THE JOURNAL OF CHEMICAL PHYSICS **130**, 094106 (2009)

# Relative importance of first and second derivatives of nuclear magnetic resonance chemical shifts and spin-spin coupling constants for vibrational averaging

Martin Dračínský,[a] Jakub Kaminský,[a] and Petr Bouř[a]
*Institute of Organic Chemistry and Biochemistry, Academy of Sciences, Flemingovo náměstí 2, 166 10 Prague, Czech Republic*

(Received 14 November 2008; accepted 26 January 2009; published online 5 March 2009)

Relative importance of anharmonic corrections to molecular vibrational energies, nuclear magnetic resonance (NMR) chemical shifts, and *J*-coupling constants was assessed for a model set of methane derivatives, differently charged alanine forms, and sugar models. Molecular quartic force fields and NMR parameter derivatives were obtained quantum mechanically by a numerical differentiation. In most cases the harmonic vibrational function combined with the property second derivatives provided the largest correction of the equilibrium values, while anharmonic corrections (third and fourth energy derivatives) were found less important. The most computationally expensive off-diagonal quartic energy derivatives involving four different coordinates provided a negligible contribution. The vibrational corrections of NMR shifts were small and yielded a convincing improvement only for very accurate wave function calculations. For the indirect spin-spin coupling constants the averaging significantly improved already the equilibrium values obtained at the density functional theory level. Both first and complete second shielding derivatives were found important for the shift corrections, while for the *J*-coupling constants the vibrational parts were dominated by the diagonal second derivatives. The vibrational corrections were also applied to some isotopic effects, where the corrected values reasonably well reproduced the experiment, but only if a full second-order expansion of the NMR parameters was included. Contributions of individual vibrational modes for the averaging are discussed. Similar behavior was found for the methane derivatives, and for the larger and polar molecules. The vibrational averaging thus facilitates interpretation of previous experimental results and suggests that it can make future molecular structural studies more reliable. Because of the lengthy numerical differentiation required to compute the NMR parameter derivatives their analytical implementation in future quantum chemistry packages is desirable. © *2009 American Institute of Physics*. [DOI: 10.1063/1.3081317]

## I. INTRODUCTION

Nuclear magnetic resonance (NMR) became a standard analytical method in many fields of chemistry and biology a long time ago.[1] Later, the possibility to calculate accurately some spectral characteristics by quantum chemical codes from the first principles provided a welcome enhancement of the technique that made molecular structural studies more accurate.[2,3] An important milestone in this process was overcoming the origin dependence of calculated chemical shifts,[4] and implementation of the coupled-perturbed techniques.[5] The computationally relatively cheap density functional theory (DFT) made it feasible to predict routinely the indirect spin-spin interaction constants (often referred to as the *J*-coupling) also for larger molecules.[4,5]

It was soon realized that the shifts and spin-spin couplings are generally very dependent not only on molecular structure, but also on the environment, molecular flexibility, and temperature.[2,6–11] The need to study the geometrical dependence of the NMR parameters was particularly initiated by increased precision of the computational methods.[6] A rotational averaging was found important and implemented for both indirect and direct spin-spin coupling.[12] In H-bonded systems, for example, a considerable influence of the potential energy surface anharmonicity on the shifts was predicted.[13] Although the averaging over vibrational coordinates requires a substantial increase in computer time it is beneficial and necessary for precise results.

Regularly, the dependence of the NMR parameters on atomic coordinates is considered as a perturbation to values obtained for an equilibrium structure. For many molecules, Taylor expansions of potential energy and NMR properties at reference geometries are appropriate. Various approximations involving limited geometry dependence of molecular parameters were proposed in the past. For example, diagonal second derivatives of the shifts were averaged over harmonic vibrational functions, or analytical derivatives were obtained and averaged using the normal mode coordinates.[8,14,15] Significant vibrational contributions to the NMR parameters can be found both in small and larger molecules.[14,15] Sometimes, *ad hoc* vibrational corrections are added.[16] An interesting

---

[a] Authors to whom correspondence should be addressed. Electronic addresses: dracinsky@uochb.cas.cz, kaminskj@gmail.com, and bour@uochb.cas.cz.

scheme of averaging with a nonequilibrium geometry as a reference point was proposed.[9,17] For small molecules, contribution of the centrifugal distortion to the temperature dependence of some NMR parameters could be considered.[10,11] However, there are only few systematic studies estimating relative contributions of various derivative terms.[18] A computation involving complete second-order Taylor expansion terms of couplings and fourth-order energy expansion is not known to us. For NMR shifts large vibrational contributions including the quartic force field and higher-order property derivatives have been found for diatomic molecules.[17]

To understand better the relative importance of the various terms, we investigate averaging of NMR shifts and *J*-couplings with harmonic wave function, and with anharmonic potential energy surface where the cubic, semidiagonal (*iijk*, see below) and all (*ijkl*) quartic constants are included. Likewise, we look at the relative contributions of first, diagonal second, and complete second derivatives of the shifts and coupling constants to the total vibrational corrections of the equilibrium values. The results suggest that many simplified approaches proposed in the past because of their computational convenience are justified and may improve the agreement with the experiment; obviously, more reliable results are still obtained with the complete set of the property derivatives. From the practical point of view, the coupling constant averaging appears more important than for the shifts, as the latter are more related to the environmental factors and less connected to the molecular structure.[19] Precise prediction of the shifts is also hampered by the limited precision of contemporary DFT functionals that are not well suited to magnetic phenomena including current density.[20,21] We observed this insufficiency for the methane derivatives, where we could estimate the DFT error by a comparison with more precise wave function (CCSD, CCSDT) computations.

As a default, the common B3LYP functional[22] is used in the present study since it allows an efficient estimation of the vibrational behavior of NMR shifts and coupling at a reasonable level of approximation.[23] The functional was also tested in numerous previous studies and provided a good reproduction of experimental results for most systems with moderate basis sets.[24–26]

Because of the ample experimental material that was acquired by other researchers we investigate the vibrational averaging effects on a series of methane derivatives. For these compounds computations on various levels of approximation can be done and accurate NMR data obtained in a variety of conditions, including extrapolated zero-pressure gas phase measurement and isotopic substitutions. For the bromine compounds, the precision of the computations is somewhat restricted by the relativistic effects[3,27] not included in the present study. However this does not affect the conclusions made for the general behavior of the vibrational contributions for light atoms. For heavy elements, however, such as the HI molecule,[28] the geometry dependence of the NMR parameters may be significantly influenced by the relativity.

In order to verify the tendencies on more applied systems and having in mind the tremendous power of NMR for biomolecular studies[1,29] we also vibrationally average *J*-coupling constants for three variously charged alanine forms and two sugar derivatives, experimental results for which are reported in previous works.[30,31] Indeed, the averaging led to a considerable increase in precision of the alanine spin-spin coupling constants. For the sugars, it may enhance the overall precision, but the vibrational effects are comparable to the error of the DFT computations and experimental inaccuracy.

## II. METHOD

### A. Vibrational averaging

We are interested in averaging of NMR properties in semirigid molecules, where nuclear potential can be expanded to Taylor series starting from the harmonic term.[32] Even for flexible molecules this approach can be used when we assume a weak coupling between lower and higher vibrational frequency motions and adopt an independent (adiabatic) averaging.[24,33,34] In this study, the potential part $V$ of the vibrational Hamiltonian is expanded up to fourth powers of all normal mode coordinates $Q_i$, as

$$V(Q_1,\ldots,Q_M)=\frac{1}{2}\sum_{i=1}^{M}\omega_i^2Q_i^2+\frac{1}{6}\sum_{i=1}^{M}\sum_{j=1}^{M}\sum_{k=1}^{M}c_{ijk}Q_iQ_jQ_k+\frac{1}{24}\sum_{i=1}^{M}\sum_{j=1}^{M}\sum_{k=1}^{M}\sum_{l=1}^{M}d_{ijkl}Q_iQ_jQ_kQ_l, \tag{1}$$

where $\omega_i$ are the harmonic frequencies, $M=3N\text{-}6$, and $N$ is number of atoms. Typically, only semidiagonal normal mode quartic constants with two and more identical indices (e.g., $d_{iijk}$) are considered, as these can be obtained by a single normal mode numerical differentiation of harmonic force fields.[35,36] For control computations indicated below, we constructed the entire quartic part including terms with four different coordinates.

