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CAVEATS AND PERSPECTIVES OF COMPUTATIONAL PHOSPHOROUS NMR: CHEMICAL SHIFTS

Abstract. *This is the first part of two closely interrelated reviews dealing with the computation of ^{31}P NMR chemical shifts in a wide series of organophosphorus compounds including complexes, clusters, and bioorganic phosphorus compounds. In particular, the analysis of the accuracy factors, such as substitution effects, solvent effects, vibrational corrections, and relativistic effects, is thoroughly discussed.*

Keywords: *chemical shifts, Equation Formalism Polarizable Continuum Model, Supermolecular Solvation Model, organophosphorus compounds.*

Introduction

Theoretical aspects of the calculation of NMR parameters are thoroughly reviewed in a fundamental handbook of molecular electromagnetism by Stephan Sauer[1] and in a number of related reviews on theoretical and computational aspects of NMR parameters,[2,3,4,5,6,7,8,9,10,11,12,13,14] together with those evaluated on relativistic level.[15,16,17,18,19] The present review covers computational aspects of ^{31}P NMR and is written in continuation of our four recent reviews[20,21,22,23] published in *Progress in NMR Spectroscopy* and three reviews[24,25,26] that appeared in *Magnetic Resonance in Chemistry* very recently dealing with computation of ^{1}H, ^{13}C, and ^{15}N NMR chemical shifts and spin-spin coupling constants involving those nuclei.

It is well known that ^{31}P NMR spectroscopy is a powerful tool for structure elucidation of organic and bioorganic phosphorus compounds providing a new guide to stereoelectronic effects involving phosphorus. This is the first part of two interrelated reviews dealing with computation and structural application of ^{31}P NMR chemical shifts while the second part will focus primarily on the computational aspects of spin-spin coupling constants involving phosphorus in particular classes of organophosphorus compounds.

The review. as a whole. is oriented mainly for NMR spectroscopists and the broader audience of researchers working in the field of organophosphorus chemistry who utilizing modern computational methods in their everyday life for the calculation and theoretical interpretation of ^{31}P NMR spectra.

Substitution effects

In the early paper by Rezaei-Sameti,[27] calculation of ^{31}P NMR shielding was performed in the series of twelve representative alkylphosphorus compounds, PH_3, $PH_2(CH_3)$, $PH(CH_3)_2$, $P(CH_3)_3$, $P(C_2H_5)(CH_3)_2$, $P(C_2H_5)_2(CH_3)$, $P(C_2H_5)_2(CHC_2H_6)$, $P(C_2H_5)(CHC_2H_6)_2$, $P(CHC_2H_6)_3$, $P(CHC_2H_6)_2(C(CH_3)_3)$, $P(CHC_2H_6)(C(CH_3)_3)_2$, and $P(C(CH_3)_3)_3$, by using HF and DFT methods with Pople's 6-311++G(2d,2p) basis set.[28] A good correlation with experimental ^{31}P NMR chemical shifts was obtained, especially when using B3LYP functional.

Three years later Tafazzoli and Ebrahimi[29] examined the performance of the HF, MP2, and DFT (B3LYP and PBEPBE functionals) methods in combination with Pople's family of basis sets, those starting from 6-31G to 6-311++G(2d,2p), used to predict ^{31}P NMR shielding constants of small phosphorus-containing compounds (some 25 molecules). Generally, uncorrelated HF calculations showed worse results as compared to the MP2 and DFT ones. For molecules containing only phosphorus and carbon atoms of sp^3 hybridization, the PBEPBE/6-311G(d,p) method was recommended as the most reliable.

Approximately at the same period of time Maryasin and Zipse[30] reported calculation of ^{31}P NMR chemical shifts of a large series of phosphanes and related compounds in solution at the DFT-MPW1K/6-311++G(2d,2p)//MPW1K/6-31G(d) level in combination with a "dual solvation model" (as labeled in the original publication) including explicit consideration of solvent molecules and a continuum IEF-PCM solvation model. In that paper, selected DFT methods, basis sets and solvation models were tested for their ability to predict ^{31}P NMR chemical shifts of large phosphorus-containing molecular

systems in solution. For larger systems, it was established that reliable ^{31}P NMR chemical shift prediction required Boltzmann averaging over all conformations.

Specifically, the authors of that publication[30] arrived at the following basic conclusions:

(1) The MPW1K functional in combination with the GIAO scheme represented a good basis for the gas-phase and condensed phase calculations of ^{31}P NMR chemical shifts for large molecular systems. Predictions with other hybrid functionals (such as B98 or B3LYP) appeared to be less reliable, while predictions at the MP2 level were significantly more accurate but computationally much more expensive.

