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Calculation of NMR Spin–Spin Coupling Constants in Strychnine

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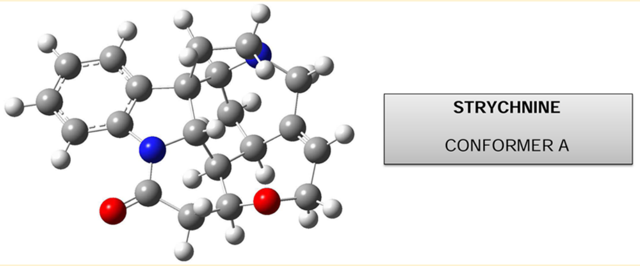
Supporting Information

ABSTRACT: We compare the NMR indirect nuclear spin–spin coupling constants in strychnine calculated using density functional theory (DFT) with the semiempirical relativistic force field (RFF) method of Kutateladze and Mukhina (KM) (*J. Org. Chem.* **2015**, *80*, 10838–10848). DFT values significantly more accurate than those obtained by KM for their comparison with RFF values can be obtained, at a lower cost, by an appropriate selection of basis set.



In a series of articles in *The Journal of Organic Chemistry*, Kutateladze and Mukhina (KM) presented a new approach to the calculation of NMR indirect nuclear spin–spin coupling constants in large organic molecules.[1−3] Their relativistic force field (RFF) method is based on a standard nonrelativistic density functional theory (DFT) calculation of the Fermi contact (FC) contribution to spin–spin coupling constants of a given molecule (ignoring all other Ramsey contributions) with the B3LYP functional[4] in a specially designed atomic orbital (AO) basis DU8, at the B3LYP/6-31G(d) optimized geometry. The RFF approach depends on a set of empirical parameters, determined by comparison with experimental spin–spin coupling constants in a training set of more than 600 constants. The RFF coupling constants are obtained as $J_{\mathrm{RFF}}(\mathrm{CH}) = \sum_{n=0}^{N} c_n F^n$, where F is the DFT-calculated FC contribution to $J(\mathrm{CH})$, the c_n coefficients are generated in an empirical manner from natural bond orbital (NBO) hybridization coefficients, using $N = 2$ for one- and three-bond couplings and $N = 3$ for two-bond couplings. In total, there are 24 empirical parameters for $J(\mathrm{CH})$ constants in the RFF method; in a similar scheme for $J(\mathrm{HH})$ constants, there are 17 empirical parameters.

As shown by KM, the RFF method can be successfully applied to large molecules. They furthermore state that their method generates spin–spin coupling constants that are as accurate as that of DFT with the hybrid B3LYP functional but with reduction in computer time of 2 orders of magnitude, achieved by omitting non-FC contributions and by using small basis sets, maintaining accuracy by combining powers of the calculated FC values in a semiempirical manner. We here show that, with an appropriate selection of basis functions, DFT provides a highly accurate spin–spin coupling constant at a reasonable cost, comparable with that of the RFF method.

The calculation of NMR spin–spin coupling constants at *ab initio* and DFT levels of theory has been reviewed elsewhere.[5,6] It has been possible for many years to calculate spin–spin coupling constants for large systems using DFT [see, for example, the calculation and analysis of all the spin–spin coupling constants in valinomycin ($C_{54}H_{90}N_6O_{18}$) published in 2004].[7] DFT calculations do not depend on training sets (except sometimes in the construction of the exchange-correlation functional) and are therefore more robust and generally applicable than empirical methods such as the RFF method.

We note that, in spite of its name, the "relativistic force field" method, the RFF method is entirely nonrelativistic, based on the nonrelativistic theory of spin–spin coupling constants presented by Ramsey in 1953[8] and on nonrelativistic DFT calculations. Relativistic methods for spin–spin coupling constants have been implemented in some program packages[9−11] but have not been used by KM or by us here because a relativistic treatment of strychnine ($C_{21}H_{22}N_2O_2$) would be not only time-consuming but also unnecessary, because relativistic corrections are negligible for molecules without heavy atoms.[12]

For comparison with the results of KM, we use the B3LYP exchange-correlation functional, widely used for spin–spin coupling constants, but note that other functionals may be preferable in different situations, depending on the system being studied.[13−16]

The choice of AO basis set is critical for spin–spin coupling constants, which require a flexible description of the core region for accurate results. Because standard energy-optimized basis sets do not have the required flexibility, special basis sets have been designed.[17,18] Such sets allow the basis set limit to be approached systematically and give accurate results with a significant reduction in computer time (which is approximately proportional to N^3, where N is the size of the basis set). In the DFT strychnine calculations performed or discussed by KM, there are 1656 basis functions in the aug-cc-pVTZ basis set,

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Table 1. RMS Deviations of the Calculated 122 $J(\mathrm{CH})$ Coupling Constants in Strychnine (hertz)[a]

	conformer A, 96.9%				conformer B, 3.1%			
KM[3]	pcJ-0	pcJ-1	6-31G-J	6-311G-J	pcJ-0	pcJ-1	6-31G-J	6-311G-J
0.7	0.57	0.18	0.51	0.45	1.42	1.23	1.39	1.37

[a] The values of all calculated constants are given in the Supporting Information.

