Conformational Analysis of Saturated *trans*-Fused 1,3,2-Benzoxazaphosphinine 2-Oxides − DFT Calculation of NMR *J*(P,H) Coupling Constants

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The $^3J_{P,H}$ and $^4J_{P,H}$ spin-spin coupling constants of a selected test set of organophosphorus compounds, calculated by density functional theory (DFT) methods, were found to correlate well with the experimentally measured coupling constants. The contribution of the spin-dipole (SD) term to the coupling constants was found to be negligible, and the diamagnetic and paramagnetic spin-orbit (DSO and PSO) terms cancelled each other, as in the case of $J_{H,H}$. Calculation solely of the Fermi contact (FC) term was found to be sufficient to provide good estimates of the coupling constants. In the second part of the work, the conformational equilibria and coupling constants in 2-bis(2-chloroethyl)amino-*trans*-octahydro-2*H*-1,3,2-benzoxazaphosphinine 2-oxide and its 3-methyl derivative were studied. DFT methods failed in predicting the relative stabilities of the conformations but yielded good geometries and coupling constants. Optimization of the conformations at the Møller-Plesset second-order perturbation theory (MP2) level resulted in energy differences compatible with previous experimental observations.

Introduction

Phosphorus occurs widely in organic and inorganic compounds, some of them playing a very important role. Phosphorus is an especially important element in many biochemical building blocks and processes, the most important examples probably being DNA and RNA, in which the nucleic acids are linked together through the sugar-phosphate backbone.

Not surprisingly, the nuclear magnetic resonance (NMR) properties of ^{31}P are commonly utilized in the structural investigation of many organic and bioorganic compounds. Indirect nuclear spin-spin coupling constants involving phosphorus often provide information about the configuration and the conformation of the organophosphorus compound under study. As an example, $^3J_{P,H}$ and $^3J_{P,C}$ coupling constants are known to have a Karplus-type dependence on the dihedral angle formed by the interconnecting bonds of the coupled nuclei, and this property has been exploited in many structural studies.[1−9] The determination of vicinal coupling constants is therefore especially important. Values of $^3J_{P,H}$ can be used in probing a conformational equilibrium if the coupling constants of the limiting structures are known. In some cases it is possible to freeze out equilibria between the interconverting conformers and to measure the limiting coupling constants by low-temperature NMR measurements; otherwise, coupling constants of similar model compounds may be used. Occasionally, however, either low-temperature NMR measurements do not provide any help or no good experimental model values are available. That is where modern theoretical methods can help.

There are not many recently published studies concerning the theoretical calculation of spin-spin coupling constants to phosphorus. The few examples to be found in the literature include studies concerning coupling constants across hydrogen bonds [$^{3h}J(^{31}P,^{15}N)$, $^{4h}J(^{31}P,^{31}P)$, and $^{2h}J(^{31}P,^{1}H)$],[10−13] properties of some transition metal phosphinidene complexes,[14] solvent effects on couplings involving heavy atoms [$^1J(^{195}Pt,^{31}P)$],[15] and the calculation of various heteronuclear couplings in phosphatranes,[16] phosphorus fluorides,[17] λ3-1-phosphaalkynes,[18] triphenylphosphane oxide,[19] trimethylphosphane selenide,[20] lithium phosphides,[21] phosphazene,[22] diphosphene,[22] neutral and ionic phosphorus hydrides and diphosphorus hydride derivatives,[23,24] and in some other types of first- and second-row hydrides and dihydrides.[25,26] There are also a number of earlier studies, dealing with $J(^{31}P,^{13}C)$ and

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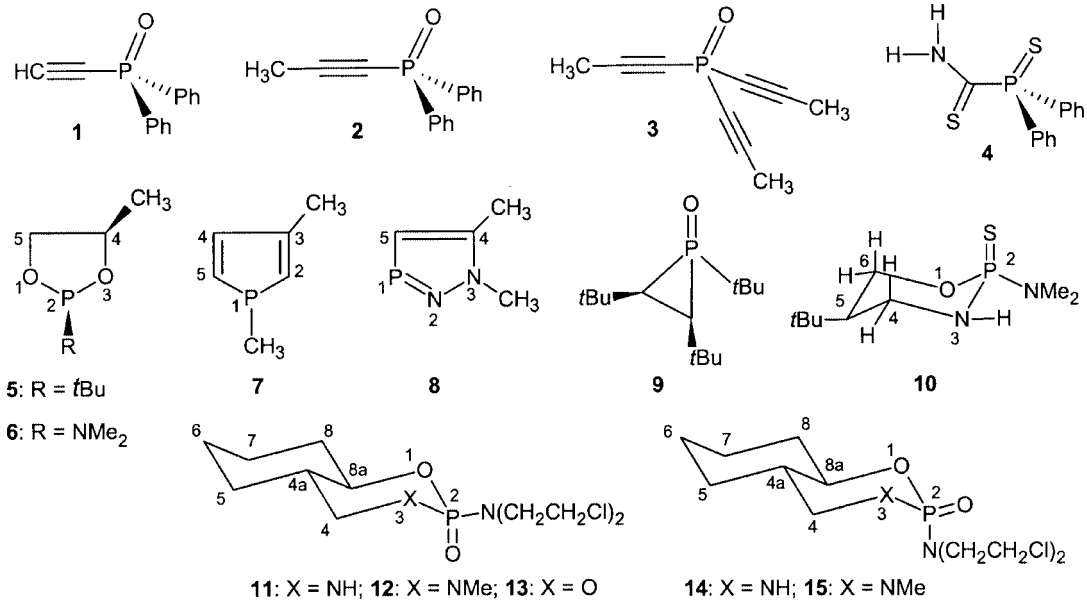
$J(^{31}P,^{1}H)$ in simple phosphanes and phosphates[1] and the $^{1}J(^{31}P,^{31}P)$ angular dependence in diphosphane,[27] mostly by semiempirical methods.[2,28−39] Obviously, the ability of modern density functional theory (DFT) methods to calculate coupling constants to phosphorus through covalent bonds, which can then be used for structural studies not only on small but also on medium-sized organophosphorus compounds, deserves a test.