The NMR properties were expanded around the equilibrium as well. For a vibrational wave function $\psi_n$ both properties $P$ ($P=\sigma$, chemical shift or isotropic shielding, or $P=J$, indirect spin-spin coupling constant) were calculated as an average,

$$P_n=\langle\psi_n|P|\psi_n\rangle, \tag{2}$$

with

$$P=P_0+\sum_i P_{1,i}Q_i+\frac{1}{2}\sum_{i,j}P_{2,ij}Q_iQ_j, \tag{3}$$

where $\mathbf{P_1}$ and $\mathbf{P_2}$ are the first and second normal mode property derivatives, respectively. Only ground state ($n=0$) is considered in the current study. If desired, the temperature-dependent effects involving vibrational excitations can be obtained from a relatively simple Boltzmann averaging.[18] Under normal circumstances, however, the temperature corrections are much smaller and contribute by less than ~10% to the total vibrational correction.[2] The normal mode derivatives were obtained from Cartesian derivatives $\mathbf{p}_1$ and $\mathbf{p}_2$ by linear transformations,

$$P_{1,i} = \sum_{\lambda,\alpha} p_{1,\lambda\alpha} S_{\lambda\alpha,i},$$

$$P_{2,ij} = \sum_{\lambda,\alpha,\mu,\beta} p_{2,\lambda\alpha\mu\beta} S_{\lambda\alpha,i} S_{\mu\beta,j}, \tag{4}$$

where $\mathbf{S}$ is the normal mode—Cartesian transformation matrix. The Cartesian derivatives were calculated by numerical differentiations formulas as

$$p_{1,\lambda\alpha} = \frac{p(R_{\lambda\alpha}+\Delta) - p(R_{\lambda\alpha}-\Delta)}{2\Delta}, \tag{5a}$$

$$p_{2,\lambda\alpha\mu\beta} = \frac{p(R_{\lambda\alpha}+\Delta,R_{\mu\beta}+\Delta) - p(R_{\lambda\alpha}+\Delta,R_{\mu\beta}-\Delta) - p(R_{\lambda\alpha}-\Delta,R_{\mu\beta}+\Delta) + p(R_{\lambda\alpha}-\Delta,R_{\mu\beta}-\Delta)}{(2\Delta)^2}, \tag{5b}$$

where, for example, $p(R_{\lambda\alpha}+\Delta, R_{\mu\beta}-\Delta)$ is the property evaluated at a geometry differing from the reference (optimized) structure by a $\Delta$-displacement of $\alpha$-coordinate ($\alpha = x,y,z$) of an atom $\lambda$, and by an opposite displacement of the $\beta$-coordinate of atom $\mu$. Based on trial computations, previous experience[35,37,38] and available literature,[36,39] the step was chosen as $\Delta = 0.05$ Å. This value minimizes numerical noise coming from DFT grid integration, solvent model inaccuracies and convergence thresholds, while such displacements still reasonably well describe the derivatives of molecular properties at the equilibrium point. Similarly, the anharmonic force field [coefficients $c_{ijk}$, $d_{ijkl}$ in Eq. (1)] was computed from Eqs. (5a) and (5b), where analytical second derivatives (Hessian) were used instead of $\mathbf{p}$. From a practical point of view it is important to realize that the diagonal second derivatives of $\mathbf{p}$ (for the force field, these are equal to the fourth energy derivatives) simplify to

$$p_{2,\lambda\alpha\lambda\alpha} = \frac{p(R_{\lambda\alpha}+\Delta) + p(R_{\lambda\alpha}-\Delta) - 2p}{\Delta^2}, \tag{5c}$$

and thus they can also be obtained by a simpler one-coordinate differentiation scheme involving $6N$ displacements, which is significantly faster than the general formula (5b) based on $(6N)^2$ displacements.

The vibrational wave function $\psi_n$ was expanded into a harmonic oscillator basis comprising up to five times excited states, within the usual vibrational configuration interaction (VCI).[35,37] Alternatively, we calculated the properties using a computationally cheaper second-order perturbation (PT2) scheme,[35,36] where the wave function $\psi_n$ is expanded in the harmonic oscillator basis around corresponding harmonic state $|n\rangle = \varphi_n$,

$$\psi_n = \varphi_n + \sum_{l \neq n} A(E_n, E_l, \langle l|V|n\rangle)\varphi_l, \tag{6}$$

where

$$A(E_n,E_l,\langle l|V|n\rangle) = -\tfrac{1}{2}\left[E_l - E_n \pm \sqrt{(E_l-E_n)^2 + 4\langle l|V|n\rangle^2}\right]/\langle l|V|n\rangle. \tag{7}$$

The "+" sign in the previous formula holds for $E_n > E_l$ and the "−" sign for $E_n < E_l$; $E_n$ are the unperturbed energies. Note that for well-separated energy levels (when $|E_n - E_l| \gg |\langle l|V|n\rangle|$) expression (7) becomes the usual term $\langle l|V|n\rangle/(E_n - E_l)$ known from the second order perturbation theory.[35,38] The general formula (7) is more numerically stable as it allows for random degeneracies of vibrational levels.

### B. Computations

The harmonic force fields were calculated by the GAUSSIAN program[40] at equilibrium geometries. For the methane derivatives, the force field and geometries calculated at the B3LYP (Ref. 22)/6-311++G** level were used. For the sugar derivatives, the BPW91 (Ref. 41) functional was additionally employed for a comparison, and for alanine the B3LYP level was combined with the CPCM (polarizable continuum model based on the conductor-like approximation, Ref. 42) solvent model. Similarly, the derivatives of the isotropic shielding (trace of the shielding tensor) and indirect spin-spin coupling constants were obtained by GAUSSIAN at the same approximation. Exceptions with different basis sets are indicated below. GAUSSIAN default gauge-invariant atomic orbital method[43] was used to ensure origin independence of the results. Program S4 (Ref. 37) was used for the anharmonic computations, enabling VCI (within the harmonic oscillator wave functions) lately expanded by the vibrational self-consistent field and degeneracy-resistant PT2.[35,38] The ACESII (Ref. 44) software was used for benchmark computations of the shielding for the methane derivatives at the CCSD, CCSD(T) and CCSDT levels, performed on DFT geometries.

## III. RESULTS AND DISCUSSION

### A. Dependence on vibrational wave function

In order to separate the role of the potential (force field) and NMR property coordinate-dependence ("anharmonicity") we compare different averaging schemes for the $CH_4$ and $CH_3F$ molecules in Table I for a complete second-order expansion of the isotropic shielding and spin-spin coupling

TABLE I. The dependence of selected NMR parameters [for the complete second-order expansion of the isotropic shielding and spin-spin coupling (Eq. (3))] in $CH_4$ and $CH_3F$ on vibrational wave function model. Equilibrium values (C1) are compared to those obtained by averaging with the harmonic wave function (C2), with wave function where the cubic (C3), cubic and semidiagonal quartic (C4, $d_{iijk}$), and complete quartic [C5, Eq. (1)] perturbations were included. The last column (C6) is also for the full force field expansion [Eq. (1)], but for a VCI variational calculation with up to five times harmonic oscillator basis functions.

| | C1 | C2 | C3 | C4 | C5 | C6 |
|---|---|---|---|---|---|---|
| | | | $\sigma_C$ | | | |
| $CH_4$ | 190.51 | 188.52 | 186.88 | 186.93 | 186.91 | 186.78 |
| $CH_3F$ | 109.31 | 105.36 | 105.30 | 105.31 | 105.31 | 105.24 |
| | | | $\sigma_H$ | | | |
| $CH_4$ | 31.73 | 31.49 | 31.24 | 31.22 | 31.24 | 31.24 |
| $CH_3F$ | 27.58 | 27.00 | 26.99 | 26.97 | 26.98 | 26.99 |
| | | | $J_{CH}$ | | | |
| $CH_4$ | 119.32 | 123.88 | 124.11 | 124.23 | 124.15 | 124.18 |
| $CH_3F$ | 140.36 | 145.47 | 145.51 | 145.58 | 145.54 | 145.58 |
| | | | $J_{HH}$ | | | |
| $CH_4$ | −11.68 | −12.40 | −12.14 | −12.15 | −12.14 | −12.14 |
| $CH_3F$ | −8.08 | −8.38 | −8.37 | −8.39 | −8.38 | −8.38 |
| $t$[a] | 0 | 1.5 min | 45 min | 45 min | 22.5 h | 22.5 h |

[a] Approximate computer time needed for the estimation of the relevant $CH_3F$ force field part, for a 64-bit Intel Xeon 2.4 GHz processor, 4-cpu parallel run, at the B3LYP/6-311++G** level.

constants. We can immediately see that the averages obtained from the harmonic vibrational wave function (in this case based on the B3LYP/6-311++G** force field, column C2 in Table I) significantly differ from the equilibrium values (column C1). The isotropic shieldings and coupling constants change by 1%–4%. This is in agreement with observations made in previous studies,[9,10] and confirms the importance of the *second* property derivatives for the averaging, as the first derivative contributions vanish in the harmonic wave function limit. Therefore, the vibrational correction to the equilibrium values can be at least qualitatively obtained with the quadratic part of the molecular potential only, computation of which is a standard part of most quantum chemical codes.

However, when the cubic force constants are included (column C3 in Table I) they can still significantly modify the harmonic results. For example, the $\sigma_C$ $CH_4$ total cubic correction $(186.88-190.51=-3.63\ \text{ppm})$ is in absolute value by ~80% larger than the harmonic one $(188.52-190.51=-1.99\ \text{ppm})$. The cubic potential part accounts for the dependence of the parameters on the geometry and, at least for the shielding, it thus should not be neglected. This is in agreement with the dependence of the chemical shift on the geometry observed also in other studies.[13] On the other hand, the addition of the cubic part to the harmonic force field does not change the coupling constants that much; for example, $J(H-H)$ for $CH_3F$ changes by ~0.03% only. The dominance of the second derivatives of the spin-spin coupling constants for the averaging effects was observed even in large molecules.[8] A relatively minor improvement can thus be achieved for the coupling by the inclusion of the cubic force field. However the rough estimates of the cpu times at the bottom of Table I indicate that this advantage is outweighed by a large computational expense. The leading semidiagonal cubic term ($c_{jii}$) can, in principle, be obtained more cheaply from the gradients; this was, however, not explored in the present implementation where the semidiagonal constants required the same cpu time as the complete cubic force field.

