_{\text{HH}}$ couplings have been used in structural analysis of xylomannan antifreeze by Walters *et al.*,⁵⁸ of bionectriol A by Clardy and co-workers,⁵⁹ in conformational analysis of 2-*O*-sulfo- α -L-idouronic acid by Gandhi and Mancera,¹⁷³ and in structural analysis of apramycin bound at the bacterial ribosome A site by Balenci *et al.*¹⁷⁴

The structure of the product of the stereoselective synthesis of the C31-C40/C43-C52 unit of Amphidinol 3 has been confirmed by Kanemoto *et al.*¹⁷⁵ with the combined use of $^3J_{\text{HH}}$ couplings and NOE.

Table 2 Peptides and proteins for which the solution structure has been calculated with $^3J_{\text{HH}}$

name	<i>a</i>	<i>b</i>	ref.
a series of 4- <i>O</i> -glycosylated (2 <i>S</i> ,4 <i>S</i>)-hydroxyprolines	1		156
a series of peptides and glycopeptides with non-natural α -methylserine	3	4	157
Ac-Phe[Orn-Pro-DCha-Trp-Arg]	6	6	158
two mixed α/β peptides	6/8	6/3	159
a series of gramicidin S related cycloundecapeptides with <i>cis</i> D-Phe-Pro peptide bond	11	9	160
Xen2174, a χ -conopeptide related peptide	13	11	161
varf F, the cyclotide from <i>Viola arvensis</i>	29	29	162
hSVHP, supervillin headpiece	67	23	163
XACb0070 from <i>Xanthomonas axonopodis</i> pv. <i>Citri</i>	79	54	164
the act ACP, a series of early polyketide intermediates of secondary preferences of disordered polypeptide chain	86+	41/51	165
the C-terminal segment of p21 ^{Waf1/Cip1/Sdi1}	20	19	166
the drk N-terminal SH3 domain unfolded state	56	47	167
ubiquitin denaturated in 8 M urea at pH 2.5	76	69	168
urea denaturated dSmt3	88	82	169
α -synuclein at low pH in an aggregation prone state	140	ca. 35	170

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

Maes *et al.*¹⁷⁶ have constructed the SOACS index for easy retrieval of existing oligosaccharide sequences from web databases. The index is NMR-based including proton-proton couplings. 1

In Table 3 are given several examples of nucleosides, nucleotides and carbohydrates whose structures have been obtained with the help of $^3J_{\text{HH}}$ couplings. 5

The isolation and structural elucidation by the use NMR techniques including analysis of spin-spin couplings of a new myricetin-rhamnoglucoside isolated from *Camellia sinensis*, myricetin-3-*O*-[β -D-glucopyranosyl-(1 \rightarrow 3)- α -L-rhamnopyranosyl-(1 \rightarrow 6)- β -D-glucopyranoside, has been published by Hilal and Engelhardt.¹⁸⁵ 10

NMR spectroscopy and molecular dynamics simulations have been applied by Kozelka and co-workers¹⁸⁶ to study cisplatin adducts on a GGG sequence with a DNA duplex. In particular, crucial information has been obtained from $^3J_{\text{HH}}$ couplings on the local conformational equilibria of dsCG*G*G. 15

Vicinal proton-proton couplings have been of great help in structural studies on a variety of natural products isolated from living organisms. This included bioactive jatrophone diterpenes isolated from *Euphorbia guayaniana*, guayanianins E and guayanian F¹⁸⁷, a novel diterpenoid from *Jatropha multifida* whose structure has been settled by Das *et al.*¹⁸⁸ with the help of $^3J_{\text{HH}}$ couplings, three new cucurbitane triterpene glycosides, momocordicosides U, V and W isolated from *Momordica charantia* fruits,¹⁸⁹ and two new labdane diterpenes isolated from the leaves of *Stemodia trifoliata*.¹⁹⁰ 20

$^3J_{\text{HH}}$ couplings have been utilized by Cachet *et al.*¹⁹¹ for structure elucidation of five hydantoin alkaloids from *Parazoanthus axinellae*, parazoanthines A-E, by Gülcemal *et al.*¹⁹² to establish the structures of monoterpenoid glucoindole alkaloids and iridoids isolated from the aerial parts of *Pterocephalus pinardii*, and by Giao *et al.*¹⁹³ to prove the structures of five new β -carboline alkaloids isolated from the stems of *Picrasma quassioides*. 25

Further examples of the application of $^3J_{\text{HH}}$ couplings in structural analysis of natural products include micromelosides A-D, four new coumarins isolated from the stem bark of *Micromelum falcatum*, studied by Luo *et al.*¹⁹⁴ 30

Proton-proton couplings have been reported for three furostane saponins from *Agave brittoniana* Trel, spp. *Brachypus*,¹⁹⁵ two new saponins from *Sechium mexicanum*,¹⁹⁶ and two new steroidal saponins from *Smilax china*.¹⁹⁷ 35

Table 3 Nucleosides, nucleotides, oligonucleotides and carbohydrates and their derivatives for which $^3J_{\text{HH}}$ has been used as a structural parameter

name	ref.	
a series of N7-substituted inosines	177	
the 14-mer cUUCGg tetralopp hairpin RNA	178	
a 14 base-pair non-self complementary DNA duplex	179	
Carbohydrates		
phosphono and carba analogues of <i>N</i> -acetyl- α -D-mannosamine 1-phosphate	180	45
α -D-Manp-(1 \rightarrow 6)- α -D-Manp-OME and β -D-GLcpNAc-(1 \rightarrow 6)- α -D-Manp-OME	181	
<i>crown-CyPLOS</i> ; a novel carbohydrate-fused bis-crown ether	182	
a series of septanoside-containing trisaccharides	183	
rebaudioside A	184	

$^3J_{\text{HH}}$ couplings have been measured for three novel ecdysteroids, 22-dehydro-20-deoxy-ajugasterone, 1-hydroxy-22-deoxy-20,21-didehydro-ecdysone and 22-deoxy-20,21-didehydro-ecdysone, isolated from the roots of *Serratula wolffii*,¹⁹⁸ and for two new furostanol glycosides, torvosides O and P, isolated from *Solanum torvum*.¹⁹⁹

^1H and ^{13}C NMR data including proton-proton couplings has been published by Bacher *et al.*²⁰⁰ for a new limonoid, a new acridone alkaloid and a new flavone isolated from *Severinia buxifolia*, and by Mahmood *et al.*²⁰¹ for two new C-alkylated flavonoids from *Prunus domestica*, prunusins A and B, whose structures were established as 2-(4-[[[(3-ethylheptanoyl)oxy]methyl]phenyl]-5-methoxy-4-oxo-4H-chromen-7-yl (*E*)-(4-methoxyphenyl)-2-propenoate and 2-(4-[[[(3-ethylheptanoyl)oxy]methyl]phenyl]-5,8-dimethoxy-4-oxo-4H-chromen-7-yl 4-methyl benzoate.