Numerous studies concerning the theoretical calculation of coupling constants can be found in the literature nowadays.[40−42] Satisfactory results have been achieved in the simulation of 1D and 2D NMR spectra based on fully theoretically calculated NMR parameters.[43−47] According to Ramsey's formulation, the isotropic nuclear spin-spin coupling constant is a sum of the Fermi contact (FC), paramagnetic spin-orbit (PSO), diamagnetic spin-orbit (DSO), and spin-dipole (SD) terms.[48] The PSO and DSO terms can have significantly high values, but a common observation, especially in the case of vicinal and longer-range coupling constants between relatively light nuclei − such as with ^{n}J(H,H; n = 3−5),[43,49−59] ^{n}J(C,H; n = 3−4),[44,49,50,57−61] and often also with ^{n}J(C,C; n = 3−4)[49,56,62] − is that their contributions tend to cancel each other because of their opposite signs. Furthermore, it is generally known that the SD term is negligible, especially for vicinal and longer-range couplings,[40,41,63−65] such as ^{n}J(H,H),[49,51,55−59] ^{n}J(C,H),[49,56−58,60] and ^{n}J(C,C),[49,62] although this assumption is not necessarily true for, for example, couplings to ^{19}F.[66,67] Additionally, the above generalizations do not necessarily apply for coupling constants over one or two bonds. However, in many cases the calculation solely of the FC term is sufficient for good approximations of ^{n}J coupling constants (n = 3−5), because of its dominant role.[43,51,68−75] In this study, we wanted to test whether the same methodology, which has been developed[43] and successfully used[51,74,75] in stereochemical studies of various organic compounds, can be extended to the calculation and application of coupling constants between phosphorus and proton.

Firstly, the structures of a selected set of well defined and conformationally rigid organophosphorus compounds (Scheme 1; **1**−**13**) were optimized and their coupling constants to phosphorus were calculated for validation and calibration purposes. In addition to the structural criteria for the calibration compounds, they were selected from the literature because their $^{3}J_{P,H}$ or $^{4}J_{P,H}$ coupling constants were considered sufficiently reliable. In the second step, the conformations of 2-bis(2-chloroethyl)amino-*trans*-octahydro-2*H*-1,3,2-benzoxazaphosphinine 2-oxide (Scheme 1; **14**) and its 3-methyl derivative (Scheme 1; **15**) were searched and optimized to test the applicability of the computational methods utilized with compounds possessing conformational equilibria.

Compounds **11**, **12**, **14**, and **15** are bicyclic derivatives of cyclophosphamide and its congeners, such as isophosphamide and trophosphamide, that have been used as drugs in cancer treatment,[76] which has spawned a multitude of studies with analogous compounds during the last few decades.[77−97] Many of these studies have shown that the conformational behavior of the oxazaphosphinane ring system is very sensitive to the influence of various substituents. The stereochemistry of compounds **11**, **12**, **14**, and **15**, together with their corresponding *cis*-fused isomers and benzyl derivatives, had been studied earlier by solution-state one- and two-dimensional ^{1}H, ^{13}C, and ^{31}P NMR and dynamic ^{31}P NMR spectroscopic methods.[98] For the *trans*-fused isomers, depending on the relative configuration of the substituents at $P\bar{2}$, either a predominant chair-chair conformation or an equilibrium between chair−chair and chair−skew conformations was found. Furthermore, the equilibrium was found to be dependent on the *N*-3 substituent. However, it was not possible to specify the explicit nat-



Scheme 1. Structures of the calibration compounds **1**−**13** and the compounds **14** and **15** prone to undergoing conformational equilibria

ure of the skew conformations of the heterorings because of the lack of good model values and difficulties in slowing down the interconversion rates sufficiently to identify the limiting equilibrium conformations, even if NMR measurements were performed in Freon solutions at temperatures as low as 135 K. Additionally, the heteroring contains three adjacent heteroatoms which are not very NMR-informative for defining the precise nature of the skew conformations. The conformational equilibria in **14** and **15** were examined by use of the $^3J(P,H_{4ax})$ and $^3J(P,H_{4eq})$ coupling constants. The equilibrium constant estimation was based on the assumption that **14** and **15** exist as two interconverting chair-chair and chair-skew conformers. Another assumption made was that the values of the $^3J(P,H_{4ax})$ and $^3J(P,H_{4eq})$ coupling constants interchange as the chair conformation of the heterocycle turns to skew, while coupling constants of the diastereomers **11** and **12** were used as model values. Later, the equilibria in the *trans*-fused compounds were reinvestigated by ^{15}N NMR spectroscopy through utilization of the $^1J(P,N)$ coupling constants.[99] As a result, better estimates for the equilibrium constants were achieved. However, the estimation was based on the previously made assumptions[98] that 7% of **14** exists in a chair-skew conformation and that there are only two interconverting conformers for both **14** and **15**. Altogether, the contributions of the chair-skew conformations in the equilibria were found to be in the range of 7−9% for the *N*-3 unsubstituted compound and 32−47% for its *N*-3 methyl-substituted counterpart, depending on the method used for the estimation.[98,99] To gain better estimates of the equilibrium ratios and to clarify the nature of the conformers participating in the equilibria the theoretical methods validated in the first part of this work for optimization of the structures and calculation of the desired J(P,H) coupling constants were applied.