Compared to the cubic correction, the inclusion of the semidiagonal ($d_{iijk}$, column C4 in Table I) and complete ($d_{ijkl}$, C5) quartic force fields leads to negligible changes both in the shielding and coupling. Note that the computation of the complete quartic force field is by an order of magnitude more expensive than for the semidiagonal terms; tremendous savings of computational time can thus be achieved when only the diagonal part obtainable by Eq. (5c) is explored. Obviously, the quartic terms can be important for more flexible molecules,[34] or for excited vibrational states.[35,38] It thus appears reasonable to include the $d_{iijk}$ part of the quartic force field in the computations with a negligible computer cost.

Some variance of the results in Table I can be caused by the approximation of the vibrational wave function: the perturbational calculus (PT2, column C5) and VCI (column C6) provide values differing by less than ~0.1%, which is, however, negligible given the overall precision of the DFT computations. The PT2 method thus appears more universal for this purpose, as it is faster and allows includes a larger number of vibrationally excited states in the wave function construction. The VCI method is significantly limited for larger molecules by the need to diagonalize a huge Hamiltonian matrix;[35] nevertheless, it cannot be completely avoided for strongly anharmonic potentials and accurate treatment of Fermi resonances. The variational treatment, however, does not seem to be necessary for the ground state NMR properties. The values of vibrational corrections are generally in

TABLE II. Chemical shifts (ppm) of the methane derivatives (related to methane) calculated with the zero, first, and second derivative corrections [zero $\sigma_0$, first $\sigma_i$, first and second (diagonal, $\sigma_{ii}$, and all, $\sigma_{ij}$) derivatives of the isotropic shielding were included, using the perturbational formula (6) by default] as compared to the experiment. Methane shifts relative to TMS were $\sigma_C = -7.0$ ppm and $\sigma_H = 0.14$ ppm (Ref. 23), zero density gas phase values are extrapolated.

| | $\sigma_0$ | $\sigma_i$ | $\sigma_{ii}$ | $\sigma_{ij}$ | $\sigma_{ij}^{\text{var}}$ [a] | $\sigma_{\text{expt}}$ | Expt. conditions |
|---|---|---|---|---|---|---|---|
| | | | | Hydrogen shift | | | |
| $CH_4$ | 0 | 0 | 0 | 0 | 0 | 0 | Gas, atmospheric pressure[b] |
| $CH_3F$ | 4.15 | 4.11 | 4.13 | 4.25 | 4.25 | 3.96 | Infinite dilution, cyclohexane[c] |
| $CH_2F_2$ | 5.53 | 5.51 | 5.55 | 5.66 | 5.67 | 5.41 | Gas phase, zero density[d] |
| | | | | | | 8.18 | Gas phase, zero density[d] |
| $CHF_3$ | 6.18 | 6.11 | 6.1 | 6.23 | 6.24 | 6.11 | Infinite dilution, cyclohexane[c] |
| $CH_3Cl$ | 2.74 | 2.68 | 2.69 | 2.82 | 2.81 | 2.96 | 5% in $CCl_4$ [e] |
| $CH_2Cl_2$ | 5.14 | 5.03 | 5.1 | 5.25 | 5.25 | 5.16 | 5% in $CCl_4$ [e] |
| $CHCl_3$ | 7.25 | 7.11 | 7.2 | 7.33 | 7.33 | 7.13 | 5% in $CCl_4$ [e] |
| $CH_3Br$ | 2.49 | 2.41 | 2.42 | 2.56 | 2.55 | 2.18 | Gas phase, zero density[f] |
| $CH_2Br_2$ | 5.16 | 5.02 | 5.12 | 5.27 | 5.27 | 4.81 | 5% in $CCl_4$ [e] |
| $CHBr_3$ | 7.62 | 7.43 | 7.53 | 7.68 | 7.69 | 6.69 | 5% in $CCl_4$ [e] |
| $\delta$ [k] | 0.32 | 0.25 | 0.29 | 0.39 | 0.40 | 0.00 | |
| | | | | Carbon shift | | | |
| $CH_4$ | 0 | 0 | 0 | 0 | 0 | 0 | Gas phase, zero density[b] |
| $CH_3F$ | 81.20 | 81.08 | 78.06 | 81.62 | 81.55 | 78.60 | 2*M* solution in $CDCl_3$ [g] |
| $CH_2F_2$ | 122.23 | 122.05 | 118.61 | 122.50 | 122.40 | 115.64 | Gas phase, zero density[h] |
| $CHF_3$ | 132.49 | 131.89 | 127.88 | 131.43 | 131.30 | 124.63 | Gas phase, zero density[d] |
| $CH_3Cl$ | 40.12 | 39.60 | 36.48 | 39.29 | 39.22 | 32.60 | 2*M* solution in $CDCl_3$ [g] |
| $CH_2Cl_2$ | 80.60 | 79.43 | 76.14 | 79.18 | 79.06 | 60.52 | Solution in $CDCl_3$ [i] |
| $CHCl_3$ | 118.36 | 116.91 | 112.99 | 116.25 | 116.11 | 84.36 | Solution in $CDCl_3$ [i] |
| $CH_3Br$ | 30.91 | 30.26 | 27.17 | 29.67 | 29.58 | 16.60 | 2*M* solution in $CDCl_3$ [g] |
| $CH_2Br_2$ | 73.21 | 71.98 | 68.88 | 71.47 | 71.36 | 33.30 | [j] |
| $CHBr_3$ | 119.12 | 117.45 | 113.29 | 116.5 | 116.36 | 24.30 | [j] |
| $\delta$ [k] | 18.95 | 18.29 | 15.29 | 18.09 | 18.00 | 0.00 | |

[a] Variational wave function was used, Eq. (2).
[b] Reference 23.
[c] Reference 49.
[d] Reference 27.
[e] Reference 50.
[f] Reference 51.
[g] Reference 52.
[h] Reference 53.
[i] Reference 47.
[j] Reference 54.
[k] The symbol $\delta$ denotes average absolute deviation to the experimental values.

agreement with the values found in previous studies; for example, the methane $\sigma_H$ correction 0.49 ppm was previously predicted as 0.59 ppm.[2,9]

### B. Shielding averaging in methane derivatives

From now on, we will use the vibrational wave function based on the complete cubic and semidiagonal quartic force field, and concentrate on the property averaging. For nine halogen methanes the differences caused by inclusion of the different derivatives for carbon and hydrogen shielding as related to methane are apparent in Table II. Before we perform a detailed analysis, we should emphasize that the vibrational correction makes only a minor contribution to the overall error of computed shifts, which thus should be cautiously compared to experimental values. Other errors might arise from the neglect of the solvent effects, from the DFT limitations,[20] and relativistic effects in case of the bromine derivatives,[27] proper analysis of which goes beyond the topic of this study. Also, even for the careful selection of accurate experimental data, a different choice of standardization of experimental shifts and further environmental factors introduces in the comparison variations beyond our control. In spite of these obstacles, many important aspects of the vibrational correction can be observed.

Inclusion of the property first derivatives (see column $\sigma_i$ in Table II) causes a modest change in the equilibrium values ($\sigma_0$), typically less than 1 ppm for carbon and ~0.1 ppm for hydrogen atoms. (Total parameter values up to the indicated level are given in all tables. Thus the values marked as diagonal second derivatives $\sigma_{ii}$ involve also the equilibrium, $\sigma_0$, and first derivatives, $\sigma_i$) The diagonal second derivative [$\sigma_{ii}$, normal mode derivatives were obtained from the Cartesian diagonal derivatives using Eqs. (4) and (5c)] contributions possess same signs as those stemming from the first derivatives. Interestingly, the relative differences between $\sigma_i$ and $\sigma_{ii}$ are quite large for carbons, typically 3%–5%. For hydrogen atoms they are smaller and of similar magnitudes as those caused by the addition of the first derivatives to the equilibrium values.