(2) The IGLO-III and 6-311++G(2d,2p) basis sets in combination with MPW1K functional provided ^{31}P NMR chemical shifts with reasonable accuracy while smaller basis sets resulted in much less satisfactory predictions.

(3) The ^{31}P NMR shifts calculated for individual conformers varied widely, underscoring the need of Boltzmann averaging over the full conformational space of the system.

(4) The ^{31}P NMR chemical shifts in solution were best predicted by including explicit solvent molecules in the computational space at both the stage of geometry optimization and the stage of chemical shift calculations. Explicit consideration of solvent effects within the so-called "supermolecular" model considering solvent molecules directly added into calculation space to form solvation complexes in the IEF-PCM medium resulted in noticeably better correlation of experimental ^{31}P NMR chemical shifts versus calculated ones.

At present, these recommendations seem to be taken for granted in any computational paper, however, when this was originally published, these recommendations weren't obvious.

Latypov, *et al*.[31] in continuation of their earlier studies[32,33,34,35,36,37] performed a series of DFT, HF, and MP2 calculations of ^{31}P NMR chemical shifts using a family of Pople's basis sets 6-31G(d), 6-31+G(d), 6-31G(2d), 6-31G (d,p), 6-31+G(d,p), 6-311G(d), 6-311G(2d,2p), 6-311++G(d,p), 6-311++G(2d,2p), and 6-311++G(3df,3pd) in a wide series of phosphorus containing compounds of different types. On the whole, it was demonstrated that the higher level of theory was not needed to obtain accurate predictions of ^{31}P NMR chemical shifts. For a routine estimation of these parameters in a wide series of the diverse phosphorus-containing compounds, the simple DFT-PBE1PBE/6-31G(d) level was sufficient. This was demonstrated by the high quality of correlation between calculated versus experimental ^{31}P NMR chemical shifts. However, special care had to be taken for compounds that may be involved in the molecular exchange and various inter- and intramolecular processes such as self-association, molecule-solvent association as well as the existence of tautomeric and conformational equilibria where basis sets of higher quality were strongly recommended.

A systematic study of substitution effects evaluated at the DFT level using a number of dedicated functionals and basis sets was performed by Fedorov, *et al*.[38] The best result was achieved with Keal-Tozer's functional KT2, as compared to the more common functionals B3LYP, B3PW91, PBE0, and LDA, the former giving an absolute error of about 5-10 ppm. However, even this excellent result was outperformed by the MP2 calculations with large basis sets, as demonstrated in Figure 1. However, even this excellent result was outperformed by the MP2 calculations with very large basis sets.

Several effective computational schemes for ^{31}P NMR chemical at the DFT and MP2 levels were proposed by Federov, *et al*., [38] and tested on a series of 53 benchmarking set of phosphorus-containing molecules, taking into account relativistic and solvent effects. It is noteworthy that relativistic corrections of ^{31}P NMR chemical shifts were of major importance in all four computational schemes, reaching as much as 20-30 parts per million (on average, about 7% of the absolute shielding constant) improving (not worsening!) the agreement between calculated and experiment data.

In a very recent publication by Fukal, *et al*.,[39] the ^{31}P NMR chemical shifts of O,O-diethyl thiophosphate and 5,5-dimethyl-2-mercapto-1,3,2-dioxaphosphorinane 2-oxide were thoroughly investigated by means of different DFT calculations in comparison with experiment involving evaluation of geometrical effects, together with solvent and relativistic effects, and the factor of the NMR reference. NMR calculations performed employed different DFT functionals (B3LYP, BP86, BPW91, M06-2X, PBE0, MP2) using the Huzinaga-Kutzelnigg's Iglo-n (n = II, III), Dunning's cc-pVnZ (n = D, T, Q, 5), and Jensen's pcS-n (n = 0, 1, 2, 3, 4) basis sets.

Performed theoretical calculations enabled accurate and reliable structural dynamic interpretation of the measured ^{31}P NMR chemical shifts. The effects originated in the explicit

solvent effects and, to some extent, relativistic effects turned out to be most essential in obtaining accurate theoretical ^{31}P NMR shifts, particularly for thiophosphates. Figure 2 shows the dependence of the total energy on the torsion angles relative to the energy of the global energy minimum. It was demonstrated, that the phospho-diester linkage possesses considerable rotational flexibility resulting in the increased sensitivity of calculated ^{31}P NMR chemical shifts to the internal rotation of the thiophosphate moiety around the P-O bond.