An analysis of $^3J_{\text{HH}}$ couplings and NOESY experiments allowed Iwasaki *et al.*²⁰² to establish the conformation of koshikalide, a 14-membered macrolide isolated from the marine cyanobacterium *Lyngbya sp.* $^3J_{\text{HH}}$ couplings have been also applied in the structure determination of six new bisacetylenic oxylipins and the absolute stereochemistry of falcariindiol by Hoffman and co-workers,²⁰³ and in the assignment of absolute configurations for a series of neolignans from the leaves of *Casearia sylvestris* Swartz by Wang *et al.*²⁰⁴

The structures of thirteen curcuminoids isolated from the rhizomes of *Curcuma longa* have been elucidated by extensive spectroscopic NMR analyses, including proton-proton couplings, among them, 5-dihydroxy-1,7-bis(4-hydroxyphenyl)-4,6-heptadiene-3-one, 1,5-dihydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-4,6-heptadiene-3-one, 1,5-dihydroxy-1-(4-hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-4,6-heptadiene-3-one, and 3-hydroxy-1,7-bis(4-hydroxyphenyl)-6-heptene-1,5-dione.²⁰⁵

The preferred conformations of ϵ -lactams, the products of the degradation of ten different spirocyclic oxaziridines, have been determined by Montalvo-González and Ariza-Castolo²⁰⁶ by examining $^3J_{\text{HH}}$ couplings and the effects of the *N*-substituent and the alkyl group of the aliphatic ring on the ^1H and ^{13}C chemical shifts in the NMR spectra.

The effects of substituents and the naphthyl ring on the conformation of a series of variously substituted naphthyl naphthoxazines have been investigated by Tóth *et al.*²⁰⁷ by the use of experimental $^3J_{\text{HH}}$ couplings and theoretical calculations. Tautomeric behaviour of 3-arylpyrimido[4,5-*c*]pyridazine-5,7(*6H,8H*)-diones and their sulfur analogues has been studied by Rimaz *et al.*,²⁰⁸ and for all of them proton-proton couplings have been measured. Most of the compounds studied exist in the lactam form only.

$^3J_{\text{HH}}$ couplings have been reported by Katritzky *et al.*²⁰⁹ for a series of pyridazine derivatives, for some new triazapentalene derivatives by Palmas *et al.*²¹⁰ and by Hsieh *et al.*²¹¹ for the Ni complex of 2-(*tert*-butylaminomethyl)pyrrole. A set of $^3J_{\text{HH}}$ couplings has been published by Sipos *et al.*²¹² for a series of ring constrained endoethenomorphinans possessing 2'-substituted thiazole ring known as an important group of semi-synthetic opioid analgesics.

Vicinal proton-proton couplings including those between NH and olefinic protons have been measured by Venkatachalam *et al.*²¹³ for a series

of variously substituted phenyl- and pyridin-2-ylamino(methylene)-naphthalene-2(3*H*)-ones. 1

Analysis of vicinal proton-proton couplings combined with the results of enantioselective deuteration results have been applied by Freire *et al.*²¹⁴ to establish the conformational composition of the tris(α -methoxy- α -phenyl-acetic acid) ester derivatives of 1,2,3-*prim, sec, sec*-triols. 5

Some interesting CH₂CH₃ spin systems in several diethyl malonate indene derivatives have been studied by Zhang *et al.*²¹⁵ with the aid of NMR and molecular modelling. They have shown that the spin systems of CH₃CH₂ of the two COOCH₂CH₃ groups in those compounds may exist in different forms (AMX₃, ABX₃ and A₂X₃) and the effect of the aromatic ring induced by the phenyl group at the end of the triple bond is the main reason for these phenomena. 10

A conformational analysis of some 2-substituted ethanesulfonates, XCH₂CH₂SO₃Na (X=Br, Cl, OH, NH₂, SH) in aqueous solution has been performed by Musio and Sciacovelli²¹⁶ by the use of ³J_{HH} couplings, and the results obtained experimentally have been compared with those derived theoretically. However, calculations in vacuum have not reproduced correctly the conformational behaviour of the compounds studied, and in order to obtain an agreement between the experiment and theory solvent effects have to be taken into account. Conformational isomerization of *cis* and *trans* isomers of 2,4,5-trimethyl-1,3, 2-dioxaborinane has been studied by Valiakmetova *et al.*,²¹⁷ who concluded that its route includes equilibrium between sofa conformers with a different steric orientation of substituents at the C-4 and C-5 ring atoms. 15 20 25

³J_{HH} couplings in α -tocopherol, a fluorescent, oxidatively sensitive polyene analogue of α -tocopherol, [(*S*)-2,5,7,8-tetramethyl-2-((1*E*/3*E*,5*E*,7*E*,9*E*)-4,8,12-trimethyltrideca-1,3,5,7,9,11-hexenyl)chroman-6-ol] and some of its intermediates have been analysed by Wang *et al.*²¹⁸ in order to establish the configuration around double bonds in these compounds. 30

Vicinal couplings across a double CC bond typical of *trans* configuration, ³J_{HH} about 16 Hz, have been observed by Barros and Silva²¹⁹ for three series of new nitro-2-styrylchromones.

An extensive use of ³J_{HH} couplings has been made by Budzisz and co-workers²²⁰ in order to establish the conformation of two chromane derivatives, 2-methyl-2,3-dihydro-4-hydroxy-2*H*-1-benzopyran-3-carboxylic acid methyl and 2-phenyl-2,3-dihydro-4-hydroxy-2*H*-1-benzopyran-3-carboxylic acid ethyl esters. 35

A series of gold(III)-triphenylphosphine-pentafluorophenyl-aryloxoimidazole complexes of the general formula [Au(PPh₃)(C₆F₅)Raa(R')](OSO₂CF₃)₂ where aai is a N(imidazole), N(azo) chelator (*p*-R-C₆H₄-N=N-imidazole-R') and R=H, Me, Cl; R'=Me, Et, CH₂Ph has been characterized by Byabartta²²¹ by the NMR spectroscopy including vicinal proton-proton couplings. 40 45

8 Three-bond couplings to hydrogen

A new ³J_{HC} coupling prediction equation has been proposed by Bifulco and co-workers.²²² It includes all of the specific electronegativity terms on both

nuclei and uses nine Pn parameters, based on the coupling database of *ca.* 2000 values obtained by DFT calculations at the MPW1PW/6-31G(d,p) level. A satisfactory accuracy in the reproduction of the experimental NMR data has been demonstrated by the authors by the use of a large set of experimental ${}^3J_{\text{HC}}$ couplings obtained from 29 benchmark organic compounds characterized by heterogeneous substitution patterns.