TABLE III. Chemical shifts (ppm) of the methane derivatives (related to methane) calculated by six theoretical models (meaning of other symbols is the same as in Table I).

| Level basis | B3LYP<br>6-311++G$^{**}$<br>$\sigma_0$ | CCSD<br>*tz2p*<br>$\sigma_0$ | CCSD(T)<br>*tz2p*<br>$\sigma_0$ | CCSD(T)<br>*qz2p*<br>$\sigma_0$ | B3L<br>6-311++G$^{**}$<br>$\sigma_{ij}$ | CCSD(T)<br>*qz2p*<br>$\sigma_{ij}^{a}$ | $\sigma_{\mathrm{expt}}$ |
|---|---|---|---|---|---|---|---|
| Hydrogen shift | | | | | | | |
| $CH_3F$ | 4.15 | 3.85 | 3.91 | 3.94 | 4.25 | 4.04 | 3.96 |
| $CH_2F_2$ | 5.53 | 5.13 | 5.22 | 5.25 | 5.66 | 5.39 | 5.41 |
| $CHF_3$ | 6.18 | 5.71 | 5.80 | 5.87 | 6.23 | 6.08 | 6.11 |
| Carbon shift | | | | | | | |
| $CH_3F$ | 81.02 | 74.01 | 74.90 | 76.36 | 81.62 | 76.71 | 78.6 |
| $CH_2F_2$ | 122.23 | 113.17 | 114.97 | 115.97 | 122.5 | 116.14 | 115.64 |
| $CHF_3$ | 132.49 | 124.71 | 126.91 | 126.92 | 131.43 | 125.73 | 124.63 |

[a] Vibrational correction obtained at the B3L/6-311++G$^{**}$ level.

The hydrogen and carbon shifts exhibit a different behavior also under the inclusion of the off-diagonal second shielding derivatives in the averaging (the $\sigma_{ij}$ column of Table II). In comparison with the equilibrium, the $\sigma_{ij}$ and $\sigma_{ii}$ carbon shift corrections have the same signs (except for $CH_3F$ and $CH_2F_2$, where $\sigma_{ii}$ exhibit a decrease and $\sigma_{ij}$ increase of the shifts), for hydrogen atoms an opposite correction caused by the "diagonal" and "complete" second derivatives occurs in majority of cases. This points out the danger for practical computations where the diagonal derivative restriction is often adopted from pragmatic reasons or the off-diagonal coupling is partially eliminated by a geometry ansatz.[8,9] Finally, as already found in Table I, we see that the perturbational and variational (c.f. columns $\sigma_{ij}$ and $\sigma_{ij}^{a}$ in Table II) wave function averaging provide very similar results indeed.

The averaging does not give a convincing improvement of the total chemical shifts calculated at the DFT level (see the average absolute deviations from experiment, $\delta$, in Table II). We estimate the role of the electronic wave function approximation in Table III, where the B3LYP results are compared to more accurate CCSD and CCSD(T) computations for $CH_3F$, $CH_2F_2$, and $CHF_3$. The DFT equilibrium values ($\sigma_0$) mostly differ from those obtained by the more precise wave function methods by a wider margin than the vibrational correction; however, when the DFT vibrational correction is added to the most precise CCSD(T)/*qz*2*p* computation (column $\sigma_{ij}^{a}$) clear improvement of the equilibrium values can be seen for $CH_2F_2$ and $CHF_3$. For $CH_3F$ the remaining error can be most probably attributed the solvent effects as the gas values are not available to us (see Table I). Unfortunately, we could not obtain the full $\sigma_{ij}$ values vibrationally corrected consistently at the CCSD(T)/*qz*2*p* level in a reasonable computer time. Nevertheless, trial computations on methane indicate that CCSD(T) shielding derivatives and vibrational correction very closely copy those obtained by DFT, which justifies the perturbation additive approach.

Proper vibrational averaging is also important for interpretation of NMR shift changes caused by isotopic substitutions. As documented for the seven methane derivatives in Table IV, the averaging comprising the complete set of derivatives ($\sigma_{ij}$) provides a good representation of the experimentally observed effects, perhaps except for $CHBr_3$ where the calculated value is strongly overestimated. More importantly, we clearly see the significance of the off-diagonal

TABLE IV. Calculated and experimental isotopic effects in chemical shifts (ppm) for selected methane derivatives (the meaning of symbols is analogous as in Table II).

| | $\sigma_0$ | $\sigma_i$ | $\sigma_{ii}$ | $\sigma_{ij}$ | $\sigma_{ij}^{\mathrm{var}}$ | Expt. |
|---|---|---|---|---|---|---|
| $^{13}$**C**(perD-perH) | | | | | | |
| $CH_2Cl_2$ | 0 | −0.15 | −0.78 | −0.47 | −0.49 | −0.3983 ± 0.0002 [a] |
| $CHCl_3$ | 0 | −0.05 | −0.41 | −0.20 | −0.21 | −0.2026 ± 0.0005 [b] |
| $CH_3Br$ | 0 | −0.37 | −1.14 | −0.69 | −0.72 | −0.4747 ± 0.0002 [a] |
| $CH_2Br_2$ | 0 | −0.19 | −0.88 | −0.48 | −0.52 | −0.1892 ± 0.0001 [a] |
| $CHBr_3$ | 0 | −0.08 | −0.38 | −0.2 | −0.21 | −0.0291 ± 0.0001(26 mol % in $CD_3OD$)[a]<br>−0.11 ± 0.05 (neat)[c] |
| $^{1}$**H** ($^{13}$C−$^{12}$C) | | | | | | |
| $CH_3F$ | 0 | 0.001 | 0.001 | 0.002 | 0.002 | 0.003 ± 0.002 [d] |
| $CH_2F_2$ | 0 | 0.001 | 0.002 | 0.002 | 0.002 | 0.002 ± 0.005 [d] |
| $CHF_3$ | 0 | 0.001 | 0.002 | 0.003 | 0.002 | 0.003 ± 0.005 [d] |

[a] Reference 55.
[b] Reference 56.
[c] Reference 57.
[d] Reference 49.

TABLE V. Spin-spin coupling constants (in hertz) in the methane derivatives calculated with the zero, first, and second derivative corrections [zero ($J_0$), first ($J_i$) and second (diagonal, $J_{ii}$, and all, $J_{ij}$) derivatives of the indirect spin-spin coupling constants are included, using the perturbational formula (6) by default] as compared to the experiment.

| | $J_0$ | $J_i$ | $J_{ii}$ | $J_{ij}$ | $J_{ij}^{\text{var}}$ [a] | $J_{\text{expt}}$ | Expt. conditions |
|---|---|---|---|---|---|---|---|
| | | | | $J$(C–H) | | | |
| $CH_4$ | 119.32 | 120.39 | 123.16 | 124.23 | 124.26 | 125.0 | 10% in $CCl_4$ [b] |
| $CH_3F$ | 140.36 | 141.64 | 145.37 | 145.58 | 145.62 | 147.25 | Gas, zero density[c] |
| $CH_2F_2$ | 173.54 | 175.47 | 180.37 | 179.78 | 179.85 | 180.42 | Gas, zero density[d] |
| $CHF_3$ | 228.87 | 230.94 | 239.63 | 237.40 | 237.55 | 235.63 | Gas, zero density[e] |
| $CH_3Cl$ | 142.42 | 143.06 | 146.98 | 146.94 | 146.89 | 150 | 10% in $CCl_4$ [b] |
| $CH_2Cl_2$ | 172.15 | 172.33 | 177.59 | 176.27 | 176.31 | 178.50 | Gas, zero density[f] |
| $CHCl_3$ | 208.40 | 208.34 | 215.92 | 212.85 | 212.93 | 208.3 | 21% in $CCl_4$ [g] |
| $CH_3Br$ | 144.75 | 145.28 | 149.28 | 149.01 | 149.00 | 149.45 | Gas, zero density[h] |
| $CH_2Br_2$ | 173.90 | 174.15 | 179.43 | 177.66 | 177.73 | 178 | 23% in $CCl_4$ [g] |
| $CHBr_3$ | 204.39 | 204.48 | 211.77 | 208.27 | 208.41 | 204.3 | 25% in cyclohexane[g] |
| $\delta$ [l] | 8.41 | 7.15 | 2.66 | 2.79 | 2.76 | 0.00 | |
| | | | | $J$(H–H) | | | |
| $CH_4$ | −11.68 | −11.55 | −11.59 | −12.15 | −12.15 | −12.38 | 10% in $CCl_4$ [b] |
| $CH_3F$ | −8.08 | −7.79 | −8.00 | −8.39 | −8.39 | −9.51 | 10% in $CCl_4$ [b] |
| $CH_2F_2$ | 3.33 | 4.27 | 4.96 | 4.63 | 4.66 | ⋯ | ⋯ |
| $CH_3Cl$ | −9.06 | −9.00 | −9.38 | −9.66 | −9.68 | −10.68 | 10% in $CCl_4$ [b] |
| $CH_2Cl_2$ | −5.11 | −5.12 | −5.37 | −5.43 | −5.47 | 6.77 | [i] |
| $CH_3Br$ | −8.18 | −8.12 | −8.51 | −8.72 | −8.76 | −10.10 | 10% in $CCl_4$ [b] |
| $CH_2Br_2$ | −3.84 | −3.71 | −3.95 | −3.93 | −3.93 | 5.54 | 10% in $CCl_4$ [b] |
| $\delta$ [l] | 1.43 | 1.56 | 1.31 | 0.94 | 0.93 | 0.00 | |
| | | | | $J$(C–F) | | | |
| $CH_3F$ | −156.60[j] | −160.86 | −162.64 | −159.90 | −160.08 | −160.2 | Gas, zero density[k] |
| $CH_2F_2$ | −220.70[j] | −225.50 | −226.06 | −224.52 | −224.52 | −234.55 | Gas, zero density[d] |
| $CHF_3$ | −242.10[j] | −237.28 | −236.81 | −238.34 | −238.28 | −272.29 | Gas, zero density[e] |
| $\delta$ [l] | 15.88 | 14.91 | 15.47 | 14.76 | 14.72 | 0.00 | |
| | | | | $J$(H–F) | | | |
| $CH_3F$ | 48.80[j] | 48.70 | 46.77 | 46.59 | 46.81 | 46.6 | Gas, zero density[k] |
| $CH_2F_2$ | 51.90[j] | 52.02 | 51.13 | 50.22 | 50.25 | 50.24 | Gas, zero density[d] |
| $CHF_3$ | 79.30[j] | 79.34 | 79.51 | 79.14 | 79.18 | 79.92 | Gas, zero density[e] |
| $\delta$ [l] | 1.49 | 1.49 | 0.49 | 0.27 | 0.32 | 0.00 | |