Computational Methods

Calculations with GAUSSIAN 98

The structures of 13 organophosphorus compounds (Scheme 1; **1**−**13**) and the conformations of the studied saturated *trans*-fused 1,3,2-benzoxazaphosphinine 2-oxides (Scheme 1; **14** and **15**) were optimized by GAUSSIAN 98[100] by use of the B3LYP DFT method.[101−104] Owing to the size of the molecules investigated, a locally dense basis set was adopted for geometry optimization, as follows (this basis set is denoted as B1 for brevity). On P, N, O, and S, which bear lone pairs, the 6−31+G(d,p) basis set was applied in order to allow the orbitals to occupy sufficiently large regions of space. Additionally, in **4**, the sp^2 carbon bonded to P, N, and S was defined with 6−31+G(d,p). For the remaining atoms the 6−31G(d,p) basis set was applied, except in the bicyclic molecules (**11**−**15**), in which the four carbons in the outermost cyclohexane ring and the hydrogens bound to them and the *tert*-butyl group atoms in **10** were treated with the 3−21G basis set. Vibrational analysis (1 bar, 298.15 K, scaling factor 0.9804)[105] was carried out on the optimized structures to confirm that the resulting optimizations were true minimum energy structures and to yield the $\Delta G°$ values.

Each of the B3LYP-optimized structures of **1**−**15** was further optimized by the ab initio MP2 method,[106] since the DFT methods had failed in predicting the relative stabilities of the conformations of **14** and **15** (vide infra). The same basis sets as in the B3LYP optimizations (MP2/B1) were utilized, but no thermochemical corrections were made.

Calculations of the FC contribution were performed on the optimized structures at the spin-unrestricted UB3LYP/cc-pVTZ level of theory with a tight SCF convergence criterion and the perturbation (0.01 au) placed on phosphorus. The FC contribution is calculated by the finite perturbation theory (FPT) method from Equation (1).

$$J(M,N) = (\mu_0/4\pi)^2\,(h/2\pi)\,(8\pi\beta/3)^2\,(1/a_0^6)\,\gamma_M\gamma_N\,(1/\lambda)B_{FC} \quad (1)$$

where B_{FC} is the Fermi contact term in au, λ is the applied perturbation, γ_M and γ_N are the gyromagnetic ratios of the involved nuclei [$\gamma(^{31}P) = 1.08394 \times 10^8\ s^{-1}T^{-1}$ and $\gamma(^1H) = 2.67522 \times 10^8\ s^{-1}T^{-1}$], and the other parameters are standard physical constants.[43,107] All the constants in Equation (1) are thus defined for calculation of J(P,H) coupling constants and the equation is reduced to $J(P,H)/Hz = 30688.25B_{FC}$.

Calculations with ADF

For comparison with the B3LYP/B1 results, and for checking the validity of the methods used, the coupling constants (FC, PSO, and DSO terms, plus the SD term in selected cases involving various functional groups) were also calculated with the Amsterdam density functional (ADF) program package,[108] with use of the Becke 88 exchange[101] plus the Perdew 86 correlation functional (BP)[109] and a triple-ζ, double-polarization (TZ2P) Slater basis set[108] for all atoms. The same level of theory was also used for the geometry optimizations prior to the coupling constant calculations starting from the structures optimized by the B3LYP method in GAUSSIAN 98. The calculation of the coupling constants was carried out with the CPL code included in ADF.[110−113]

Conformational Searching

Thorough searching of the conformations of the studied saturated *trans*-fused 1,3,2-benzoxazaphosphinine 2-oxides (Scheme 1; **14** and **15**) was carried out by systematic modification of the $\varphi(C_4-C_{4a}-C_{8a}-O_1)$ torsion angle in 10° steps in the opened heteroring and subsequent closure of the ring before preoptimization of the geometry either by molecular mechanics or by the semiempirical PM3[114,115] method. In the initial structures the carbocycle was kept in a chair conformation in each case and the bis(2-chloroethyl)amino groups were simplified as dimethylamino groups. Additionally, a random search method implemented in Sybyl[116] was used to ensure that all the possible heteroring conformations were found. In the subsequent step, the most favorable conformation and position for the bis(2-chloroethyl)-

amino group in different heteroring conformations was searched for and optimized. Finally, the same overall conformation and position of the bis(2-chloroethyl)amino group were used in each structure. By starting from these conformations with various possible spatial arrangements [(pseudo)axial, (pseudo)equatorial, etc.] of the ring nitrogen substituent, the geometries were optimized by the B3LYP/B1 and subsequently by the BP/TZ2P methods (vide supra). The mol fractions (based on Boltzmann populations, where $p_i = e^{-\Delta E(i)/kT}/\Sigma_j\ e^{-\Delta E(j)/kT}$) of the conformations within each equilibrium at 298.15 K were used to estimate the population-weighted averages (pwas) of the calculated coupling constants in a manner similar to that recently applied to ^{13}C chemical shifts.[46,47]

Results and Discussion

Method Validation

The computational methods for calculation of the J(P,H) spin-spin coupling constants were tested and validated with thirteen structurally well defined organophosphorus compounds by calculation of 25 of their $^3J_{P,H}$ and $^4J_{P,H}$ coupling constants and comparison with the experimentally measured coupling constants found in the literature. The resulting structures of the optimizations by different methods for each calibration compound were not found to be exactly the same. In comparison by superimposition of the structures, however, the DFT-optimized structures were found to be generally very similar, whereas the MP2-optimized structures varied slightly from those in each case. The calculated and experimentally measured coupling constants of the calibration compounds are collected in Table 1. Additionally, as a measure of the level of performance, the mean unsigned deviations between the experimentally derived and calculated values produced by each computational method are also included. The $^4J(P,H_{CMe})$ coupling constant in **8** has been reported as a positive value, but the sign of the coupling was not determined.[121] The coupling constant calculations in this study, with all the methods used, indicate that the value is actually negative (Table 1), so the correct negative experimental value was used for linear regression analyses.