Intrinsic conformational propensities of amino acid residues in short host-guest G-X-G tripeptides have been studied with the aid of ${}^3J_{\text{HC}}$, ${}^3J_{\text{HN}}$ and ${}^3J_{\text{HH}}$ couplings by Hagarman *et al.*²²³ Grzesiek and co-workers²²⁴ have applied the same ${}^3J_{\text{HC}}$, ${}^3J_{\text{HN}}$ and ${}^3J_{\text{HH}}$ scalar couplings and additionally ${}^1D_{\text{HC}}$ RDCs for estimation of the populations of χ_1 side-chains rotamers in urea-denaturated ubiquitin and protein G. Allison and van Gunsteren²²⁵ have used a set of experimental side chain χ_1 3J couplings (${}^3J_{\text{HN}}$ and ${}^3J_{\text{HH}}$) of FH506 binding protein bound to ascomycin to show that LE (Local Elevation) MD is the best method for producing ensembles of structures.

The relative configurations of chiral centres of the polyketide residues of a series of depsipeptides from an Indonesian sponge have been established by the combined analysis of ${}^{2,3}J_{\text{HC}}$ and ${}^3J_{\text{HH}}$ couplings by Plaza *et al.*²²⁶

An analysis of $\delta(^{13}\text{C})$, $\delta(^{15}\text{N})$ chemical shifts and ${}^3J_{\text{HC}}$ couplings in adenine and its derivatives performed by Dybiec *et al.*²²⁷ by the use of GIAO DFT data has confirmed earlier reports of *ca.* 15:85 proportion of N7-H and N9-H adenine tautomers in DMSO solution. So far, there is no firm NMR evidence of participation of N3-H tautomer in the dynamic equilibrium.

${}^3J_{\text{H}4'\text{C}1}$ and ${}^3J_{\text{H}1\text{C}4'}$ couplings have been used by Engelsen and co-workers²²⁸ in their NMR-MD investigations of the structure of 3'-*O*- and 6'-*O*-maltose phosphorylated disaccharides.

Other examples of carbohydrates and nucleotides whose structures were solved with the aid of 3J heteronuclear couplings are listed in Table 4.

The structure of six new bisacetylenic oxylipins and the absolute stereochemistry of faltarindiol from carrots (*Daucus carota* L.) have been determined with the aid of ${}^{1-3}J_{\text{HC}}$ couplings by Hoffman and co-workers,²⁰³ and relative configurations of four novel oxylipins from *Dracontium lorentense* have been assigned by Benavides *et al.*²³⁴

A configurational analysis of nhantrangins A and B, two aplysiatoxin-related metabolites isolated from the cyanobacterium *Lyngbya majuscula* has been performed by Chlipala *et al.*²³⁵ by the use of ${}^3J_{\text{HC}}$ and ${}^3J_{\text{HH}}$ couplings, and NOE experiments.

Vicinal H-C couplings have been found to be a very useful tool for the determination of the configuration around the double bond, in particular in compounds where three substituents are attached to it. Recently, they have been applied by Trofimov and co-workers²³⁶ to establish the structure of functionalized L-cysteine and L-methionine obtained by reaction with electron-deficient acetylenes. This included (2*R*)-2-ammonio-3-[[*(Z)*-2-cyano-1-phenylethenyl]sulfanyl]propanoate, (2*R*)-2-ammonio-3-[[*(Z)*-2-cyano-1-(1-hydroxy-1-methylethyl)ethenyl]sulfanyl]propanoate and some related compounds.

${}^3J_{\text{HC}}$ couplings have been also used by García *et al.*²³⁷ to establish unequivocally the configuration around the double bond in the oxylipin

Table 4 Nucleosides, nucleotides and carbohydrates for which heteronuclear vicinal couplings have been used as a structural parameter

name	^a	ref.
guanosine and deoxyguanosine	^{1,3} J _{HC}	229
the 14-mer cUUCGg tetralopp hairpin RNA	³ J _{HP} , ³ J _{CP}	178
carbohydrates		
methyl- α -cellobioside; -laminarabioside and -sophoroside	³ J _{HC} , ³ J _{CC}	230
methyl- β -cellobioside and -laminarabioside	³ J _{HC}	231
<i>crown-CyPLOS</i> ; a novel carbohydrate-fused bis-crown ether	³ J _{HP}	182
α -D-Manp-(1 \rightarrow 6)- α -D-Manp-OMe and β -D-GLcpNAc-(1 \rightarrow 6)- α -D-Manp-OMe	² J _{HC} , ² J _{CC}	181
heparin Δ U-tetrasaccharide	³ J _{HC}	232
a complex polysaccharide from <i>Shigella flexneri</i> 5a	³ J _{HC} , ³ J _{CC}	230
O-chain polysaccharide from <i>Halomonas alkaliantarctica</i>	¹ J _{HC}	233
^a type of vicinal heteronuclear couplings measured.		

natural products peyssonenyne A and B isolated from the Fijian red marine alga *Peysonneli caulifera* and their synthetic analogues derived from palmitic acid.

^{2,3}J_{HC} couplings have been applied by Böhm *et al.*²³⁸ for discrimination between two possible products of the reaction between 2-substituted 1-(9-acridinyl)thiosemicarbazide and dimethyl acetylene dicarboxylate, *i.e.* 1,3-thiazolidin-4-one and 1,3-thiazin-4-one shown in Fig. 6. The experimentally determined ³J_{H6C4} coupling of 4.6 Hz is in good agreement with the coupling of *ca.* 4.8 Hz calculated for the compound containing five membered ring. The predicted for the other structure H5-C4 coupling is of 2.2 Hz only.

³J_{HC} and ³J_{HH} couplings have been of great help in structural studies on aryl-substituted enaminketones and their thio analogues²³⁹ and the couplings, ³J_{H2'C3} of 5 Hz and ³J_{H2'C1} of 7 Hz, allowed to establish the correct arrangement of substituents around the double bond in *E*-methyl-5-(*tert*-butoxy-carbonylamino)-2-[(dimethylamino)methylidene]-3-oxopentanoate,²⁴⁰ see Fig. 7.

Vicinal proton-carbon couplings have been applied by Ding *et al.*²⁴¹ to determine the configuration of the unique phenylpropanoyl 2, 7-anhydro-3-deoxy-2-octulosonic acid derivative isolated from horseweed (*Conyza*

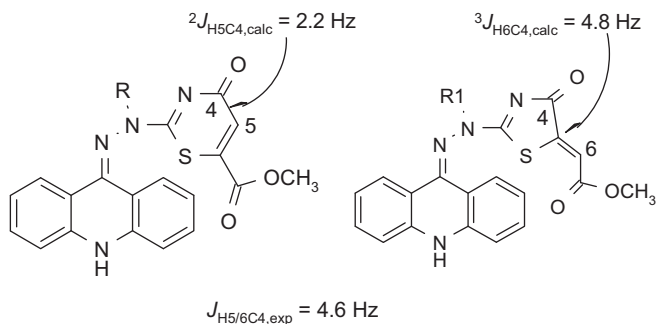


Fig. 6

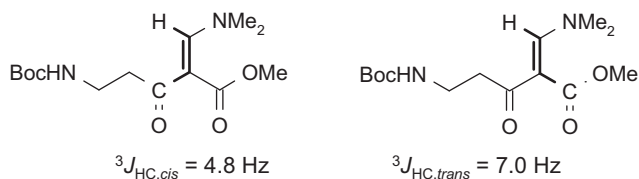


Fig. 7

Canadensis), i.e. *rel*-(1*S*,2*R*,3*R*,5*S*,7*R*)-methyl 7-caffeoyloxymethyl-2-hydroxy-3-feruloyloxy-6,8-dioxabicyclo[3.2.1]octane-5-carboxylate, the compound which reveals inhibitory effect on catecholamines secretion.