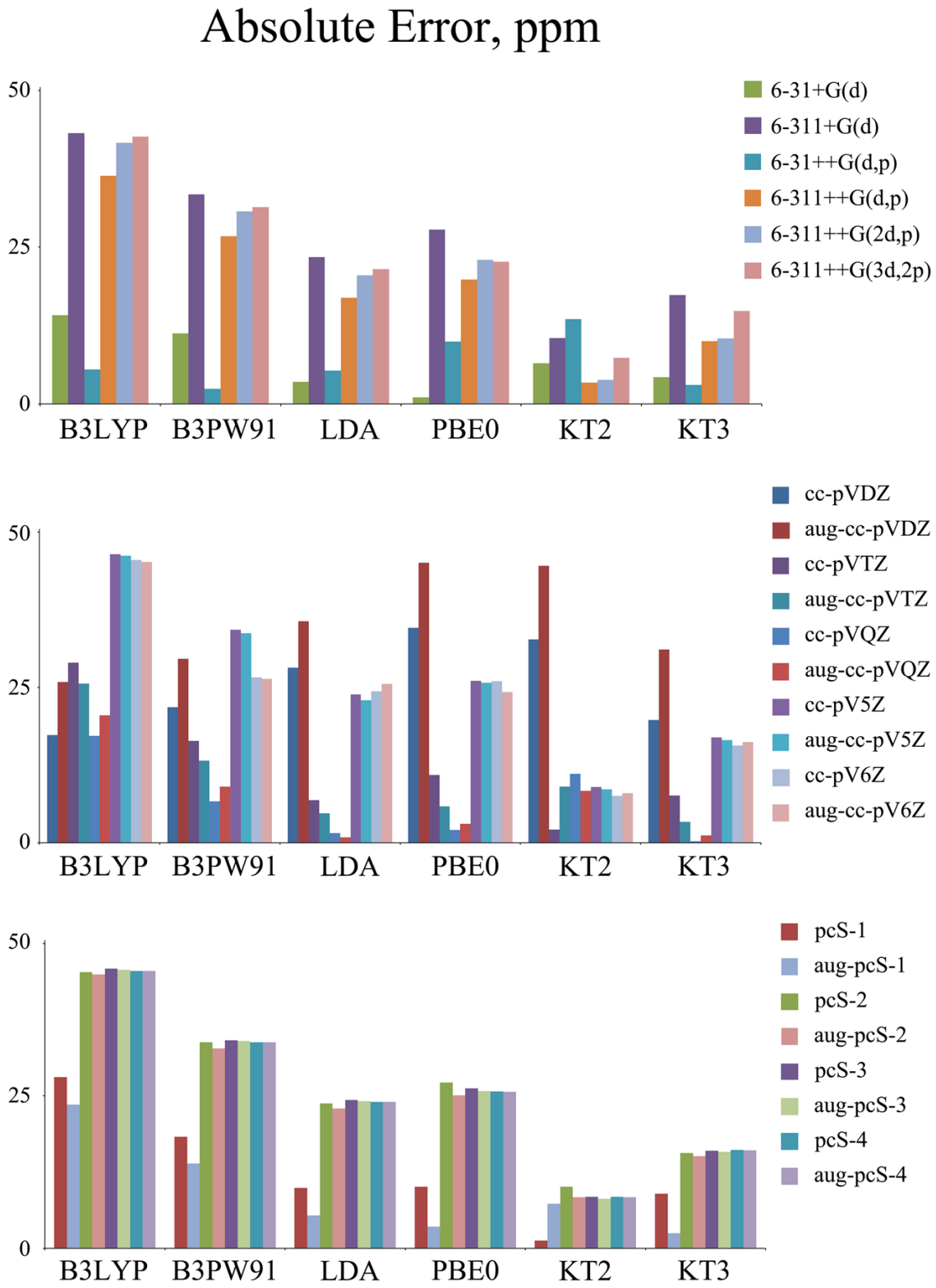

Figure 1. Absolute errors of the phosphorus shielding constant of phosphine calculated at the GIAO-DFT level using different functionals in combination with different basis sets of Pople (top), Dunning (middle), and Jensen (bottom), as compared with the CCSD(T) result. Reproduced from Fedorov, *et al*.[38] with the permission of *John Wiley and Sons*.