[a] Variational wave function was used, Eq. (2).
[b] Reference 58.
[c] Reference 52.
[d] Reference 53.
[e] Reference 27.
[f] Reference 59.
[g] Reference 60.
[h] Reference 51.
[i] Reference 61.
[j] These equilibrium $J$-values were taken from Ref. 47 as calculated at a MRSCF level.
[k] Reference 47.
[l] Average absolute deviation from experiment.

shift derivatives for the averaging: the D–H isotope shifts in the $^{13}C$ spectra obtained with $\sigma_{ii}$ are almost twice as big as those based on $\sigma_{ij}$.

### C. Spin-spin coupling vibrational averaging

Unlike for the shielding, DFT established as a reliable method for estimation of the indirect spin-spin coupling constants.[24,26,31,45] Indeed, the calculated equilibrium $J$(C–H) and $J$(H–H) coupling constants in the methane derivatives ($J_0$ in Table V) faithfully mimic the experimental values. However, couplings involving the fluorine atom are notoriously difficult for DFT.[2,46] Therefore, for $J$(C–F) and $J$(H–F) we used reference values obtained by Lantto *et al.*[47] from a multiconfiguration SCF calculation.

The vibrational averaging further improves the equilibrium constants. However the first and second coupling constant derivatives contribute in a different manner than for the shielding. While a comparatively large effect was caused by the first derivatives for the shielding, only minor changes are caused by their inclusion for the spin-spin coupling (c.f. the $J_0$ and $J_i$ columns in Table V). Neither this correction leads

TABLE VI. Contribution of the spin-spin coupling constant derivatives (in hertz) to primary ($^{*}\Delta J$) and secondary ($\Delta J$) isotopic effects in bromomethane (the meaning of symbols is the same as in Table V).

| | $J_0$ | $J_i$ | $J_{ii}$ | $J_{ij}$ | $J_{ij}^{\mathrm{var}}$ | $J_{\mathrm{expt}}$ [a] |
|---|---|---|---|---|---|---|
| | | | $^{*}\Delta J$ ($^{13}$C–H, relative to $CH_3Br$)[b] | | | |
| $CH_2DBr$ | 0 | 0.16 | −0.78 | −0.21 | −0.25 | −0.29 |
| $CHD_2Br$ | 0 | 0.01 | −1.08 | −0.72 | −0.74 | −0.62 |
| $CD_3Br$ | 0 | −0.14 | −1.44 | −1.22 | −1.23 | −0.94 |
| | | | $\Delta J$($^{13}$C–H, relative to $CH_3Br$)[c] | | | |
| $CH_2DBr$ | 0 | −0.145 | −0.32 | −0.47 | −0.29 | −0.31 |
| $CHD_2Br$ | 0 | −0.295 | −0.63 | −0.94 | −0.95 | −0.61 |

[a] Reference 62.

[b] The primary effect is defined as $J$(C–H, in $CH_3Br$)–($\gamma_H/\gamma_D$) $J$(C–D, in deuterated analogs).

[c] The secondary effect is $J$(C–H, in $CH_3Br$)–$J$(C–H, in deuterated analogs).

to a convincing statistical improvement: although the average absolute deviation decreases from 8.41 to 7.15 Hz for $J$(C–H), it increases from 1.43 to 1.56 Hz for $J$(H–H), and it nearly stagnates for the $J$(C–F) and $J$(H–F) couplings.

The decisive contribution to the vibrational averaging of the coupling constants thus comes from the second derivatives. For averaged $J$(H–F) constants (column $J_{ij}$) the error $\delta$ decreases about four times if compared to the equilibrium. For $J$(C–F) the improvement is rather minor, but this mostly reflects inaccuracies in the equilibrium values. The diagonal terms $J_{ii}$ improve all the $J$(C–H), $J$(H–H), $J$(C–F), and $J$(H–F) average deviations. Unlike for the shifts, the off-diagonal second derivatives (c.f. $J_{ij}$ in Table V) do not seem to be decisive for an overall enhancement, although in most cases they do improve the diagonal results. For example, for $CH_4$ the $J$(C–H)=123.16 Hz obtained with $J_{ii}$ increases to 124.23 Hz with $J_{ij}$, which is much closer to the experimental value of 125.0. The total vibrational correction of this constant is close to the value obtained by an alternate zero-point vibrational correction.[14]

Previous studies suggest that the off-diagonal coupling second derivatives might be more important for a correct modeling of isotopic effects.[48] Indeed, a striking importance of this term is encountered for the primary and secondary isotopic effects in the $CH_3Br$ molecule (Table VI). For example, the mono- and dideuterated compounds exhibit −0.29 and −0.62 Hz primary isotopic shifts for the $J$(C–H) constants, which are very well reproduced by the full $J_{ij}$ calculation (as −0.25 and −0.74 Hz, respectively). The isotopic effects calculated with the diagonal second derivatives only (−0.78 and −1.08 Hz) are strongly overestimated.

Nevertheless, the dominant role of the diagonal second derivatives makes it possible to roughly estimate contributions of individual normal modes to the vibrational parts of the coupling constants, as done for the $CH_3F$ molecule in Fig. 1. We can observe that all vibrational modes contribute similarly; perhaps surprising is the modest contribution of the strongly energy-anharmonic C–H stretching modes (7–9), but this fact is in line with the aforementioned observation (c.f. Table I) that the potential energy anharmonicity is not so important for the averaging and that the harmonic wave function recovers most of the vibrational effects. At the harmonic limit the first property derivatives vanish and the second derivatives dominate. It is also important to note that within the harmonic approximation the average square of the coordinate is the same for all modes (i.e., $\langle q^2\rangle=\frac{1}{2}$ in the dimensionless normal mode coordinates[32]). In other words, property second derivatives and not the potential energy surface determine individual vibrational mode contributions to the averaging.

### D. Basis set dependence

As pointed out in many previous studies[2,5] calculated NMR shifts and spin-spin coupling constants might be generally very dependent on the basis set. In Fig. 2, the zero, first, and second derivative contributions to selected isotropic shieldings and couplings in the $CH_4$, $CH_3F$, and $CH_3Cl$ molecules are plotted as calculated with four common basis sets of GAUSSIAN (Ref. 40) (Pople-type 6-31G, 6-31$^{**}$, and 6-311++G$^{**}$ functions, and Dunning's aug-cc-pVTZ and aug-cc-pVQZ). Although the NMR shift derivatives in this comparison do not exhibit a significant dependence, closer look reveals some variations that increase as $\sigma_0<\sigma_i<\sigma_{ii}$. As an extreme, the $\sigma_{ii}$ vibrational correction to the carbon shift in methane reduces to ~50% when the basis set is increased from 6-31G to aug-cc-pVQZ. This trend is much more pronounced for the coupling constants, where some small $J_i$ and $J_{ii}$ contributions even change signs when calculated with different bases. Obviously, the computer time increases sharply with the basis set size (for example, 55 and 9906 s were needed for the 6-31G (28 b.f.) and aug-cc-pVQZ (302 b.f.) computations on $CH_3Cl$, respectively). Nevertheless, we can estimate that the 6-311++G$^{**}$ basis set used in this study as

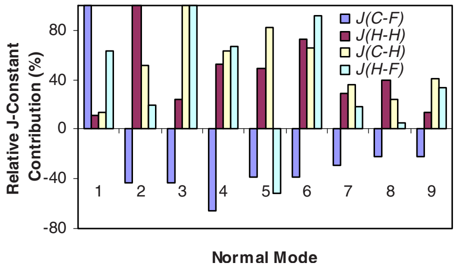

FIG. 1. (Color online) Relative normal mode contributions to the second derivative vibrational corrections [$\partial^2P/\partial x_i\partial x_i$, see the last term in Eq. (3)] of the coupling constants in $CH_3F$.