Biotransformation of 2,3,3,3-tetrafluoropropene in rabbits²⁴² and *trans*-1,1,1,3-tetrafluoropropene in rats²⁴³ has been studied by Schuster *et al.*,^{242,243} and the metabolites have been identified by ¹⁹F NMR shifts, signal multiplicity, proton-fluorine couplings and by comparison with synthetic reference compounds.

Fluorophenylalanine ³J_{HF} couplings have been used by Kitevski-Leblanc *et al.*²⁴⁴ to establish proton-proton connectivities in ¹⁹F edited NOESY spectra of 3-fluorophenylalanine labelled calmodulin.

New advanced basis sets are constantly produced for the calculation of indirect spin-spin couplings owing to the difficulty of their accurate estimation. However, it has been shown by Ambati and Rankin²⁴⁵ that the small, simple 6-31G basis set is sufficient to provide accurate results for ⁿJ_{Hsi} couplings, n = 1, 2, 3, in organosilicon alkoxides and some products of their hydrolysis and condensation. The authors have also shown that a strong dihedral dependence exists in the compounds studied for ³J_{Hsi} couplings.

Analysis of the NMR data including ³J_{HP} and ³J_{HH} couplings allowed Coppola *et al.*¹⁸² to establish conformational preferences in a novel sugar-based macrocycle consisting of a phosphate-linked 12-membered disaccharide ring (cyclic phosphate-linked oligosaccharide, *CyPLOS*), fused to two 18-crown-6 ether residues.

Interresidual ³J_{HSe} couplings of *ca.* 2 Hz and intraresidual ²J_{HSe} of *ca.* 35 Hz have been measured by King and co-workers²⁴⁶ for proteins in which inactive ³²S nucleus was replaced with Se at natural abundance of 7.6% of ⁷⁷Se. The replacement allows a direct determination of disulfide bridge connectivities using scalar couplings.

Complete ¹H, ¹³C, ¹⁹F and ³¹P NMR data which also included long-range J_{HF}, J_{HP} and ¹J_{FP} couplings has been published by Sharma *et al.*²⁴⁷ for *N,N*-dialkyl-P-alkyl phosphonamidic fluorides.

³J_{HP} couplings in L- α -phosphatidylcholine and L- α -phosphatidic acid sodium salt from egg yolk have been determined by Rojruthai *et al.*²⁴⁸ ³J_{HP} couplings found for CH₂OP linkage of glyceride backbone was about 6.5 Hz, while that of CH₂OP linkage of the choline group was about 9.0 Hz. These assignments have been used by the authors as models of the terminal group of natural rubber, which is presumed to contain a phosphate group at the chain end.

Two papers devoted to structural trends of the H-Se spin-spin couplings and conformational behaviour of 2-substituted selenophenes have been

published by Rusakov *et al.*^{249,250} In particular, vicinal H-Se couplings have displayed remarkable stereochemical behaviour with respect to the internal rotation of the formyl group, which is of major importance in stereochemical studies of the related selenium-containing compounds.²⁴⁹

³J_{H113Cd} and ³J_{H111Cd} couplings of 44 and 42 Hz, respectively, have been observed by Lu *et al.*²⁵¹ for a bi-Cd complex, [Cd₂(bis(2-pyridyl)formamidine)₃].

A huge amount of the NMR data has been already collected for organotin(IV) derivatives, including H-Sn and C-Sn spin-spin couplings across one, two and three bonds. Recently, the Karplus-type dependence proposed in the literature for vicinal ³J_{H_{Sn}} and ³J_{C_{Sn}} couplings has been confirmed theoretically by Saielli and co-workers,²⁵² who performed DFT calculations both at the non-relativistic and scalar ZORA relativistic level.

Rochon and co-workers have continued their studies on synthesis of anti-tumor platinum mixed ligands complexes and investigation of their structure by the use of NMR spectroscopy. The following series of the complexes of the general formula have been obtained, *cis*- and *trans*-[Pt(amine)₂(pyrimidine)₂](NO₃)₂,²⁵³ Pt(amine)₂(pyrimidine)₂X₂ and *trans,trans*-X₂(amine)Pt(μ -pyrimidine)Pt(amine)X₂,²⁵⁴ and for all them ³J_{H_{Pt}} and a variety of J_{CP} couplings have been measured. Generally, the couplings ³J_{H_{Pt}} and ³J_{CPt} are larger in the *cis* isomers than in the equivalent *trans* analogues.

Trends in vicinal proton-platinum couplings, ³J_{H_{Pt}}, have been analysed by Pazderski *et al.*²⁵⁵ in Pt(II) chloride organometallics with N(1),(C2')-chelated, deprotonated 2-phenylpyridine (2ppy*) of general formulae, *trans*(*N,N*) [Pt(2ppy*)(2ppy)Cl] and *trans*(*S,N*)-[Pt(2ppy*)(DMSO-d₆)Cl]. Two different ³J_{H_{Pt}} couplings of 30 and 37 Hz have been observed by Shen *et al.*²⁵⁶ for H6 and H6' protons, respectively, in the [PtCl(MeNH₂)(bpy)]²⁺; this difference has been interpreted by the authors in terms of the different ligands in *trans* position of the ring-N atoms and their different electronegativities. Additionally, a full set of experimental and calculated proton-proton couplings has been obtained for 2,2'-bipyridine (bpy), good agreement being observed between experiment and theory.

The molecular structures of protonated and mercurated derivatives of thimerosal, *i.e.* sodium ethylmercury thiosalicylate have been studied by Sattler *et al.*²⁵⁷ with the aid of ¹H NMR including ²J_{H_{Hg}} and ³J_{H_{Hg}} couplings across of the ethyl group which have been found to be of opposite signs.

9 Three-bond couplings not involving hydrogen

Vicinal carbon-carbon and proton-carbon couplings have been discussed by Guvench *et al.*²⁵⁸ as a source of information on disaccharide conformation properties in solution. The main goal of the authors was to develop a highly optimized force field for the glycosidic linkages between hexopyranoses, with validation focusing on disaccharide crystalline molecular geometries and unit cell parameters, solution densities, and conformational properties in aqueous solution. Xia and Margulis²³⁰ have implemented ³J_{HC} and ³J_{CC} couplings in their Fast Sugar Prediction Software. ¹⁻³J_{CC} and ²J_{CC} couplings have been applied by Serianni and co-workers²⁵⁹ for detection of isomers in *cis-trans* isomerisation of methyl *N*-formyl and *N*-acetyl-D-glucosaminides.