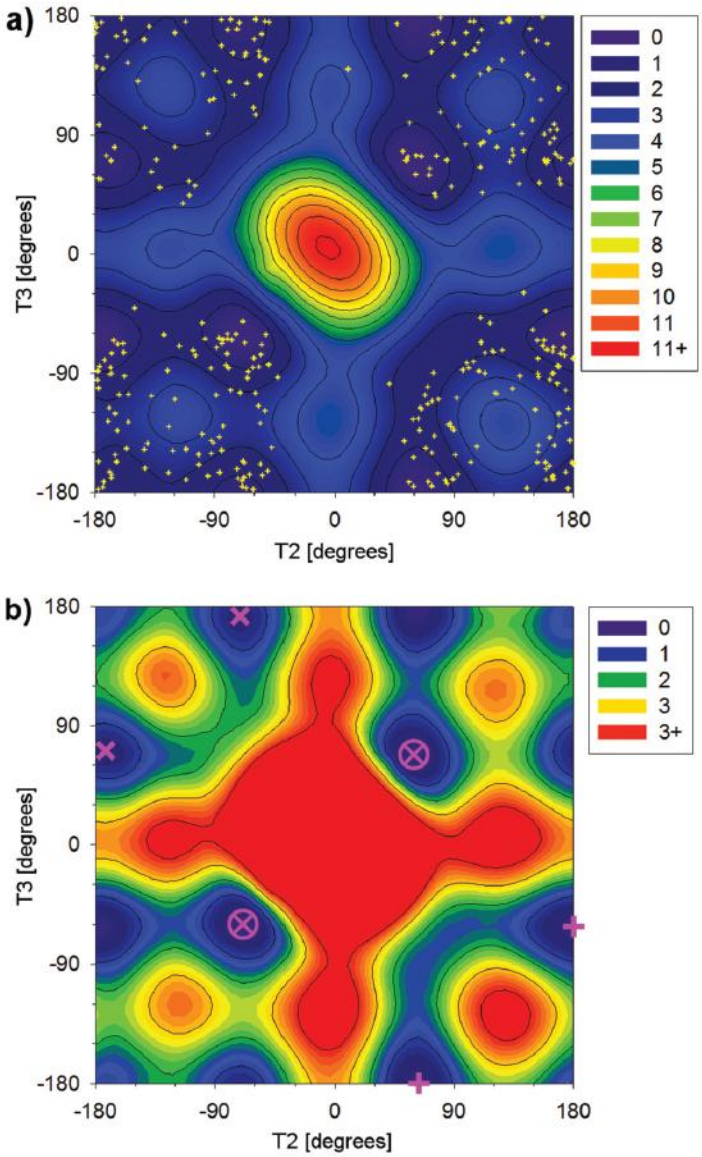

Figure 2. The dependence of energy on the torsion angles relative to the energy of the global energy minimum calculated for 88. The relative energies in kcal/mol are indicated with colors, as depicted in the right-upper boxes. The global energy minima are indicated with the cross within the circles. The local energy minima are indicated with two kinds of crosses to distinguish between their different energies. Reproduced with minor editing privilege from Fukal, *et al*.[39] with the permission of the *Royal Society of Chemistry*.

Solvent effects

It is well known that within the Integral Equation Formalism Polarizable Continuum Model (IEF-PCM) scheme (for references, see the original papers by Tomasi and coworkers[40,41,42,43], the topic reviewed later by the same principal authors[44]), the solvent effect is simulated as an apparent charge distribution spread on the cavity surface not taking into account the

solute-solvent interactions at short distances, so that all solvent effects calculated within the this solvation scheme are constrained not to take into account any specific solvation effects.

In very much the same fashion, the Conductor-like Polarizable Continuum Model (CPCM),[45,46,47,48,49] embeds the solute molecule into a cavity surrounded by a dielectric continuum characterized by dielectric constant, ε. The accuracy of this model depends on several factors; the most important is the use of proper boundary conditions on the surface of the cavity containing the solute. The CPCM defines the cavities as envelopes of spheres centered on atoms or atomic groups. Inside the cavity the dielectric constant is the same as in a vacuum; outside the cavity it takes the value of a particular solvent. Once the cavity has been defined, the surface is smoothly mapped by small regions that are characterized by the position of its center, its area, and the electrostatic vector normal to the surface passing through its center.

The IEF-PCM and CPCM models work quite well when no specific intermolecular solvate-solvent interactions are expected. However, in the opposing case, an explicit consideration of solvent molecules within the Supermolecular Solvation Model (SSM) taking into account solvent molecules directly added into calculation space to form solvation complexes in the IEF-PCM or CPCM medium is highly recommended.

Thus, in the early report by Aminova, *et al*.[50] the ^{31}P NMR chemical shifts of trimethylphosphine (Me_3P), and trimethylbetaine (Me_3PCS_2), together with their intermolecular complexes with one to eight molecules of acetone used as a solvent were investigated using the molecular mechanics method (MM), the combination of quantum chemistry and molecular mechanics methods (QM/MM), and the Own N-layered Integrated Molecular Orbital Method (ONIOM)[51,52,53] at the unrestricted DFT and the HF levels with Pople's 6-31G(d,p) and 6-31G++(d,p) basis sets. However, inferior agreement between the calculated and experimental ^{31}P NMR chemical shifts was found by using the ONIOM unrestricted B3LYP/6-31G(d,p) approach for the trimethylphosphine cluster with acetone molecules.