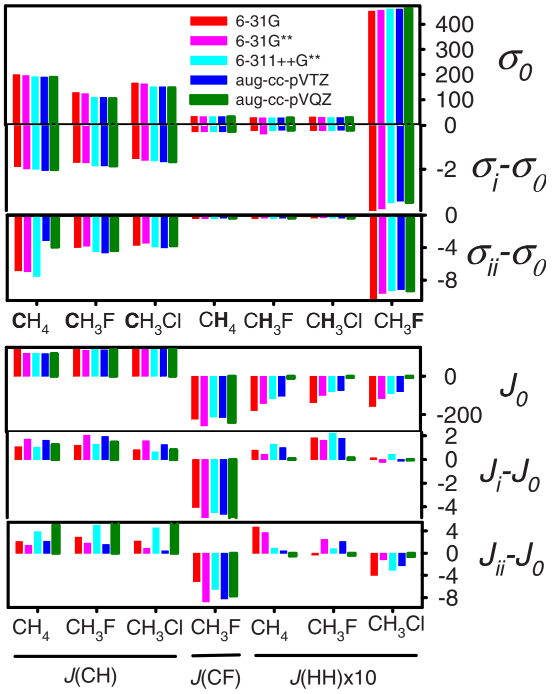

FIG. 2. (Color online) Basis set dependence of the equilibrium (0), first (i) and diagonal second (ii) vibrational corrections to selected isotropic shielding [$\sigma$ (ppm), for bold atoms indicated on the $x$-axis] and spin-spin coupling [$J$ (Hz)] constants, for the B3LYP functional and the B3LYP/6-311++G** force field.

the default provides consistent results well balancing the accuracy and the computational cost. In particular, the basis set dependence does not affect the general conclusions about the importance of individual derivative terms.

## E. Spin-spin coupling in variously charged alanine forms

Many previous results confirm that the spin-spin coupling is dependent on fine changes in molecular environment and structure. This was also documented on the $p$H dependence of alanine spin-spin coupling constants that was reported for isotopically labeled ($^{15}$N, $^{13}$C) alanine previously.[30] We use this molecule (Fig. 3) as a typical example to show how the vibrational averaging behaves for larger polar systems. In fact, based on the results given in Table VII where the constants calculated with different involvements of the $J$-coupling derivatives are compared to experiment, we observe similar trends as found for the methane derivatives above. The coupling first derivatives themselves do not improve the equilibrium values, although their contribution cannot be neglected in the total sum. On the other hand, the spin-spin coupling second derivatives significantly improve the agreement with experiment. The results obtained with the perturbational and variational wave functions are almost the same for the zwitterion, but larger differences between the two approaches can be seen for the other two forms: The average absolute error is almost halved for the cation, whereas it decreases for the anion by ~10% under the variational wave function treatment. This might reflect conformational and dynamical differences between these three forms[30] and a large anharmonicity of the molecular potential energy surface.

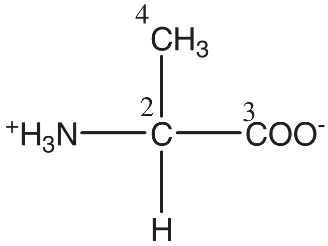

FIG. 3. Numbering of atoms in the alanine zwitterion. The anion and cation were numbered analogously.

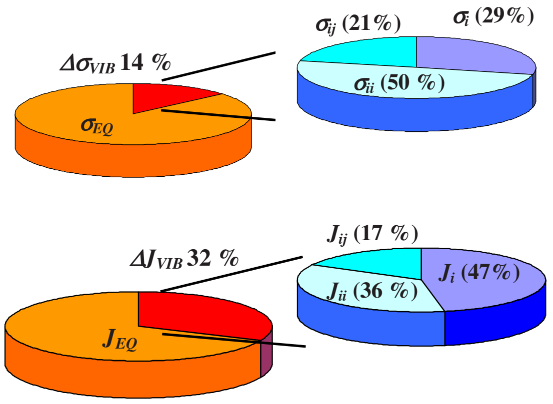

FIG. 4. (Color online) Calculated averaged equilibrium and vibrational parts of absolute shifts ($\sigma$) and spin-spin coupling constants ($J$) in the alanine zwitterion are plotted on the left. For the vibrational parts, average relative ratios of the first ($i$), diagonal ($ii$), and off-diagonal ($ij$) second derivatives are plotted at the right hand side.

Due to the limited precision of DFT and lack of a reliable standard, the vibrationally corrected alanine NMR shifts (not shown) did not convincingly improve the equilibrium values reported in Ref. 30. Also, for some vibrational modes, e.g., the $CH_3$ and $NH_3$ rotations, expansion (1) might not be appropriate. However, the overall trend in the chemical shift vibrational corrections is similar to that found for the methane derivatives. This can also be seen in Fig. 4 showing average relative importance of the first and second shift and spin-spin constant derivatives as calculated for the alanine zwitterion: the shifts are less sensitive to the molecular vibrations, and the role of the second derivatives is at least as important as that of the first ones.

The relative importance of the $J$-coupling derivatives plotted in the lower part of Fig. 4 seems to provide somewhat different message than the analysis based on Table VII. The diagonal second derivatives ($J_{ii}$) that are most important for the correct reproduction of the experiment in Table VII make on average only 36% of the relative vibrational corrections. On the other hand the relative contribution of the $J_{ij}$-type derivatives that were not found so important in the previous examples is relatively high (17%). However, this apparent paradox is caused by taking into account all constants in Fig. 4, while only measurable ones were included in Table VII. Very small constants amplify the differences of the relative changes (in percent). For the measurable zwitterion constants the $J_{ij}$ contribution did not provide any further improvement if compared to $J_{ii}$ (therefore, it is not included

TABLE VII. Spin-spin coupling constants (in hertz) in the three alanine charged forms calculated with the derivative corrections as compared to the experiment. Meaning of symbols is the same as in Table V (the numbering of atoms is defined in Fig. 3).

| Coupled atoms | $J_0$ | $J_i$ | $J_{ii}$ | $J_{ii}^{\mathrm{var}}$ | $J_{\mathrm{expt}}$ [a] |
|---|---|---|---|---|---|
| Zwitterion | | | | | |
| N–C2 | −3.01 | −2.78 | −2.98 | −2.76 | −5.7 |
| C2–C4 | 34.34 | 35.46 | 35.94 | 35.52 | 34.9 |
| C2–C3 | 51.28 | 49.96 | 50.27 | 51.16 | 54.0 |
| C2–H2 | 146.24 | 147.31 | 151.65 | 151.60 | 145.1 |
| C4–H4 | 123.58 | 123.64 | 129.77 | 130.37 | 129.7 |
| N–H2 | −1.33 | −1.47 | −1.23 | −1.30 | 0.0 |
| N–C4 | −0.46 | −0.53 | −0.37 | −0.31 | 0.0 |
| N–C3 | −0.06 | −0.05 | −0.01 | 0.03 | 0.0 |
| C2–H4 | −3.11 | −3.12 | −3.89 | −3.81 | −4.4 |
| C4–H2 | −3.05 | −3.16 | −3.84 | −3.73 | −4.6 |
| C3–C4 | −1.10 | −1.07 | −1.25 | −1.25 | −1.2 |
| C3–H2 | −3.81 | −4.01 | −4.62 | −4.48 | −5.0 |
| N–H4 | −3.45 | −3.33 | −3.70 | −3.92 | −3.1 |
| C3–H4 | 3.60 | 3.73 | 4.03 | 4.02 | 4.2 |
| H2–H4 | 6.43 | 6.62 | 7.65 | 7.43 | 7.3 |
| $\delta$ | 1.40 | *1.54* | *1.23* | *1.23* | *0* |
| Cation ($A^+$) | | | | | |
| N–C2 | −5.27 | −4.67 | −5.18 | −5.10 | −6.55 |
| C2–C4 | 32.12 | 31.69 | 33.89 | 33.73 | 34.1 |
| C2–C3 | 54.85 | 54.24 | 54.87 | 57.78 | 59.6 |
| C2–H2 | 147.13 | 149.20 | 154.29 | 150.27 | 146.6 |
| C4–H4 | 126.41 | 128.06 | 134.54 | 131.23 | 131 |
| N–H2 | −0.69 | −0.75 | −0.44 | −0.50 | 0 |
| N–C4 | −0.28 | −0.21 | 0.09 | −0.16 | 0 |
| N–C3 | 0.03 | 0.01 | 0.14 | −0.02 | 0 |
| C2–H4 | −3.06 | −3.21 | −4.30 | −3.85 | −4.6 |
| C4–H2 | −3.41 | −3.05 | −3.95 | −4.41 | −4.95 |
| C3–C4 | −1.22 | −1.23 | −1.62 | −1.74 | −1.3 |
| C3–H2 | −4.36 | −3.84 | −4.69 | −5.19 | −6 |
| N–H4 | −3.58 | −3.52 | −4.06 | −3.79 | −3.05 |
| C3–H4 | 4.37 | 4.31 | 4.78 | 4.70 | 4.55 |
| H2–H4 | 6.39 | 6.40 | 7.64 | 7.17 | 7.3 |
| $\delta$ | 1.37 | *1.55* | *1.51* | *0.79* | *0* |
| Anion ($A^-$) | | | | | |
| N–C2 | −2.54 | −2.36 | −2.08 | −2.79 | −4.3 |
| C2–C4 | 35.75 | 36.43 | 37.76 | 37.38 | 35.2 |
| C2–C3 | 50.00 | 49.29 | 48.99 | 51.13 | 52.7 |
| C2–H2 | 132.34 | 133.61 | 139.95 | 137.41 | 138.4 |
| C4–H4 | 120.04 | 119.95 | 131.87 | 132.52 | 127.6 |
| N–H2 | −3.37 | −3.68 | −3.73 | −2.64 | −2.2 |
| N–C4 | −4.22 | −3.69 | −3.55 | −4.64 | 0 |
| N–C3 | 0.95 | 1.00 | 0.74 | 0.75 | 0 |
| C2–H4 | −3.03 | −2.88 | −4.72 | −4.82 | −4.3 |
| C4–H2 | −4.20 | −3.78 | −4.62 | −5.46 | −4.75 |
| C3–C4 | 0.22 | 0.38 | 0.09 | 0.43 | 0 |
| C3–H2 | −3.34 | −3.15 | −4.03 | −4.31 | −4.3 |
| N–H4 | −3.59 | −3.29 | −4.01 | −4.65 | −3 |
| C3–H4 | 3.56 | 3.74 | 4.55 | 4.41 | 4.3 |
| H2–H4 | 6.36 | 6.32 | 8.48 | 8.20 | 7.1 |
| $\delta$ | 2.00 | 2.05 | 1.58 | 1.44 | 0 |

[a] Reference 30.