Angular relationships have been established by Rusakov *et al.*²⁶⁰ in the direct and vicinal J_{CC} and J_{HC} couplings in the vinyrrole fragment, making it possible to use them in stereochemical investigations of the *N*-vinyl derivatives of pyrrole. 1

Trends in long-range C-F couplings have been applied by Yoder *et al.*²⁶¹ for assignment of ^{13}C NMR chemical shifts in some substituted tetrakis(phenyl)germanes. 5

Sagi and co-workers²⁶² in their studies of modified nucleotides have found that in the series of 3'-substituted phosphoramidite derivatives of thymidine the difference between the values of $^3J_{C4'P}$ and $^3J_{C2'P}$ couplings is induced rather by the electronegativity of the substituents than the differences in rotational preferences about the C3'-O3' bond. 10

The conformational analysis of two diastereomeric series of 2-*p*-X-anilino-2-thio-4,6-dimethyl-1,3,2λ⁵-dioxaphosphorinanes, *cis-eq* and *cis-ax*, based on $^3J_{HH}$, $^3J_{HP}$, $^4J_{HP}$ and $^3J_{CP}$ couplings allowed Gordillo and co-workers¹⁰⁰ to conclude that both groups of compounds exist in a chair form. 15

An analysis of the ^{19}F NMR spectra of a series of arylfluoroalkylsulfides has been performed by Zhang *et al.*²⁶³ yielding two- and three-bond F-F couplings and a two-bond H-F coupling.

Three-bond F_{ortho} -Pt couplings in the range 453–476 Hz have been measured by Calvet *et al.*²⁶⁴ for $[\text{Pt}(\text{C}_6\text{F}_5)_2\{\text{Me}_2\text{NCH}_2\text{CH}_2\text{NCH}(2\text{-BrC}_6\text{H}_4)\}]$ and $[\text{Pt}(\text{C}_6\text{F}_5)_2\{\text{Me}_2\text{NCH}_2\text{CH}_2\text{NCH}(2,6\text{-Cl}_2\text{C}_6\text{H}_3)\}]$ complexes, respectively; for both compounds also $^3J_{FF}$ couplings of 458.5 and 475.6 Hz, respectively, have been determined. 20

10 Couplings over more than three bonds and through space 25

$^4J_{H4,OH3}$ couplings have been measured in methyl α -cellobioside and its angular dependence followed with DFT calculations by Serianni and co-workers.²⁶⁵ 30

Germann and co-workers²⁶⁶ have shown that adenine $^6/7J_{H2H8}$ coupling of ca. 0.6 Hz may be a useful tool in structural studies of nucleic acids for unambiguous assignment of H2 resonances.

Proton-proton couplings across three and four bonds, $^3J_{HH} = \text{ca. } 2$ and $^4J_{HH} = \text{ca. } 1$ Hz, respectively, have been reported by Steinmetz²⁶⁷ for the β -D-glucopyranose ring of the more abundant isomer of granatin B, a complex ellagitannin extracted from pomegranate fruit, in agreement with the $^1\text{C}_4$ conformation. 35

$^4J_{HH}$ and $^5J_{HH}$ couplings have been measured by Grandbois *et al.*²⁶⁸ for *cis* and *trans* isomers of some novel 2*H*,5*H*-dihydrofuran-3-yl ketones. The larger coupling values $J = 6$ Hz have been observed for the major *trans* isomer and the smaller ones of 5 Hz have been found for the minor isomer *cis*. This assignment is in an agreement with the Karplus relationship. 40

A complete analysis of the higher order ^1H NMR spectra of diastereomeric mixtures of (*R,S*- and *S,S*)-3,6-dimethoxy-2,5-dihydropyrazine-substituted indoles has been performed by Akhmedov *et al.*²⁶⁹ yielding the precise values of the proton-proton couplings across three, four, five and six bonds. The obtained results allowed the authors to establish the conformational preferences of the studied compounds in solution. 45

Proton-proton couplings across three and four bonds have been measured by Salgado *et al.*²⁷⁰ for a series of [1,2,4]triazolo[1,5-a]pyrimidine and [1,2,4]triazolo[4,3-a]pyrimidine regioisomers. 1

Four-bond proton-proton couplings have been observed by Gholivand *et al.*²⁷¹ for the aromatic protons of some *N*-nicotiny and *N*-2,4-dichlorobenzoyl phosphorictriamides, and a long-range coupling between the NH and vinylic protons has been observed by Zakavi *et al.*²⁷² for *meso*-tetracinnamylporphyrin. 5

Strong H-F couplings observed by Popeney *et al.*²⁷³ in the spectrum of the [(F-Cyc)PdMe(NCMe)]Ar₄ complex, where F-Cyc = fluorinated cyclophane, Ar = 3,5-(CF₃)(C₆H₃) provided clear evidence that the fluorine atoms were interacting with the metal axial site approaching the coordination centre. Thus, J_{HF} coupling of 4.5 Hz has been found between two nearby fluorine atoms and the protons of the methyl ligand, and a coupling of similar strength has been found between protons of the acenaphthyl diimine backbone and two other nearby fluorine atoms. 10 15

Analyses of the complex ¹H NMR spectra of four isomers of dihalogenated benzanilides have been carried out by Suryaprakash and co-workers²⁷⁴ yielding the H-H and H-F couplings across three, four and five bonds. In order to extract the precise coupling values and the relative signs of heteronuclear couplings the authors applied the recently developed by them combination of independent spin system filtering and the spin-state selective detection of single quantum transitions by the two-dimensional multiple quantum methodology without resorting to numerical iterations. The systematic studies performed by the authors²⁷⁵ for a variety of fluorobenzanilides revealed that in the phenyl ring systems ⁵ J_{HF} is always negative in all the molecules irrespective of their spin topologies. 20 25

An analysis of the ¹H, ¹³C, ¹⁵N and ¹⁹F spectra of 10 fluoronitroanilines performed by Gierczyk *et al.*²⁷⁶ yielded a full set of H-F, C-F and F-F couplings including those across three, four and five bonds. 30

Long-range couplings, ⁿ J_{HP} (n = 5, 6, 7) in the range of 1.2–2.1 Hz have been observed by Gholivand *et al.*²⁷⁷ in some novel phosphoric triamide derivatives of nicotinamide and isonicotinamide of the general formula, RP(O)R'₂ where R = nicotinamide, R' = NHC(CH₃)₃ or NH(C₆H₁₁); R = isonicotinamide, R' = NH(C₆H₁₁). The coupling values were considerably reduced or vanished on coordination to Sn in the corresponding complexes. 35

Intramolecular and distance dependent through-space C-F and F-F couplings have been applied by Bröring and co-workers to study conformational dynamics of various BODYPY's complexes, potent fluorescent dyes.^{278,279} This included investigation of [bis-(*N,N'*-difluoroboryl)]-3,3'-diethyl-4,4',8,8',9,9',10,10'-octamethyl2,2'-bidipyrrin and some related compounds,²⁷⁹ and an analysis of the solution structure of a 3,3-diethyl-4,4',8,8',9,9',10,10'-octamethyl-6,6'-di-*p*-tolyl-bisBODYPY (where BODYPY = boron-dipyrrromethene).²⁷⁸ 40 45

A through space coupling between F and C6 atoms of 4.2 Hz has been found by Zheng *et al.*²⁸⁰ in the *S*-conformer of 1-((2*R*4*S*)-3,3-difluoro-4-hydroxytetrahydrothiophen-2-yl)uracil; a similar coupling J_{HF} of 1.8 Hz has been observed for the H6 hydrogen atom.