A year later Chernyshev, *et al*.[54] performed a systematic study of solvent effects on ^{31}P NMR chemical shifts in the phosphorus derivatives of *N*-vinylimidazole (**92**) in its intermolecular complexes with phosphorus pentachloride, the products of its phosphorylation, namely, tetra-, penta- and hexacoordinated *N*-vinylpyrazoles. It was demonstrated that either intra- or intermolecular coordination involving phosphorus results in a dramatic ^{31}P NMR shielding amounting by as much as 150 parts per million on changing phosphorus coordination number by one, which indicated the major importance of solvent effects on ^{31}P NMR chemical shifts of intra- and intermolecular complexes with N→P coordinate bond.

Specific solvation of these compounds with nitromethane reported by Chernyshev, *et al*.[54] had been investigated by adding several molecules of CH_3NO_2 into solvation cavity, the latter in turn being polarized within the IEF-PCM scheme, thereby accounting for the electrostatic, dispersion-repulsion, and cavitation non-specific solvation effects. It followed that ^{31}P NMR chemical shifts calculated for isolated molecules were in a reasonably good agreement with experiment whereas in the case of their complexes theoretical values exceeded experiment by about 150 parts per million. The reason for this marked discrepancy between theory and experiment was due to the fact that compounds studied being optimized as isolated molecules didn't show the formation of the coordinate N→P bond. However, this situation changed dramatically when specific solvation was taken into account by adding the molecules of CH_3NO_2 directly into solvation cavity in an explicit way, the latter polarized within the IEF-PCM scheme. Indeed, calculations of ^{31}P NMR chemical shift of studied compounds with the successive additions of from n = 1 to 5 molecules of nitromethane into the solvation cavity resulted in dramatic shielding of phosphorus nucleus from *ca* +100 to –32 ppm, in perfect agreement with experiment.

Vibrational corrections

Theory and applications of vibrational corrections to NMR parameters is well covered in the fundamental monograph on molecular electromagnetism by Sauer[1] and discussed in a number of earlier[55,56,57,58] and more recent publications.[59,60,61] Not surprisingly, taking into account molecular vibrational motion may play a significant role in the calculation of ^{31}P NMR

chemical shifts, as demonstrated, for example, for the molecule PF_3 in a recent publication by Field-Theodore, *et al*.[62] and much earlier by the same principal authors for the molecule of PN.[63] However, this consideration is usually omitted since computation of the vibrational corrections to chemical shifts represents a very demanding task. Indeed, it requires evaluation of the parameters that are defined as the second and third derivatives of the electronic potential energy together with corresponding gradients and Hessians with respect to the Cartesian displacement coordinates. This aspect of chemical shift calculation is discussed in more detail in our recent review.[23]

Relativistic effects

It has been noted by many authors that in the case of phosphorus atoms directly bound to the elements of the third period (and higher), the manifestation of relativistic effects may be far from negligible. It is most advisable that in these cases, Pople's basis sets,[28,64] together with those of Dunning (see five classical papers[65,66,67,68,69]), and Jensen[70,71,72,73,74,75,76] or other commonly used "non-relativistic" basis sets be changed to the "relativistic" ones of Dyall.[77,78,79,80,81,82,83,84]

In a continuation of the earlier publications by Chernyshev and coauthors,[85,86,87,88,89,90,91] in the paper[38] the molecule of phosphine, PH_3, was taken as a reference with a value of phosphorus shielding constant of 606.11 ppm, as evaluated by Lantto, *et al*.[92] at the CCSD(T)/cc-pwCV5Z level without taking into account relativistic, rovibrational, and temperature corrections. This non-relativistic GIAO-CCSD(T)/cc-pwCV5Z shielding constant was then corrected by evaluating relativistic contribution at the four-component Dirac-Coulomb level to give 624.309 ppm and finally rovibrationally and temperature corrected to give the final value of 614.758 ppm. The contribution of relativistic effects in the value of ^{31}P NMR shielding constant of PH_3 was thus accurately evaluated as 3.0 % of the total ^{31}P NMR shielding constant.

Similar conclusions were arrived at in a very recent publication by Field-Theodore, *et al*.[62] dealing with the calculation of NMR shielding constants in a group 15 trifluorides - NF_3, PF_3, and AsF_3. By combining large basis sets and the complete basis set limit of the coupled-cluster equilibrium geometry with the vibrational and relativistic corrections, it was shown that it was possible to achieve near-quantitative accuracy for NMR shielding constants, including those of phosphorus. These molecules provided a robust test set for the calculation of dynamic electron correlation effects together with relativistic corrections to NMR shielding constants. In this study, basis sets as large as the augmented six-fold splitted aug-cc-pCV6Z were employed, together with a coupled-cluster expansion of up to the CCSDT level with taking into account relativistic effects.