All of the terms (FC, DSO, PSO, and SD) contributing to the spin-spin coupling were calculated for three compounds (**3**, **7**, and **11**) by ADF. The SD terms of the $^3J_{P,H}$ and $^4J_{P,H}$ coupling constants appear to be negligible, which is similar to what has been observed earlier for couplings between relatively light nuclei (vide supra). The largest calculated SD contribution is only 0.22 Hz (2% of the total value), and the average of the six calculated values is less than 0.05 Hz. Therefore, since the calculation of the SD term is computationally the most demanding of the four

Table 1. Calculated and experimentally measured coupling constants (Hz) for the calibration compounds

Comp.	Coupling	DSO[a]	PSO[a]	SD[a]	FC[a]	DSO+PSO+FC[a]	FC[b]	FC[c]	Exp.
1	$^3J(P,H_{C\equiv C})$	−0.43	0.32		6.15	6.04	8.62	9.15	10.0[d]
2	$^4J(P,H_{Me})$[e]	−0.14	0.14		−2.35	−2.35	−4.17	−4.23	−3.8[d]
3	$^4J(P,H_{Me})$[e]	−0.19	0.20	0.05	−3.20	−3.19	−4.76	−4.85	−4.3[d]
4	$^3J(P,H_{trans})$	−0.56	0.48		30.00	29.92	33.33	32.01	34.2[f]
	$^3J(P,H_{cis})$	0.68	−0.54		7.19	7.33	6.66	5.92	7.8[f]
5	$^3J(P,H_{tBu})$[e]	0.04	−0.20		10.15	9.99	12.26	12.61	11.6[g]
6	$^3J(P,H_{NMe})$[e]	−0.12	−0.37		7.24	6.75	7.90	8.87	8.4[g]
7	$^3J(P,H_4)$	−0.68	0.70	0.22	10.97	10.99	11.35	10.93	12.5[h]
	$^4J(P,H_{3\text{-}Me})$[e]	−0.35	0.25	0.02	5.04	4.94	3.93	3.90	3.3[h]
8	$^4J(P,H_{NMe})$[e]	−0.50	0.25		−0.20	−0.45	1.34	1.32	1.1[i]
	$^4J(P,H_{CMe})$[e]	−0.43	0.16		−0.38	−0.65	−1.74	−1.81	−1.8[i] [j]
9	$^3J(P,H_{tBu})$[e]	0.16	−0.19		15.57	15.54	17.88	16.94	17.4[k]
10	$^3J(P,H_{4ax})$	0.40	−0.38		4.55	4.57	4.97	5.92	6.8[l]
	$^3J(P,H_{4eq})$	−0.37	0.47		33.19	33.29	33.42	33.24	28.0[l]
	$^3J(P,H_{6ax})$	0.47	−0.46		5.46	5.47	6.05	6.78	5.4[l]
	$^3J(P,H_{6eq})$	−0.47	0.58		25.95	26.06	26.70	25.53	23.2[l]
	$^3J(P,H_{NMe})$[e]	0.04	−0.23		12.14	11.95	12.03	12.70	11.7[l]
11	$^3J(P,H_{4ax})$	0.33	−0.38	−0.07	1.65	1.60	2.30	3.38	1.6[m]
	$^3J(P,H_{4eq})$	−0.37	0.44	0.17	30.39	30.46	30.81	31.33	27.1[m]
	$^3J(P,H_{8a})$	0.54	−0.65	−0.12	2.38	2.27	3.53	3.87	1.3[m]
12	$^3J(P,H_{4ax})$	0.35	−0.40		0.99	0.94	1.78	3.07	1.3[m]
	$^3J(P,H_{4eq})$	−0.34	0.42		26.25	26.33	27.44	28.14	24.6[m]
	$^3J(P,H_{8a})$	0.54	−0.65		2.38	2.27	3.87	4.20	1.8[m]
13	$^3J(P,H_{4ax})$	0.39	−0.54		1.35	1.20	2.36	3.13	4.1[n]
	$^3J(P,H_{4eq})$	−0.46	0.58		25.41	25.53	25.66	24.95	22.8[n]
$\lvert\Delta x\rvert$[o]					1.79	1.82	1.45	1.62	

[a] Calculated by ADF (BP/TZ2P). [b] Calculated by GAUSSIAN 98 for the B3LYP structures (B3LYP/cc-pVTZ//B3LYP/B1). [c] Calculated by GAUSSIAN 98 for the MP2 structures (B3LYP/cc-pVTZ//MP2/B1). [d] Ref.[117] [e] Averages of the methyl proton values shown. [f] Ref.[118] [g] Ref.[119] [h] Ref.[120] [i] Ref.[121] [j] The sign of the value is corrected. [k] Ref.[122] [l] Ref.[123] [m] Ref.[98] [n] Ref.[87] [o] Mean unsigned deviation between the calculated and experimentally measured values.

terms (it increases running time by a factor of ca. 10) it appears justifiable to omit its contribution from the rest of the calculations.

The experimentally ascertained coupling constants of the calibration compounds are plotted as a function of the coupling constants [$J = J$(FC) + J(DSO) + J(PSO)] calculated at the BP/TZ2P level in Figure 1. Additionally, the experimentally derived couplings are plotted against the FC terms calculated at the BP/TZ2P (Figure 2) and B3LYP/cc-pVTZ levels (Figures 3 and 4). The FC terms calculated at the B3LYP/cc-pVTZ level for either the DFT- (Figure 3) or MP2-optimized (Figure 4) structures are in good linear correlation with the experimentally measured couplings in both cases. The correlation between the BP/TZ2P FC terms and the experimentally measured couplings is somewhat worse according to the correlation coefficient (Figure 2), and the inclusion of the DSO and PSO terms does not improve the situation in this respect (Figure 1). The mean unsigned deviations between the calculated and the experimentally measured values (Table 1) indicate a similar trend in the levels of performance of the computational methods. It is notable, however, that the slope is closest to unity at the BP/TZ2P level, yet the FC terms calculated at the B3LYP/cc-pVTZ level for the MP2-optimized structures correlate best with the experimentally measured ones with respect both to the correlation coefficient and to the slope, and additionally, the intercept in this case is nearly at the origin.