A new approach to studying coupling pathways for the Fermi contact term of NMR spin-spin couplings (SSCCs) has been presented by Contreras *et al.*²⁸¹ It is based on the known form of propagating the Fermi hole through a canonical molecular orbital (CMO). To demonstrate the usefulness of this approach, dubbed FCCP-CMO (Fermi contact term coupling pathways-CMO), it has been applied to analyze the through-space transmission of the FC term of J_{PP} SSCCs by overlap of the P lone pairs.

$^nJ_{CM}$ couplings ($n = 1 - 4$, $M = \text{Si, Sn, Pb}$) have been reported by Yoder *et al.*²⁸² for PhMO_X and PhMCl compounds. Couplings across four bond have been observed for PhMCl compounds only.

trans-Orientation of perfluoroalkyl substituents in 2-amino-5-fluoro-4,5-bis(perfluoroalkyl)-4,5-dihydrooxazol-4-ols, the unexpected products of internal perfluoroolefin oxides with urea, has been established by Saloutina *et al.*²⁸³ with the help of long-range F-F couplings including those across four and five bonds.

Beckmann and co-workers²⁸⁴ have reported $^2J_{FF}$ and $^4J_{FF}$ couplings measured for a series of square-planar 2-toluenido(triphenylphosphane)nickel(II) complexes containing bidentate N,O ligands.

The increase of the four-bond couplings, $^4J_{\text{SeSe}}$, has been observed by Lari *et al.*²⁸⁵ in a series of methyl-2-(methylselenyl)benzyl selenide, ethynyl 2-(methylselenyl)benzyl selenide and 2-(methylselenyl)benzyl selenocyanate, 37.8, 40.9 and 58.8 Hz, respectively. This result has been interpreted by the authors in terms of a growth in the intramolecular $\text{Se} \cdots \text{Se}$ interaction. In order to confirm this supposition, the $^4J_{\text{SeSe}}$ coupling of 34 Hz was determined for 2-(cyanoselenyl)benzyl selenocyanate in which the substituents on the two selenium centres are electron-withdrawing groups.

11 Couplings through hydrogen bonds

The properties of the intramolecular hydrogen bonds of doubly ^{15}N -labelled protonated sponges of the 1,8-bis(dimethylamino)naphthalene (DMANH^+) type have been studied by Pietrzak *et al.*²⁸⁶ as a function of the solvent, concentration and temperature. Information about the NHN hydrogen bond symmetries has been obtained by the analysis of the scalar couplings $^{2h}J_{\text{NN}}$, $^1J_{\text{HN}}$, $^{1h}J_{\text{HN}}$. It has been shown by the authors that the sum $|^1J_{\text{HN}} + ^{1h}J_{\text{HN}}|$ represents a measure of the hydrogen-bond strength in a similar way to $^{2h}J_{\text{NN}}$ and δ_{H} .

Theoretical study of bifurcated hydrogen bonding effects on the $^{1h}J_{\text{HN}}$, $^{2h}J_{\text{NN}}$, $^1J_{\text{HN}}$ and ^1H , ^{15}N shielding in model pyrroles has been performed by Afonin and Vashchenko.²⁸⁷

The intra- and intermolecular spin-spin couplings have been calculated by Cybulski and Sadlej²⁸⁸ for formamide-formic acid and formamide-formamidine complexes at the B3LYP/HuzIIIIsu3 level. It included a large number of various spin-spin couplings across hydrogen bonds, such as, for example, $^{1h}J_{\text{HO}}$, $^{1h}J_{\text{HN}}$ and $^{2h}J_{\text{OO}}$. Surprisingly substantial values of ca. 0.7–1.5 Hz have been calculated for the $^6J_{\text{HH}}$ couplings between protons bound to the carbon atoms. Very interesting are the one-bond couplings between migrating protons and heavier nuclei since they are connected with breaking and creation of the hydrogen bonding and, thus, they change

character from intra- to intermolecular along the double proton exchange path.

Molecular dynamics simulations based on the standard nonpolarizable AMBER force fields and on quantum derived polarized protein-specific charge have been performed by Ji and Zhang²⁸⁹ to compute NMR scalar couplings, $^3\text{h}J_{\text{C}'\text{N}}$, across hydrogen bonds for three benchmark protein systems: ubiquitin, the GB1 domain of protein G, and the SMN Tudor domain. A comparison of the simulation results with experimental data allowed the authors to conclude that intraprotein hydrogen bonds are significantly stabilized by electronic polarization, both in terms of NMR scalar couplings and X-ray determined geometries of hydrogen bonds.

Schanda *et al.*²⁹⁰ have measured 7 solid-state $^3\text{h}J_{\text{C}'\text{N}}$ couplings in ubiquitin and found that their values are identical within error with those measured for solution state. However, 24 other couplings of this type measured for this protein in solution were below limit of detection in the solid-state.

Compounds for which couplings through hydrogen bonds were used in structural analysis are listed in Table 5.

A rather high value of the two-bond spin-spin coupling, $^2\text{h}J_{\text{NHF}} = 61$ Hz, observed by Golubev *et al.*²⁹³ for a strongly hydrogen-bonded anionic cluster, CNHF involved in an ion pair with a tetrabutylammonium cation, indicates the covalent character of the hydrogen bond in this complex. $^1J_{\text{NHF}}$ coupling = 92 Hz for non-deuterated and $^1J_{\text{NDF}} = 14$ Hz in deuterated forms of this complex have been measured.

A linear correlation has been established by Nazarski²⁹⁴ between the experimental and calculated $^2\text{h}J_{\text{HP}}$ couplings across $\text{NH} \cdots \text{O} = \text{P}^+$ bonds in some phosphorous esters.