In the recent publication by Rusakov, *et al*.[93] the four-component DFT calculations of ^{31}P NMR chemical shifts have been performed for the representative series of 56 phosphine chalcogenides $R_3P{=}X$ with R = Alk, SiH_3, CF_3, $CH{=}CH_2$, C≡CH, C≡N, NH_2, NO_2, OCH_3, $OCOCH_3$, F and X = O, S, Se, Te in order to investigate the influence of different functional groups on the heavy atom relativistic effect on the NMR chemical shifts of the "light" phosphorus atom (known as the "HALA" effect). The validity of the four-component DFT approach used for the wide-scale calculations of the phosphorus chemical shifts in a wide series of phosphine chalcogenides has been tested on a small series of five representative compounds with the aid of the high-quality CCSD calculations taking into account solvent, vibrational, and relativistic corrections in comparison with experiment. In these calculations, the MAE relative to experimental data was about 6 ppm, while the largest absolute deviation was about 10 ppm; for the compounds under consideration the phosphorus chemical shift scale spanned a range of about 80 ppm.

As one can see, the pure CCSD values without any corrections have been considerably overestimated relative to the experimental ^{31}P NMR chemical shifts. It is evident that it was the relativistic corrections that lowered calculated values to an acceptable level. Relativistic effects on phosphorus chemical shifts are all negative in sign. It means that they shift the phosphorus signal to a higher filed, resulting in an additional shielding of the phosphorus atom. The ranges of relativistic corrections to ^{31}P NMR chemical shifts are shown in Figure 3 taken from the same publication.[93]

The contribution of vibrational corrections to ^{31}P NMR chemical shifts was found to be rather large being negative of about 8-12 ppm

in absolute value. This finding was explained by the observation that vibrational correction to the phosphorus shielding constant in reference compound Me_3P was rather large in an absolute value as compared to the rest of compounds. Solvent corrections to phosphorus chemical shifts were found to be much smaller, not exceeding 6 ppm. It followed that the decreasing influence of solvent effects on phosphorus chemical shifts in the series of compounds $R_3P=X$ with increasing the atomic number of chalcogen, X, was an overall trend.

In a very recent publication by the same authors[94] the relativistic HALA effect has been proven to depend on the spatial deformation of the lone electron pairs of the heavy atom, as was exemplified by several phosphine tellurides. It was demonstrated that the HALA effect on ^{31}P NMR shielding constant is strongly dependent on the spatial arrangements of light substituents on phosphorus, resulting in a deformation of the lone electron pairs on the heavy tellurium atom. In this study, a possible mechanism implying the deformation of tellurium lone pairs governing the stereochemical behavior of HALA correction on ^{31}P NMR shielding constants in alkyl- and alkene-substituted phosphine tellurides was suggested.

Complexes and clusters

In the early report by Alam,[95] calculations of ^{31}P NMR chemical shielding anisotropy tensors were performed at the Hartree-Fock level in the series of differently sized acyclic and cyclic phosphate clusters as a function of a number of phosphate tetrahedral moieties in the system. It was shown that both the ^{31}P NMR chemical shift tensor anisotropy and the isotropic chemical shielding could be used for the structural identification of cyclic phosphates of different size. The differences between the ^{31}P NMR chemical shift anisotropy tensor in acyclic and cyclic phosphate systems was shown to become less pronounced with an increase in the number of phosphate groups within the cycle.

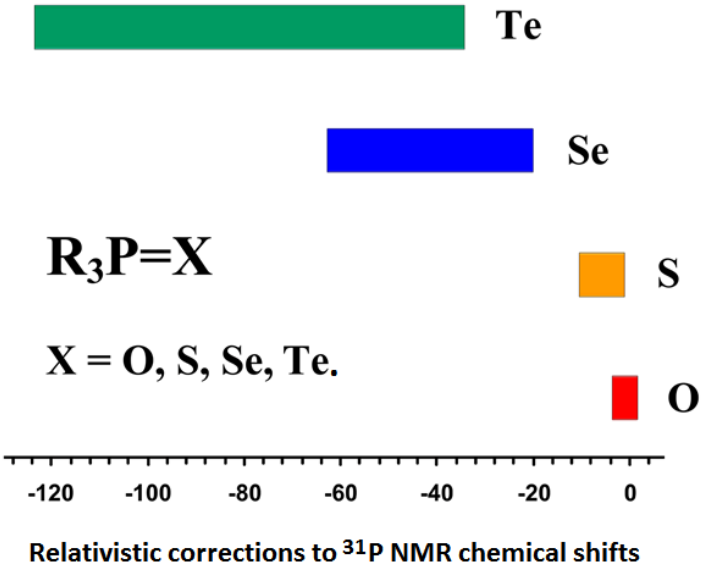

Figure 3. The ranges of relativistic corrections to ^{31}P NMR chemical shifts of phosphine oxides, sulfides, selenides and tellurides. Reproduced with minor editing privilege from Rusakov, *et al*.[93] with the permission of *John Wiley and Sons*.