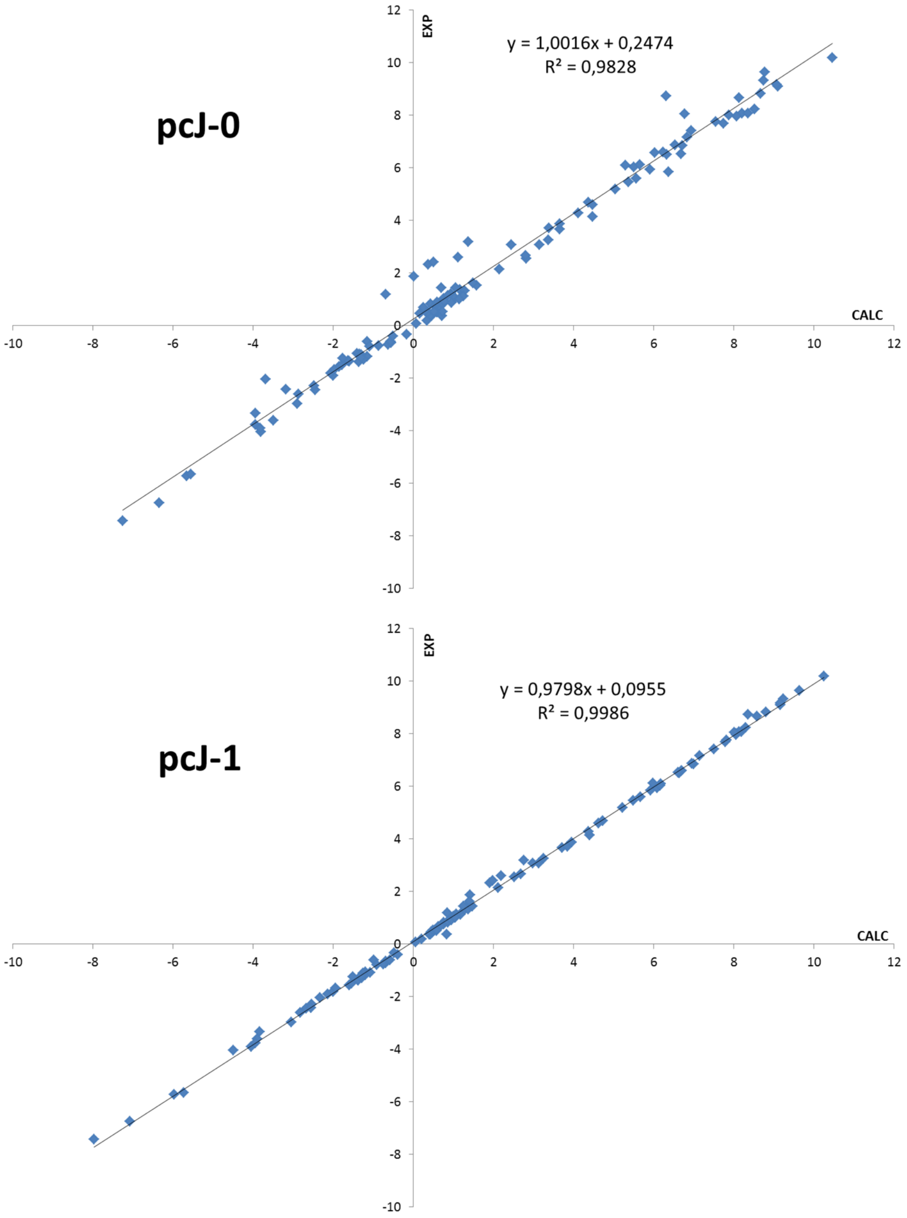

Figure 1. Comparison of calculated and experimental $J(\mathrm{CH})$ values for two basis sets.

1242 functions in the EPR-III basis set, and 704 functions in the 6-311++G(d,p) basis set.