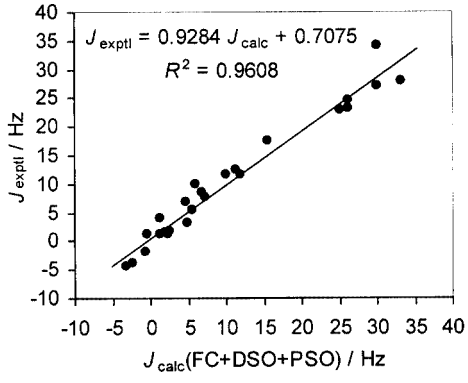


Figure 1. Regression analysis of experimentally measured vs. calculated coupling constants (FC + DSO + PSO terms) of the calibration compounds **1**−**13** (BP/TZ2P level)

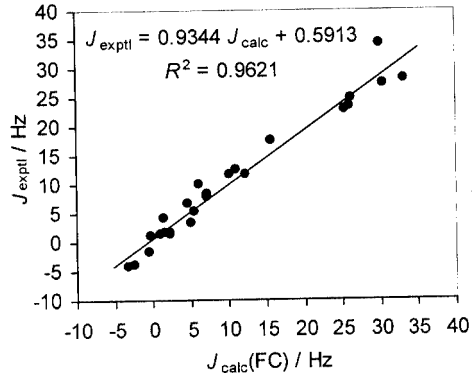


Figure 2. Regression analysis of experimentally measured vs. calculated coupling constants (only FC terms) of the calibration compounds **1**−**13** (BP/TZ2P level)

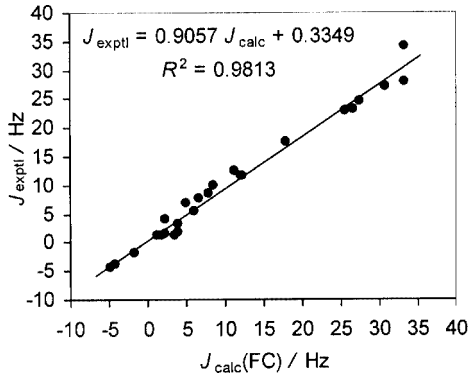


Figure 3. Regression analysis of experimentally measured vs. calculated coupling constants (only FC terms) of the DFT-optimized structures of the calibration compounds **1**−**13** (B3LYP/cc-pVTZ level)

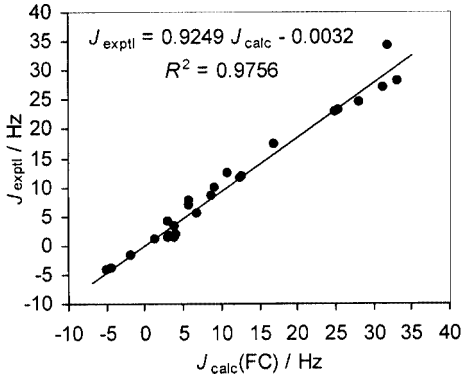


Figure 4. Regression analysis of experimentally measured vs. calculated coupling constants (only FC terms) of the MP2-optimized structures of the calibration compounds **1**−**13** (B3LYP/cc-pVTZ level)

In most cases the DSO and PSO terms are opposite in sign (except for **6**) and they nearly cancel each other (Table 1). On the other hand, the absolute values of the DSO and PSO terms are fairly small in many cases, inherently making their contributions relatively insignificant. The largest absolute value of J(DSO) + J(PSO) is 0.49 Hz (7.3% of the total value) for **6**. In all the other cases the absolute value of J(DSO) + J(PSO) is less than 0.27 Hz and the average value of the sum is only −0.06 Hz (0.6% of the average total value). From these results it can be concluded that the FC term is the dominant contribution to the $^3J_{P,H}$ and $^4J_{P,H}$ coupling constants and that it is not necessary to calculate the SD, DSO and PSO terms. Fairly good estimates of the $^3J_{P,H}$ and $^4J_{P,H}$ coupling constants of a molecule under study are achieved by calculation only of the FC terms and by scaling them with an appropriate calibration line. An advantage of the scaling procedure is that the solvent effects, which were not included in the calculations, are at least partially compensated for. On the other hand, the good correlations between the calculated

and experimentally measured coupling constants obtained in this study suggest that the influence of the solvent in the studied cases is small.

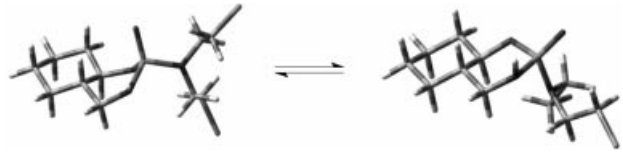
Preferred Conformations of the Saturated *trans*-Fused 1,3,2-Benzoxazaphosphinine 2-Oxide Derivatives

The conformations of the *N*-3 unsubstituted 2-bis(2-chloroethyl)amino-*trans*-octahydro-2*H*-1,3,2-benzoxazaphosphinine 2-oxides and their *N*-3 methyl and benzyl derivatives had previously been experimentally studied by NMR spectroscopy.[98,99] However, in the present study the conformations of the benzyl derivatives have not been searched for and studied in detail, since in the preliminary studies they were found to be extremely flexible.