The orientation of the principal components for the ^{31}P NMR chemical shift anisotropy tensor was shown to be dependent on cyclization, most notably with the small highly strained ring systems.

More recently, Huang, *et al*.[96] performed a computational ^{31}P NMR study of Fe-M interactions in the series of $Fe(CO)_3(EtPhPpy)_2MX_2$ complexes with the metals M = Zn, Cd, Hg and ligands X = NCS, SCN, Cl at the DFT level with using the PBE0 functional. It was found that

basically due to the Fe→M interactions together with a corresponding charge transfer, the electron density of the phosphorus atom was increasing resulting in the notable upfield calculated ^{31}P NMR chemical shifts, in good agreement with the available experiment.

Approximately at the same time, Koo, *et al*.[97] performed the DFT, HF, and MP2 calculations of ^{31}P NMR chemical shifts in the series of organophosphorus esters and corresponding sulfur derivatives together with the O,O-dimethylthiophosphorate ion complexed with metal counterions Ag^+ and Hg^{2+}. In that work, the electronic influence of substituents at phosphorus on calculated ^{31}P NMR chemical shifts has been examined theoretically. It was demonstrated that the major contribution to ^{31}P NMR chemical shifts was derived from the total paramagnetic tensor and the variation of the *d* orbital population on phosphorus atom by the d_π -p_π back-donation.

In a much more recent publication, Pascual-Borràs, *et al*.[98] performed DFT calculations of ^{31}P NMR chemical shifts in a series of polyoxometalates containing a central phosphorus. The best reproducibility and accuracy was obtained for OPBE and PBE functionals used with a triple-zeta polarization basis set (TZP) with taking into account solvent effects and including ZORA formalism to account for relativistic effects. The authors performed a comparison between the three sets of results - experimental, computed and fittedIn view of the fact that calculated ^{31}P NMR chemical shifts were systematically too negative, the authors decided to perform a scaling approach to "*correct*" them. The improvement of the results upon fitting was clearly obvious, albeit a bit artificial. The fitted values (red circles) provided much smaller errors when compared to the calculated ones with respect to the experimental values. In general, the agreement with experiment after the fitting procedure was significant. These data also showed that the most negative chemical shifts needed a major improvement, and the fitting procedure properly accounted for this trend.

The accurate determination of ^{31}P NMR chemical shifts in polyoxometalates performed in the aforementioned paper[98] was achieved at the DFT level with the selected functionals (OPBE, PBE, and KT2) and basis sets (TZP and TZ2P), taking into account spin-orbit and solvent effects. The influence of these factors on the accuracy of the calculated ^{31}P NMR chemical shifts was investigated in a large number of complexes based on $[XW_{12}O_{40}]^{n-}$ and $[X_2W_{18}O_{62}]^{n-}$ basic frameworks with X = Mo, W, V, Nb, Ru, Pd, and Ti. This work suggested that using a PBE/TZP for the NMR calculation step and OPBE/TZ2P for the geometry optimization was the best DFT procedure for the accurate determination of the ^{31}P NMR chemical shifts of these and related complexes.

In a continuation of their earlier studies,[99,100,101,102,103,104,105,106] recently reviewed by the principal authors,[107] Dawson, *et al*.[108] performed a systematic DFT investigation of the solid-state ^{31}P NMR isotropic chemical shifts of the local structure of aluminophosphates, capable of providing information on the number of crystallographic phosphorus sites, their relative populations, and the positions of any dopant atoms in the framework. Based on the recently demonstrated simple relationship between the local structure around phosphorus atom (first of all, the mean P-O bond length and P-O-Al bond angle) and calculated at the DFT level ^{31}P NMR isotropic chemical shift, δ_{iso}, for a series of calcined aluminophosphates,[103] the authors extended this approach to "as-made" aluminophosphates. It was demonstrated that the presence of the framework-bound anions and/or guest species within the pores of aluminophosphates could be translated directly to a distortion of the local framework geometry without considering any additional structural parameters. These results allowed the prediction of δ_{iso} even in the cases where the structure was highly disordered or partially incomplete.