TABLE VIII. Spin-spin coupling constants (in hertz) in methyl 2,3-anhydro-$\alpha$-L-erythrofuranoside (see Fig. 5 for the structure).

| | BPW91 | | | B3LYP | | | |
|---|---|---|---|---|---|---|---|
| Coupled atoms | $J_0$ | $J_i$ | $J_{ii}$ | $J_0$ | $J_i$ | $J_{ii}$ | $J_{\mathrm{expt}}$ [a] |
| H1–H2 | 0.72 | 0.77 | 0.82 | 1.00 | 1.13 | 1.21 | 0.7 |
| H2–H3 | 2.06 | 2.19 | 2.34 | 2.31 | 2.50 | 2.73 | 3.0 |
| H3–H4*R* | 0.93 | 1.02 | 1.02 | 1.21 | 1.39 | 1.46 | 1.0 |
| H3–H4*S* | −0.31 | −0.45 | −0.39 | −0.20 | −0.36 | −0.22 | <0.5 |
| H4*R*–H4*S* | −8.71 | −8.02 | −8.73 | −9.34 | −8.80 | −10.08 | −10.6 |

[a] Reference 31.

in Table VII). Because of the limited accuracy of present computations and the long time needed for the evaluation of $J_{ij}$, their neglecting remains justified. The total vibrational contribution to the coupling constants ($\Delta J_{\mathrm{vib}}=32\%$) is larger than the vibrational shielding correction ($\Delta\sigma_{\mathrm{vib}}=14\%$). However, for measurable coupling constants, such as those in Table VII, the vibrational contributions rarely exceed 20%.

### F. Spin-spin coupling in sugar derivatives

Finally, to document the behavior of the vibrational corrections in yet another important class of compounds, we computed the *J*-coupling constants for relatively rigid methyl 2,3-anhydro-$\alpha$-L-erythrofuranoside and methyl 2,3-anhydro-$\beta$-L-erythrofuranoside. Because the results for the $\alpha$- and $\beta$-isomer were quite similar, we report only those obtained for the former. The relative vibrational corrections of the spin-spin coupling constants are similar as for the aforementioned molecules; yet the contribution of the first derivatives ($J_i$ in Table VIII) is remarkably big. Similarly as before, the $J_{ii}$ correction improves the results on average. Unfortunately, the precision of the DFT computations is limited, and from the comparison of the B3LYP and BPW91 values in Table VIII we can estimate that the overall error is similar as the vibrational part itself. As discussed before[31] the error might also be caused by incomplete basis set; even a presence of another conformer in the sample cannot be completely excluded. As for the methanes, it is pleasant to see that the *J*-coupling vibrational corrections obtained at the two levels (BPW91, B3LYP, c.f. Table VIII) are similar; thus the vibrational part can still be used for an improvement of the equilibrium values even if calculated at a different level.

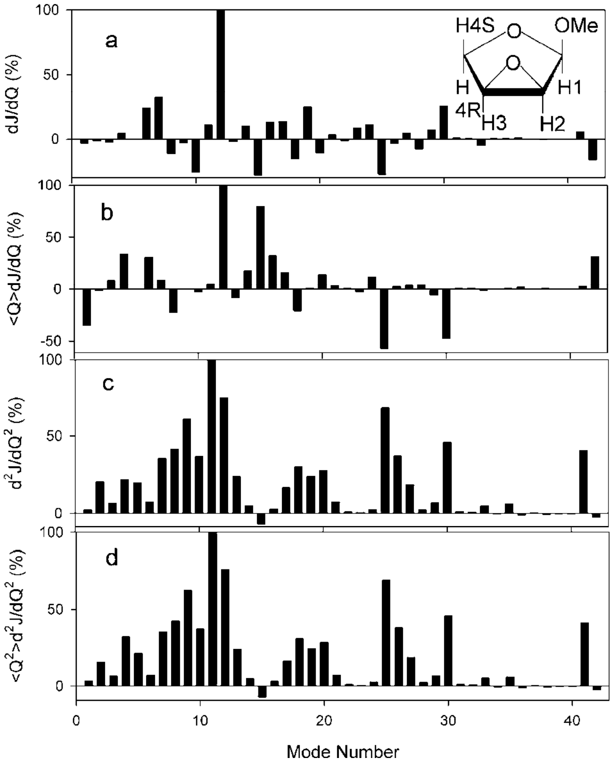

FIG. 5. Relative sizes of the first (a) and second (c) normal mode derivatives of the *J*(H2–H3) coupling constant in methyl 2,3-anhydro-$\alpha$-L-erythrofuranoside, and their weighed contributions [(b) and (d)] to the total vibrational correction.

In order to better understand the role of individual vibrations in the averaging, in Fig. 5 we plot all the normal mode derivatives of the (with respect to sugar chemistry) most important *J*(H2-H3) constant. The relative values of the $\partial J/\partial Q_i$ and $\partial^2 J/\partial Q_i^2$ derivatives as well as the contributions weighed by the coordinate averages [$\langle Q_i\rangle \partial J/\partial Q_i$, $\langle Q_i^2\rangle \partial^2 J/\partial Q_i^2$, Eq. (3)] are plotted. The vibrational contributions are spread over the entire range of vibrational frequencies, but less evenly than for $CH_3F$ (Fig. 1). As said above, the weighing $\partial^2 J/\partial Q_i^2$ by $\langle Q_i^2\rangle$ is mostly formal, as $\langle Q_i^2\rangle \sim 0.5$ is almost the same for all modes. On the other hand, weighing of $\partial J/\partial Q_i$ by $\langle Q_i\rangle$ is important since both the geometry and property anharmonicity contribute to the first-order correction. With a closer look, we can observe that the dominant contributions both to the first and second derivatives come from modes involving the three-membered epoxy ring [number 11 (799 $\mathrm{cm}^{-1}$), 12 (855 $\mathrm{cm}^{-1}$), 15 (938 $\mathrm{cm}^{-1}$), 25 (1218 $\mathrm{cm}^{-1}$), 30 (1396 $\mathrm{cm}^{-1}$) 41 (3086 $\mathrm{cm}^{-1}$), and 42 (3101 $\mathrm{cm}^{-1}$)]. Modes 11, 12, and 15 involve ring deformations, modes 25 and 30 involve also C–H bending, and 41 and 42 are C–H stretches.

Another interesting aspect comes from the local (*Cs*) symmetry of the epoxy ring with the H2 and H3 hydrogen atoms. Nearly symmetric modes ("in phase," 12 and 42) provide the largest first derivative contributions, these are negligible for the asymmetric modes (11, 41). The latter, however, contribute considerably through the second derivatives. This complementary behavior can partially be explained by a primary dependence of the *J*-coupling on the interatomic distance H2…H3. For example, the distance is not much changed in asymmetric stretching vibration when one bond becomes shorter and the other longer and, consequently, the first *J*-derivatives are small for such modes.

## IV. CONCLUSIONS

We have systematically estimated the importance of the first and second shielding and spin-spin coupling constant derivatives for vibrational corrections in a model set of previously measured compounds. The corrections were found necessary for a good theoretical interpretation of the experiment. However, the improvement was strongly dependent on the accuracy of the equilibrium values. The *J*-coupling constants, for example, could be computed more accurately at the DFT level than for the shielding, and their corrections were more beneficial. The behavior of the vibrational corrections in halogen-methanes, variously charged alanine forms, and the sugar derivatives was similar. Individual vibrational modes contribute differently, but for accurate results all normal modes must be included in the averaging.

The role of the energy derivatives was also investigated, but a limited variance was caused by the vibrational wave function model. The perturbational approach yielded almost the same results as the VCI. The inclusion of the full off-diagonal quartic force field made a negligible difference, which is important for computer time savings. A minimalistic and computationally efficient vibrational correction of the equilibrium values can thus be obtained with the harmonic vibrational wave function and semidiagonal spin-spin constant derivatives. The complete (off-diagonal) second derivatives of the chemical shifts and spin-spin coupling constants, however, were found extremely important for the isotope NMR effects.