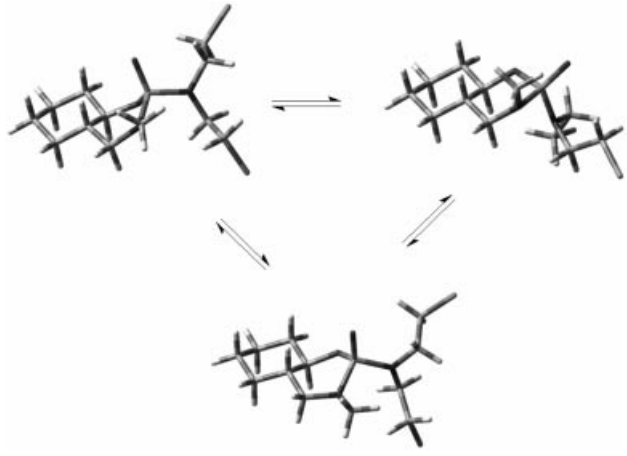
It was already known from the earlier experimental study that chair-chair conformations with axial P=O and equatorial *N*-3 substituents are predominant in **11** and **12**.[98] The B3LYP/B1 geometry optimizations and the subsequent vibrational analysis confirmed the earlier observations and showed that the axial position of the *N*-3 substituent is more than 12 kJ·mol^{-1} and nearly 26 kJ·mol^{-1} less stable for **11** and **12**, respectively. For that reason, it was safe to choose diastereomers **11** and **12** as calibration compounds.

For diastereomers **14** and **15**, possible heteroring conformations were first searched for with simplified molecular structures (i.e., the 2-chloroethyl substituents of the exocyclic nitrogens were changed to methyls). The searching with each simplified structure resulted in various chair-boat and chair-skew forms, and chair-chair forms with the ring nitrogen substituent positioned either axially or equatorially. The resulting structures were then optimized at the B3LYP/B1 level. The calculated free energy differences for the optimized chair-chair conformations of the simplified structures of **14** and **15** indicate that the axial position of the ring nitrogen substituent is preferred over the equatorial by 13.8 kJ·mol^{-1} and 6.9 kJ·mol^{-1}, respectively. These results are consistent with the observations made in the previous experimental study.[98] From the stability difference of the chair-chair conformations of **14**, the conformation with the ring nitrogen substituent in the equatorial position was discarded from the rest of the optimizations made for the non-simplified forms of **14** [i.e., compound **14** with exocyclic bis(2-chloroethyl)amino substituent]. For **15** [with exocyclic bis(2-chloroethyl)amino substituent] an attempt to optimize the chair-chair conformation with the ring nitrogen in an equatorial position was also made, but this resulted in a $^{2,4a}B$ boat conformation.

The relative energies of the optimized conformations of **14** and **15** are collected in Table 2. The results indicate that only two residual minimum energy conformations should be observable (on the NMR timescale) for **14** (Scheme 2) and three for **15** (Scheme 3). The heteroring in the two forms of **14** adopts either a $^{1}C_4$ chair or a $^{4a}S_1$ skew conformation. The proton on the ring nitrogen is in an axial position in the chair conformation (vide supra) and on the same side of the heteroring as the P=O bond in an isoclinal position in the skew conformation of **14**. The geometries of the conformations of **14** optimized by DFT methods are essentially similar for each conformation type, whereas the MP2-optimized conformations are a shade different from these. In **15** the heteroring is variously in a $^{1}C_4$ chair, a $^{2,4a}B$ boat, or a $^{2}S_{8a}$ skew conformation. Again, the DFT-optimized



Scheme 2. Optimized conformations of **14** (left: $^{4a}S_1$ skew; right: $^{1}C_4$ chair)



Scheme 3. Optimized conformations of **15** (upper left: $^{2,4a}B$ boat; upper right: $^{1}C_4$ chair; bottom: $^{2}S_{8a}$ skew)

Table 2. The calculated relative energies (kJ/mol) and derived mol fractions for the optimized conformations of **14** and **15** compared with the experimental results

Comp.	Conf.	$\Delta E_{BP/TZ2P}$	$\Delta E_{B3LYP/B1}$	$\Delta G°_{B3LYP/B1}$	$\Delta E_{MP2/B1}$	$x_{BP/TZ2P}$[a]	$x_{B3LYP/B1}$[b]	$x_{MP2/B1}$[a]	x_{obs}[c]
14	$^{1}C_4$	0.7	1.0	4.3	0.0	0.43	0.15	0.92	0.93
	$^{4a}S_1$	0.0	0.0	0.0	5.9	0.57	0.85	0.08	0.07
15	$^{1}C_4$	3.6	3.6	7.7	0.0	0.11	0.02	0.47	0.53
	$^{2,4a}B$	0.1	0.0	0.3	1.2	0.44	0.52	0.29	0.00
	$^{2}S_{8a}$	0.0	0.2	0.0	1.6	0.45	0.46	0.24	0.47

[a] Based on Boltzmann populations calculated with ΔE values (T = 298.15 K). [b] Based on Boltzmann populations calculated with $\Delta G°$ values (T = 298.15 K). [c] The most reliable experimental estimates of the mol fractions based on the ^{1}J[P,N(exocyclic)] were selected for comparison from ref.[99]

structures are very similar within each conformation type and the MP2-optimized structures vary slightly from those. In particular, the MP2-optimized $^{2,4a}B$ conformation differs from the DFT-optimized ones, being slightly skewed towards a $^{4a}S_1$ conformation. A pseudoequatorial position of the *N*-methyl is predominant in the skew and boat forms while the axial position is preferred in the chair conformation (vide supra). These results are consistent with the experimental observations,[98] except that three conformations for **15** were found in the calculations instead of two.