The effect of substituent and hybridization on the properties of $\text{F-H} \cdots \text{N}$ hydrogen bond and two-bond N-F couplings across the hydrogen bond, $^2\text{h}J_{\text{NF}}$, have been theoretically studied by Ebrahimi *et al.*²⁹⁵ in the $\text{F-H} \cdots \text{NCX}$, $\text{F-H} \cdots \text{N(H)-CX}$ and $\text{F-H} \cdots \text{N(H}_2\text{)-CX}$ complexes. Similar studies have been performed on $^1\text{h}J_{\text{HX}}$ and $^2\text{h}J_{\text{XF}}$ couplings in $\text{CX} \cdots \text{H-F}$ complexes in halomethanes, haloethylenes and haloacetylenes.²⁹⁶ Huang and Meuwly²⁹⁷ have applied several improved H-bond potentials in their studies of model proteins and compared the calculated values of $^3\text{h}J_{\text{C}'\text{N}}$ couplings with experimental ones.

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

name	<i>a</i>	<i>b</i>	<i>c</i>	ref.
the 14-mer cUUCG tetralopp hairpin RNA	N-H ⋯ N	$^2\text{h}J_{\text{NN}}$	15	178
β -PGM-MgF ₃ ⁻ -G6P, β -phosphoglucomutase sugar phosphate complex	N-H ⋯ F	$^1\text{h}J_{\text{HF}}$	3	291
β -PGM-MgF ₃ ⁻ -G6P, β -phosphoglucomutase sugar phosphate complex	N-H ⋯ F	$^2\text{h}J_{\text{NF}}$	3	291
calmodulin, <i>holo</i>	N-H ⋯ O=C	$^3\text{h}J_{\text{CN}}$	20	292

^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

In contrast to the short-range information content of 3J couplings and NOE's, residual dipolar couplings (RDCs) provide long-range structural information and can also be used to relate non-interacting spins in biomolecular and recently organic compounds.

An elegant example of application of RDCs for determination of the conformation of the key intermediate in an enantioselective palladium-catalyzed allylic substitution has been published by Thiele and co-workers.²⁹⁸ The complex studied by the authors has been a self-organizing palladium catalyst system described previously by Helmchen *et al.*²⁹⁹ bearing two monodentate ligands. Orientation of the sensitive intermediate was possible in high-molecular-weight poly(γ -benzyl-L-glutamate) which has been recently shown by Thiele and co-workers to be superior to the commercially available low-molecular-weight PBLG.³⁰⁰ The authors were able to demonstrate that the cyclohexenyl ligand involved in the catalytic system is flexible with almost equally populated chair- and boat-like conformations. Thiele *et al.*³⁰¹ have shown that it was possible to assign the relative configuration of a diastereoisomer when residual dipolar couplings were used in the joint treatment of an unknown configuration and conformational averaging. The α -methylene- γ -butyrolactone served as an example for which the simultaneous determination of configuration (*trans*) and conformer populations were calculated. The same group has also proposed the use of local alignment tensor for the determination of the relative configurations in organic compounds with the aid of residual dipolar couplings.³⁰²

Residual dipolar couplings (RDCs) have been applied by Şerbescu and Saalwächter³⁰³ to study particle induced network formation in linear PDMS filled with silica. The relaxational dynamics of trapped entanglements in model silicone polymer networks has been studied by Acosta *et al.*³⁰⁴ through the residual dipolar couplings obtained by DQ NMR experiments. Among others, the authors observed that according to the viscoelastic response, the networks prepared with A4 cross-linkers show systematically higher values of the residual dipolar coupling values than trifunctional cross-links networks.

García *et al.*³⁰⁵ have applied the combined use of X-ray and NMR residual dipolar couplings in stereochemical analysis of withanolides, a group of C₂₈ steroids. $^1D_{\text{HC}}$ RDCs have been used by Swarbrick and Ashton³⁰⁶ in the assignment of chiral centres and validation of diastereomer configuration of dextromethorphan. Navarro-Vázquez and co-workers³⁰⁷ have used the same type of coupling in conformational analysis of salsolidine hydrochloride, isoquinoline alkaloid.

Fujita and co-workers³⁰⁸ have utilized self-assembled hosts with parallel aligned aromatic stacks to orient small organic molecules in a magnetic field, inducing RDCs by encapsulation.

$^1D_{\text{HC}}$ and $^1D_{\text{HN}}$ have been employed by Kiran *et al.*³⁰⁹ in determination of secondary structure of unnatural homooligomers comprised of β -aminoacid building blocks *cis*- and *trans*- β -bornene.

New tags have been developed for the lanthanide labelling of proteins. Häussinger *et al.*³¹⁰ have presented very rigid and high-affinity lanthanide chelating tag [M8] that produces large values RDCs (>20 Hz); Otting and

co-workers³¹¹ have presented non-covalent binding tag (DPA) that produces sufficiently large RDCs and does not require protein modification. 1

A new method for computing the molecular alignment tensor based on the molecular shape has been offered by Fushman and co-workers.³¹² The method contains program PATI (Prediction of Alignment Tensor using Integration) 5 that, according to the authors, yields the structure with the accuracy similar to PALES but is computationally more efficient. RDC-exact module to calculate the core structure of proteins has been included by Zeng *et al.*³¹³ in their structure determination package, called RDC-PANDA. The module calculates the global optimal solution of backbone dihedral angles for each secondary structure element by precisely solving a system of quartic RDC 10 equations whose roots are consistent with $^1D_{\text{HN}}$, $^1D_{\text{HC}}$, $^1D_{\text{C}\alpha\text{C}'}$, and $^1D_{\text{C}'\text{N}}$ couplings. Salvatella and co-workers³¹⁴ have found in MD simulations of chemically denaturated ubiquitin that it consists of 10^3 conformations of this unstructured protein yielding the best cross-validation against experimental RDCs. It has been shown by Raman *et al.*³¹⁵ that the CS-RDC-Rosetta procedure using backbone-only RDCs consistently generates accurate models for proteins up to 120 residues. Stratmann *et al.*³¹⁶ have demonstrated the efficiency of inclusion of $^1D_{\text{HN}}$ RDCs in NOENet, their structure-based complete search algorithm used in an automated resonances assignment. 20

Residual dipolar couplings have been applied in the studies of multi-component systems. Ortega-Roland *et al.*³¹⁷ have used RDCs for accurate characterization of weak interactions between ubiquitin and CD2AP SH3-C ($K_d = 132 \mu\text{M}$). Wang *et al.*³¹⁸ have reported a methodology that simultaneously uses RDCs and SAXS data to mutually orient subunits and define 25 the global shape of the protein-protein complex. Sattler and co-workers³¹⁹ have presented a general protocol based on RDCs for the structural analysis of multidomain proteins and protein complexes.

There is a growing application of residual dipolar couplings in studies of dynamics in biomolecules. Frequently ubiquitin is used as a model compound 30 in these studies. Farès *et al.*³²⁰ have shown that with $^1D_{\text{HC}}$ measured for methyl groups of this protein one may access the nanosecond-microsecond dynamics of the side chains. Kay and co-workers³²¹ have presented an experimental method for establishing the relative orientations of methyl groups in the excited state of protein by measuring methyl $^1D_{\text{HC}}$ RDCs. Salmon *et al.*³²² have 35 described the RDCs-based procedure for the quantitative determination of the average orientation of each peptide plane of the protein backbone.