## ACKNOWLEDGMENTS

The work was supported by the Grant Agency of the Czech Republic (Grant Nos. 203/06/0420 and 202/07/0732), and Grant Agency of the Academy of Sciences (Grant No. A400550702). We thank Láďa Benda for the suggestions to the manuscript.

[1] J. N. S. Evans, *Biomolecular NMR Spectroscopy* (Oxford University Press, Oxford, 1995).

[2] M. Kaupp, M. Bühl, and V. G. Malkin, *Calculation of NMR and EPR Parameters: Theory and Applications* (Wiley-VCH, Weinheim, 2004).

[3] L. B. Casabianca and A. C. Dios, J. Chem. Phys. **128**, 052201 (2008).

[4] V. Sychrovský, J. Gräfenstein, and D. Cremer, J. Chem. Phys. **113**, 3530 (2000).

[5] T. Helgaker, M. Watson, and N. C. Handy, J. Chem. Phys. **113**, 9402 (2000).

[6] O. Vahtras, H. Ågren, P. Jørgensen, H. J. A. Jensen, S. B. Padkjaer, and T. Helgaker, J. Chem. Phys. **96**, 6120 (1992).

[7] O. Vahtras, H. Ågren, P. Jørgensen, T. Helgaker, and H. J. A. Jensen, Chem. Phys. Lett. **209**, 201 (1993).

[8] J. N. Woodford and G. S. Harbison, J. Chem. Theory Comput. **2**, 1464 (2006).

[9] K. Ruud, P. O. Åstrand, and P. R. Taylor, J. Am. Chem. Soc. **123**, 4826 (2001).

[10] J. Vaara, J. Lounila, K. Ruud, and T. Helgaker, J. Chem. Phys. **109**, 8388 (1998).

[11] C. J. Jameson and H. J. Osten, J. Chem. Phys. **81**, 2556 (1984).

[12] J. Kaski, P. Lantto, T. T. Rantala, J. Schroderus, J. Vaara, and J. Jokisaari, J. Phys. Chem. A **103**, 9669 (1999).

[13] R. Janoschek, Mol. Phys. **89**, 1301 (1996).

[14] T. A. Ruden, O. B. Lutnaes, T. Helgaker, and K. Ruud, J. Chem. Phys. **118**, 9572 (2003).

[15] T. A. Ruden, T. Helgaker, and M. Jaszunski, Chem. Phys. **296**, 53 (2004).

[16] T. W. Keal, T. Helgaker, P. Sałek, and D. J. Tozer, Chem. Phys. Lett. **425**, 163 (2006).

[17] P. O. Åstrand, K. Ruud, and D. Sundholm, Theor. Chem. Acc. **103**, 365 (2000).

[18] C. H. Gee and W. T. Raynes, Chem. Phys. Lett. **330**, 595 (2000).

[19] V. G. Malkin, O. L. Malkina, G. Steinebrunner, and H. Huber, Chem.-Eur. J. **2**, 452 (1996).

[20] S. Kümmel, L. Kronik, and J. P. Perdew, Phys. Rev. Lett. **93**, 213002 (2004).

[21] G. Vignale and M. Rasolt, Phys. Rev. B **37**, 10685 (1988).

[22] A. D. Becke, J. Chem. Phys. **98**, 5648 (1993).

[23] T. Zuschneid, H. Fischer, T. Handel, K. Albert, and G. Häfelinger, Z. Naturforsch., B: Chem. Sci. **59**, 1153 (2004).

[24] P. Bouř, M. Buděšínský, V. Špirko, J. Kapitán, J. Šebestík, and V. Sychrovský, J. Am. Chem. Soc. **127**, 17079 (2005).

[25] W. Schöfberger, V. Sychrovský, and L. Trantírek, in *Computational Studies of RNA and DNA*, edited by J. Šponer and F. Lankaš (Springer, Netherlands, 2006).

[26] T. Helgaker, M. Jaszunski, and K. Ruud, Chem. Rev. (Washington, D.C.) **99**, 293 (1999).

[27] M. Kubiszewski, W. Makulski, and K. Jackowski, J. Mol. Struct. **737**, 7 (2005).

[28] B. Minaev, J. Vaara, K. Ruud, and O. Vahtras, Chem. Phys. Lett. **295**, 455 (1998).

[29] S. Meier, M. Blackledge, and S. Grzesiek, J. Chem. Phys. **128**, 052204 (2008).

[30] V. Sychrovský, M. Buděšínský, L. Benda, V. Špirko, Z. Vokáčová, J. Šebestík, and P. Bouř, J. Phys. Chem. B **112**, 1796 (2008).

[31] P. Bouř, I. Raich, J. Kaminský, R. Hrabal, J. Čejka, and V. Sychrovský, J. Phys. Chem. A **108**, 6365 (2004).

[32] D. Papoušek and M. R. Aliev, *Molecular Vibrational/Rotational Spectra* (Academia, Prague, 1982).

[33] A. Čejchan and V. Špirko, J. Mol. Spectrosc. **217**, 142 (2003).

[34] J. Chalupský, J. Vondrášek, and V. Špirko, J. Phys. Chem. A **112**, 693 (2008).

[35] P. Daněček and P. Bouř, J. Comput. Chem. **28**, 1617 (2007).

[36] V. Barone, J. Chem. Phys. **122**, 014108 (2005).

[37] P. Bouř and L. Bednárová, J. Phys. Chem. **99**, 5961 (1995)

[38] P. Daněček and P. Bouř, J. Chem. Phys. **126**, 224513 (2007).

[39] P. Carbonniere, T. Lucca, C. Pouchan, N. Rega, and V. Barone, J. Comput. Chem. **26**, 384 (2005).

[40] M. J. Frisch, G. W. Trucks, H. B. Schlegel *et al.*, GAUSSIAN 03, Revision C.02, Gaussian, Inc., Wallingford CT, 2004.

[41] A. Becke, Phys. Rev. A **38**, 3098 (1988).

[42] V. Barone, M. Cossi, and J. Tomasi, J. Comput. Chem. **19**, 404 (1998); A. Klamt, in *The Encyclopedia of Computational Chemistry*, edited by P. R. Schleyer, N. L. Allinger, T. Clark, J. Gasteiger, P. A. Kollman, H. F. Schaefer III, and P. R. Schreiner (Wiley, Chichester, 1998), Vol. 1, p. 604.

[43] R. Ditchfield, Mol. Phys. **27**, 789 (1974).

[44] J. F. Stanton, J. Gauss, J. D. Watts, P. G. Szalay, and R. J. Bartlett, ACESII (Mainz, Austin, Budapest, 2007).

[45] P. Bouř, V. Sychrovský, P. Maloň, J. Hanzlíková, V. Baumruk, J. Pospíšek, and M. Buděšínský, J. Phys. Chem. A **106**, 7321 (2002); O. L. Malkina and V. G. Malkin, Angew. Chem., Int. Ed. Engl. **42**, 4335 (2003).

[46] T. W. Keal, T. Helgaker, P. Sałek, and D. J. Tozed, Chem. Phys. Lett. **425**, 163 (2006).

[47] P. Lantto, J. Kaski, J. Vaara, and J. Jokisaari, Chem. Eur. J. **6**, 1395 (2000).

[48] R. D. Wigglesworth, W. T. Raynes, S. P. A. Sauer, and J. Oddershede, Mol. Phys. **92**, 77 (1997).

[49] S. G. Frankiss, J. Phys. Chem. **67**, 752 (1963).

[50] A. L. McClellan and S. W. Nicksic, J. Phys. Chem. **69**, 446 (1965).

[51] K. Jackowski, M. Kubiszewski, and M. Wilczek, Chem. Phys. Lett. **440**, 176 (2007).

[52] K. B. Wiberg, W. E. Pratt, and W. F. Bailey, J. Org. Chem. **45**, 4936 (1980).

[53] M. Kubiszewski, W. Makulski, and K. Jackowski, J. Mol. Struct. **704**, 211 (2004).

[54] J. Gasteiger and I. Suryanarayana, Magn. Reson. Chem. **23**, 156 (1985).

[55] N. M. Sergeyev, N. D. Sergeyeva, and W. T. Raynes, J. Chem. Soc., Chem. Commun. **1994**, 485.

[56] J. R. Everett, Org. Magn. Reson. **19**, 169 (1982).

[57] E. Breitmaier, G. Jung, W. Voelter, and L. Pohl, Tetrahedron **29**, 2485 (1973).

[58] M. J. Lacey, C. G. Macdonald, A. Pross, J. S. Shannon, and S. Sternhell, Aust. J. Chem. **23**, 1421 (1970).

[59] N. M. Sergeyev, P. Sandor, N. D. Sergeyeva, and W. T. Raynes, J. Magn. Reson., Ser. A **115**, 174 (1995).

[60] V. S. Watts and J. H. Goldstein, J. Phys. Chem. **70**, 3887 (1966).

[61] R. A. Bernheim and H. Batiz-Hernandez, J. Chem. Phys. **45**, 2261 (1966).

[62] N. D. Sergeyeva, N. M. Sergeyev, and W. T. Raynes, Magn. Reson. Chem. **36**, 255 (1998).