In the previous experimental study, the conclusion was drawn that no appreciable amount of a chair-boat conformation (the $^{2,4a}B$ type in particular) can contribute to the equilibrium in **14** and **15** on the grounds of the observed $^4J(P,C_7)$ and $^3J(P,H_{8a})$ values.[98] The mol fraction of the optimized $^{2,4a}B$ conformation in **15** derived from the calculated stability differences between each conformation is significant regardless of the method selected (Table 2). However, the mol fractions derived from the MP2 energy differences correlate best with the experimentally observed ones.[99] In particular, the mol fractions derived from the MP2 energy difference of the conformations of **14** are in excellent agreement with the experimental observations. The influence of electron correlation seems to be important in the optimization of these compounds. The selected DFT methods, however, are not capable of calculating acceptably good energies for the structures. The discrepancy between DFT and MP2 methods in energy calculations has also been noticed elsewhere in the literature.[124−127]

Calculated Coupling Constants for the Saturated *trans*-Fused 1,3,2-Benzoxazaphosphinine 2-Oxide Derivatives

The FC, DSO, and PSO terms for $^3J(P,H_{4ax})$, $^3J(P,H_{4eq})$, and $^3J(P,H_{8a})$ of the conformations of **14** and **15** were calculated at the BP/TZ2P level (Table 3). As with the observations made with the calibration compounds (vide supra), the DSO and PSO terms of the individual couplings nearly cancel each other in most cases, which further justifies the exclusion of these terms from the calculation of the coupling constants. In each case the absolute value of J(DSO) + J(PSO) is less than 0.25 Hz. Thus, as concluded in the method validation, to calculate the $^3J(P,H_{4ax})$, $^3J(P,H_{4eq})$, and $^3J(P,H_{8a})$ couplings of the conformations of **14** and **15**, it is only necessary to calculate the FC terms and subsequently to scale them by use of the equation obtained in the linear regression analysis of the calibration compounds (Figures 3 and 4). The couplings constants calculated in this way for both the DFT- and the MP2-optimized conformations of **14** and **15** (B3LYP/cc-pVTZ) are presented in Table 4; for comparison, the coupling constants [J = J(FC) + J(DSO) + J(PSO)] (BP/TZ2P) are also shown. The assignment of the experimentally measured $^3J(P,H_{4ax})$ and $^3J(P,H_{8a})$ for **14** was verified and it is correctly shown in Table 4, although the calculated couplings indicate that $^3J(P,H_{4ax})$ should be smaller than $^3J(P,H_{8a})$.

Table 3. Contributions (Hz) to the $^3J_{P,H}$ coupling constants of the optimized conformations of **14** and **15**

Comp.	Conf.	Coupling[a]	DSO	PSO	FC
14	$^1C_4$	$^3J(P,H_{4ax})$[b]	0.31	−0.55	−0.50
		$^3J(P,H_{4eq})$[b]	−0.36	0.45	25.07
		$^3J(P,H_{8a})$	0.40	−0.55	0.56
	$^{4a}S_1$	$^3J(P,H_{4ax})$[b]	−0.04	−0.17	3.15
		$^3J(P,H_{4eq})$[b]	−0.27	0.33	13.74
		$^3J(P,H_{8a})$	−0.21	0.16	14.63
15	$^1C_4$	$^3J(P,H_{4ax})$[b]	0.45	−0.68	−0.47
		$^3J(P,H_{4eq})$[b]	−0.35	0.43	21.35
		$^3J(P,H_{8a})$	0.42	−0.57	0.50
	$^{2,4a}B$	$^3J(P,H_{4ax})$[b]	−0.11	−0.03	10.23
		$^3J(P,H_{4eq})$[b]	−0.16	0.15	4.16
		$^3J(P,H_{8a})$	−0.12	0.02	8.85
	$^2S_{8a}$	$^3J(P,H_{4ax})$[b]	−0.23	0.17	20.71
		$^3J(P,H_{4eq})$[b]	0.00	−0.05	−0.60
		$^3J(P,H_{8a})$	0.04	−0.23	2.32

[a] Calculated with ADF (BP/TZ2P). [b] Subscripts ax and eq refer to the axial and equatorial positions of the corresponding protons in the chair conformation of the heteroring.

To calculate the population-weighted averages of the coupling constants, mol fractions derived from the MP2 energy differences (Table 2) were used, because they were found to correlate best with the experimental observations (vide supra). The population-weighted averages (pwa_{MP2}s) of the coupling constants are in reasonably good agreement with the experimentally measured coupling constants (Table 4). Interestingly, the best match seems in these cases to be achieved by the combined use of the coupling constants calculated with B3LYP/cc-pVTZ for the DFT-optimized structures and the mol fractions derived from the MP2 energies. The population-weighted averages (similarly, the pwa_{MP2} values were used) of the coupling constants calculated by ADF are no better than the scaled coupling constants calculated with GAUSSIAN 98, when compared to the experimentally measured values, even though the DSO and PSO terms are included.