Unfolded and intrinsically disordered proteins draw more and more attention, and residual dipolar couplings give important information on structural properties of such states of proteins. Marsh and Forman-Kay¹⁶⁷ 40 have used $^1D_{\text{HN}}$ and $^3J_{\text{HNH}\alpha}$ couplings among many other experimental restraints in their program ENSEMBLE which calculates unfolded-states ensembles of proteins. De Simone *et al.*³²³ have used ensemble-averaged $^1D_{\text{HN}}$ couplings as restraints in their molecular dynamics simulations of protein structure. Blackledge and co-workers¹⁶⁸ have developed the ASTEROIDS 45 approach for the determination of a representative ensemble to describe the conformational behaviour of denaturated ubiquitin. In this approach the $^1D_{\text{HC}}$, $^1D_{\text{HN}}$, $^1D_{\text{CC}}$ and $^nD_{\text{HH}}$ calculated for the selected conformations are validated against experimental values. The correlation between values of $\text{H}^{\text{N}}\text{-N}$

dipolar couplings and the amide proton chemical shifts in the solid-state NMR of α -spectrin SH3 domain has been observed by Reif and co-workers.³²⁴ In Table 6 one may find examples of proteins whose structures were solved or refined using RDCs.

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

name	<i>a</i>	<i>b</i>	<i>c</i>	ref.
SDF-1/CXCL12, monomeric	70	34	¹ <i>D</i> _{HN}	325
two tandem WW domains of FBP21	75	ca. 70	¹ <i>D</i> _{HN}	326
Mg ²⁺ -sCaM4-NT, N-terminal domain of Mg ²⁺ -loaded soybean calmodulin isoform 4	77	185	¹ <i>D</i> _{HC} , ¹ <i>D</i> _{HN} , ¹ <i>D</i> _{CC}	327
XACb0070 from <i>Xanthomonas axonopodis</i> pv. <i>citri</i>	79	68	¹ <i>D</i> _{HN}	164
the C-terminal EF-hand domain of Na _v 1.2	105	149	¹ <i>D</i> _{HC} , ¹ <i>D</i> _{HN} , ¹ <i>D</i> _{CN}	328
a homodimeric GB1	56 × 2	86	¹ <i>D</i> _{HN}	318
the actuator domain of ATP7A	119	102	¹ <i>D</i> _{HN}	329
the first four ankryin repeats of IκBα	140	102	¹ <i>D</i> _{HN}	330
L11	147	150	¹ <i>D</i> _{HN}	318
Zn ²⁺ -CzrA	106	112	¹ <i>D</i> _{HN}	331
Zn ²⁺ -CzrA*28-bp DNA complex	106 + 56nt	110	¹ <i>D</i> _{HN}	331
the C-terminal globular domain of EMILIN1	162	234	¹ <i>D</i> _{HN} , ¹ <i>D</i> _{CC} , ¹ <i>D</i> _{CN}	332
the Bem1*Cdc24 PB1 heterodimer	168	109	¹ <i>D</i> _{HN}	333
P23T γD-crystallin	182	118	¹ <i>D</i> _{HN}	318
S100A1 bound to the CapZ peptide	93 × 2 + 12	248	¹ <i>D</i> _{HC} , ¹ <i>D</i> _{HN}	334
IIA ^{Chitobiose} – IIB ^{Chitobiose} complex	103 + 103	153	¹ <i>D</i> _{HN}	335
the bb' domains of human protein disulfide isomerase	223	206	¹ <i>D</i> _{HN}	336
ILK ARD*PINCH LIM1 complex	171 + 70	109	¹ <i>D</i> _{HN}	318
RRM12*U9RNA complex	195 + 130nt	102	¹ <i>D</i> _{HN} , ¹ <i>D</i> _{CN}	319
the human Cdc37*Hsp90 complex	210 + 129	77 + 120	¹ <i>D</i> _{HN}	337
the DH-PH module of PDZRhoGEF	370	69	¹ <i>D</i> _{HN}	338
TTh-NBD*ADP · PO ₄	381	197	¹ <i>D</i> _{HN}	339
TTh-NBD*AMPPNP		185		
BelxLATM*p54DBD complex	212 + 219	ca70	¹ <i>D</i> _{HN}	340
the putidaredoxin-cytochrome P450cam complex	414 + 106	59	¹ <i>D</i> _{HN}	341
the DH-PH module of PDZRhoGEF*RhoA complex	370 + 181	37	¹ <i>D</i> _{HN}	338
secondary preferences of disordered polypeptide chain				
the drk N-terminal SH3 domain unfolded state	56	28	¹ <i>D</i> _{HN}	167
ubiquitin, chemically denaturated	76	ca300	ⁿ <i>D</i> _{HH} , ¹ <i>D</i> _{HC} , ¹ <i>D</i> _{CC}	314
ubiquitin, urea denaturated	76	419	ⁿ <i>D</i> _{HH} , ¹ <i>D</i> _{HC} , ¹ <i>D</i> _{HN} , ¹ <i>D</i> _{CC}	342
the natively unfolded N-terminal domain of human c-Src kinase	84	ca50	¹ <i>D</i> _{HN}	343
CTL9, the C-terminal domain of L9 in the cold denaturated state	90	68	¹ <i>D</i> _{HN}	344
all-Ala α-lactalbumin, denaturated in 4/6/8/10 M urea	123	33/103/103/101	¹ <i>D</i> _{HN}	345
α-synuclein at low pH	140	ca115	¹ <i>D</i> _{HN}	170
α-synuclein at low pH	140	129	¹ <i>D</i> _{HN}	346

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

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

name	<i>a</i>	<i>b</i>	<i>c</i>	ref.
the 14-mer cUUCGg tetralopp hairpin RNA	14	32	$^1D_{HC}$, $^1D_{HN}$	178
a non-self complementary DNA duplex	28	56	$^1D_{HC}$	179
riboA, the adenine riboswitch	71	33	$^1D_{HN}$	347
carbohydrates:				
heparin Δ U-tetrasaccharide	4	26	$^3D_{HH}$, $^1D_{HC}$	232
hyaluronic acid, HA ₁₀	10	40	$^1D_{HC}$	350

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

A method for determination of global RNA structure which combines SAXS data with $^1D_{HN}$ RDCs has been proposed by Wang *et al.*³⁴⁷ The latter have been used to derive the discrete relative orientations of duplexes. Frank *et al.*³⁴⁸ have described a strategy for constructing dynamic ensembles of RNA molecules by applying RDCs in the selection phase from a large pool of conformations created in molecular dynamics simulations. The methodology has been described in more detail by the same group.³⁴⁹

Nucleic acids and carbohydrates for which RDCs have been measured and applied in structural analysis are listed in Table 7.

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