It should be noted that theoretical prediction of the solid-state ^{31}P NMR chemical shifts by the DFT calculations has become a well-established method, especially in the investigation of the geometry of the adsorption structure together with the relevant NMR parameters of the guest-host systems, namely the molecules bounded on the acid sites of a catalyst. Indeed, a comprehensive review on this topic by Zheng, *et al*.[109] has recently appeared. In particular, correlations between the observed ^{31}P NMR chemical shifts of the phosphorus-containing probes and acidic strengths were heavily discussed in the light of their DFT calculations, rendering practical and reliable acidity scales for Brønsted and Lewis acidities. As illustrated for a variety of different solid phosphorus-based systems,

such as microporous zeolites, mesoporous molecular sieves, and metal oxides, the ^{31}P NMR chemical shifts being calculated in comparison with a solid-state experiment provided the important acid features of various catalysts, surpassing most conventional methods such as titration, pH measurement, Hammett acidity function, and some other commonly used physicochemical techniques. Herewith, we will not go into more details of this topic redirecting the Reader to the abovementioned review.[109]

Bioorganic phosphorus compounds

This is a rather special aspect to be covered in a more special review. It is well known that approximately 80% of phosphorus in the human body is found in the calcium phosphate salts, which makes up the inorganic substance of bone. The remainder is involved in the esterification of carbohydrate metabolism intermediaries and is also found as a component of phospholipids, phosphoproteins, nucleic acids and nucleotides. A vast number of papers deal with biological applications of experimental and computational ^{31}P NMR to the studies of phosphorus-containing nucleosides and nucleotides, natural and synthetic peptides, small enzymes, DNA and RNA, and many other biological molecules, and by no means present review attempts to cover this topic which is a subject of a more specialized survey.

In an early paper by Pereira and Cadete,[110] semiempirical calculations of ^{31}P NMR chemical shifts were performed to show that adenosine 5'-(2-methylimidazol-1-ylphosphonate) and guanosine 5'-(2-methylimidazol-1-ylphosphonate), known as possible prebiotic precursors of polynucleotides, produced corresponding diphosphonucleotides. Much later Santner, *et al*.[111] studied ^{31}P NMR spectra of the novel modified nucleoside triphosphates 2'-methylseleno-2'-deoxyadenosine and -guanosine 5'-triphosphates representing powerful building blocks to generate nucleic acids with novel properties by enzymatic RNA synthesis with RNA polymerases.

In earlier related studies, Ruman, *et al*.[112,113] performed the B3LYP/aug-cc-pVTZ calculations of ^{31}P NMR chemical shifts of phosphorylated and thiophosphorylated *N*-thiophosphoramidates together with related aminoacids including P-Arg, P-Cys, 3-P-His, P-Lys, P-Ser, and P-Thr as the most representative examples. The best match of calculated ^{31}P NMR chemical shifts with experiment was obtained for the neutral thiophosphorylated amino acids. It was found that precise estimation of phosphorus NMR chemical shift was still an unsolved and a very difficult problem because of: (i) unreliable estimation of the concentration of neutral, mono- and dianionic forms in solution; (ii) complexity of interactions between analyzed compounds and buffer ingredients; and (iii) inaccurate calculations of ^{31}P NMR chemical shifts of those forms at this level. The unresolved conformational aspect should be added to this list. It seems that all these observations remain on the cutting edge of the modern computational ^{31}P NMR in our days as well.

We leave further demonstrative examples of the structural application of computational ^{31}P NMR chemical shifts of bioorganic phosphorus compounds for a more comprehensive review.

Conclusions

In conclusion it should be emphasized that computational ^{31}P NMR is rapidly progressing presenting a driving force in structural investigation of organophosphorus compounds together with biological species involving phosphorus containing nucleosides and nucleotides, natural and synthetic peptides, small enzymes, DNA and RNA, and many other biological molecules. Most recently, DFT-based calculations of ^{31}P NMR chemical shifts are rapidly turning to a non-empirical wave function methods, the latter markedly increasing and becoming more and more common in a practice of theoretical and computational ^{31}P NMR.

Glossary of abbreviations

CBS: Complete Basis Set
CCSD: Coupled Cluster Singles and Doubles
CCSD(T): Coupled Cluster Singles and Doubles with Perturbative Triples Corrections
CPCM: Conductor-like Polarizable Continuum Model
DFT: Density Functional Theory
DNA: DeoxyriboNucleic Acid
HALA: Heavy Atom on Light Atom (effect)
HF: Hartree-Fock
IEF-PCM: Integral Equation Formalism Polarizable Continuum Model
LDBS: Locally Dense Basis Set
MAD: Mean Absolute Deviation

MAE: Mean Absolute Error
MP2: Second-Order Møller-Plesset Perturbation Theory
NMR: Nuclear Magnetic Resonance
QM/MM: Quantum Mechanics/Molecular Mechanics
HF: Hartree-Fock
RMS: Root Mean Square
RNA: RiboNucleic Acid
ONIOM: Own N-layered Integrated Molecular Orbital Method
SSM: Supermolecular Solvation Model
ZORA: Zeroth Order Regular Approximation
ZPVC: Zero-Point Vibrational Correction

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