For comparison, experimentally measured mol fractions were used in the calculation of population-weighted average (pwa_{obs}) coupling constants of **14** and **15** (Table 4). An equilibrium between $^1C_4$ and $^2S_{8a}$ conformation was assumed for **15**, because, as previously discussed, the $^{2,4a}B$ conformation should not be present in considerable amount.[98] This is indicated by the small observed value (1.6 Hz) of $^3J(P,H_{8a})$ in comparison to the reasonably large calculated value (8.0−14.3 Hz, depending on the method used) in the $^{2,4a}B$ conformation. The variation between the sets of coupling constants of the $^{2,4a}B$ conformation of **15** calculated by the different methods is mainly due to the slightly skewed nature of the $^{2,4a}B$ conformation optimized with the MP2/B1 method (vide supra). The results shown in Table 4 indicate that the observed coupling constants are in slightly better agreement with the population-weighted average coupling constants from the experimentally measured mol fractions (pwa_{obs}) than with those calculated from the mol fractions derived from the MP2 energy differences (pwa_{MP2}). Overall, the best match seems to be achieved by the combined use of the coupling constants calculated for

Table 4. $^3J_{P,H}$ Coupling constants (Hz) for the optimized conformations of **14** and **15** compared with the experimental results

Comp.	Conformation	Coupling	DFT_{B3LYP}[a]	DFT_{BP}[b]	$MP2_{B3LYP}$[c]	Exp.[d]
14	$^1C_4$	$^3J(P,H_{4ax})$[e]	0.6	−0.8	0.3	
	(x_{MP2} = 0.92)	$^3J(P,H_{4eq})$[e]	23.6	25.2	23.4	
	(x_{obs} = 0.93)	$^3J(P,H_{8a})$	1.5	0.4	2.0	
	$^{4a}S_1$	$^3J(P,H_{4ax})$[e]	2.4	2.9	1.3	
	(x_{MP2} = 0.08)	$^3J(P,H_{4eq})$[e]	14.1	13.8	16.0	
	(x_{obs} = 0.07)	$^3J(P,H_{8a})$	13.2	14.6	16.4	
	pwa_{MP2}[f]	$^3J(P,H_{4ax})$[e]	0.7	−0.5	0.4	
		$^3J(P,H_{4eq})$[e]	22.8	24.3	22.8	
		$^3J(P,H_{8a})$	2.4	1.5	3.2	
	pwa_{obs}[g]	$^3J(P,H_{4ax})$[e]	0.7	−0.5	0.4	3.5
		$^3J(P,H_{4eq})$[e]	22.9	24.4	22.9	21.2
		$^3J(P,H_{8a})$	2.3	1.4	3.0	1.3
15	$^1C_4$	$^3J(P,H_{4ax})$[e]	0.8	−0.7	0.4	
	(x_{MP2} = 0.47)	$^3J(P,H_{4eq})$[e]	20.3	21.4	20.7	
	(x_{obs} = 0.53)	$^3J(P,H_{8a})$	1.3	0.4	1.6	
	$^{2,4a}B$	$^3J(P,H_{4ax})$[e]	8.7	10.1	3.2	
	(x_{MP2} = 0.29)	$^3J(P,H_{4eq})$[e]	4.9	4.2	11.0	
	(x_{obs} = 0.00)	$^3J(P,H_{8a})$	8.0	8.8	14.3	
	$^2S_{8a}$	$^3J(P,H_{4ax})$[e]	19.4	20.7	21.9	
	(x_{MP2} = 0.24)	$^3J(P,H_{4eq})$[e]	−0.1	−0.7	0.4	
	(x_{obs} = 0.47)	$^3J(P,H_{8a})$	1.9	2.1	1.3	
	pwa_{MP2}[f]	$^3J(P,H_{4ax})$[e]	7.6	7.6	6.4	
		$^3J(P,H_{4eq})$[e]	10.9	11.1	13.0	
		$^3J(P,H_{8a})$	3.4	3.2	5.2	
	pwa_{obs}[g]	$^3J(P,H_{4ax})$[e]	9.5	9.4	10.5	8.8
		$^3J(P,H_{4eq})$[e]	10.7	11.0	11.2	10.7
		$^3J(P,H_{8a})$	1.6	1.2	1.5	1.6

[a] Calculated by GAUSSIAN 98 for the B3LYP structures (B3LYP/cc-pVTZ//B3LYP/B1). Coupling constants calibrated with equation J = 0.9057 J(FC) + 0.3349. The estimated error for the calibrated coupling constants is 0.7 Hz, which is twice the standard error of the mean. [b] Calculated by ADF (BP/TZ2P). Uncalibrated J = J(FC) + J(DSO) + J(PSO). [c] Calculated by GAUSSIAN 98 for the MP2 structures (B3LYP/cc-pVTZ//MP2/B1). Coupling constants calibrated with equation J = 0.9249 J(FC) − 0.0032. The estimated error for the calibrated coupling constants is 0.8 Hz which is twice the standard error of the mean. [d] From ref.[98] [e] Subscripts ax and eq refer to the axial and equatorial positions of the corresponding protons in the chair conformation of the heteroring. [f] Population-weighted averages (pwa) of the coupling constants based on the mol fractions derived from the ΔE_{MP2} values. [g] Population-weighted averages (pwa) of the coupling constants based on the experimentally determined mol fractions.

the DFT-optimized structures with the GAUSSIAN 98 method and the experimentally measured mol fractions.

Conclusion

Calculation of the FC terms by a DFT method and subsequent scaling is sufficient to provide good estimates of $^3J_{P,H}$ and $^4J_{P,H}$ coupling constants. The contribution of the SD term to the coupling constants was found to be negligible. The DSO and PSO terms practically cancel each other, making their added contribution also negligible. DFT methods at the theory levels utilized are capable of producing good geometries and coupling constants but they fail with the energies. MP2 calculations provided energy differences between the conformations of the studied 2-bis(2-chloroethyl)amino-*trans*-octahydro-2*H*-1,3,2-benzoxazaphosphinine 2-oxides comparable with the experimentally determined stability differences. However, the best match in the conformational equilibrium cases between the experimentally measured coupling constants and the population-weighted averages of the calculated coupling constants was achieved by the combined use of the coupling constants calculated for the DFT-optimized structures with the FPT method implemented in GAUSSIAN 98 and the experimentally determined mol fractions. No thermochemical corrections were made at the MP2 level, nor was the solvent effect included in the calculations at any level, which might have further improved the results.

Supporting Information (Cartesian coordinates and energies of the optimized geometries) for this article is available (see footnote on the first page of this article).

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