We present here spin−spin coupling constants of strychnine calculated using the Dalton program[19] with four basis sets developed for spin−spin calculations: the pcJ-0 (391 AOs) and pcJ-1 (895 AOs) basis sets of Jensen[17] and the 6-31G-J (388 AOs) and 6-311G-J (557 AOs) basis sets of Kjær and Sauer.[18] Among these, pcJ-0 and 6-31G-J are smaller than the DU8 basis set recommended by KM for the RFF approach [containing 457 AOs for strychnine (see ref 2)], while 6-311G-J is smaller than the 6-311++G(d,p) basis set used in the corresponding full DFT calculations. We use the same geometries and same atom numbering as KM.[3]

In Table 1, we report the root-mean-square (RMS) deviations from the experimental data for the 122 $J(\mathrm{CH})$ constants in Table 5 of ref 3. For all four basis sets used by us, the RMS values are smaller than the RFF value of 0.7 Hz and the B3LYP/6-311++G(d,p) value of 0.6 Hz reported by KM. The pcJ-1 basis set, in particular, gives a significantly smaller RMS deviation of 0.18 Hz. We note that, in the pcJ-1 basis set, the RMS deviation for the 96.9% A/3.1% B conformation mixture (see Figure 9 of ref 1) is 0.181 Hz, very similar to that of conformer A (0.176 Hz). Considering only the $^{1}J(\mathrm{CH})$

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Table 2. ^3J(C−O−C−H) Coupling Constants in Conformers A and B of Strychnine (hertz)

			KM		pcJ-0		pcJ-1		6-31G-J		6-311G-J	
		exp	J	Δ^2	J	Δ^2	J	Δ^2	J	Δ^2	J	Δ^2
C12−H23a		6.10	5.10	1.00								
	A				5.29	0.65	6.18	0.01	6.35	0.06	6.29	0.04
	B				9.64	12.52	10.47	19.13	11.33	27.31	11.28	26.87
C12−H23b		9.32	7.91	1.99								
	A				8.74	0.33	9.23	0.01	9.95	0.40	9.91	0.35
	B				2.14	51.60	2.51	46.40	2.66	44.34	2.63	44.73
C23−H12		3.07	2.66	0.17								
	A				2.44	0.40	2.98	0.01	2.95	0.02	3.02	0.00
	B				8.92	34.19	9.98	47.78	10.68	57.92	10.73	58.65

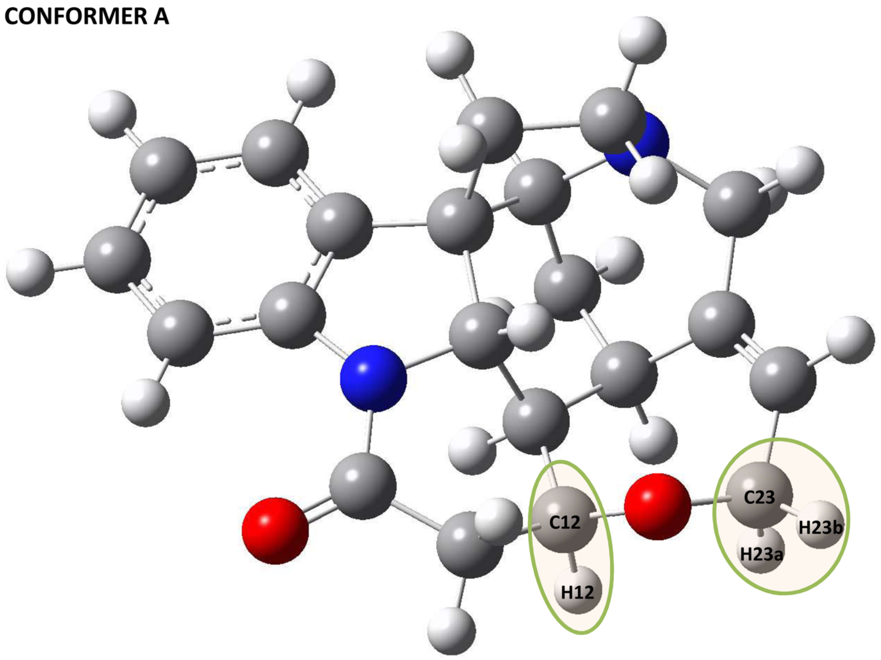

Figure 2. Conformer A of strychnine. The indirect nuclear spin−spin coupling constants between the labeled nuclei differ significantly from those of conformer B.

constants computed with the pcJ-1 basis set, we find that these are systematically slightly too large relative to the experimental values in ref 20, with errors in the range of 0.6−2.2%.

In the calculations described above, all four Ramsey contributions to the spin−spin constants have been calculated using the same basis set. Bearing in mind that the basis set requirements for the FC term are considerably higher than for the non-FC terms and that the FC term requires only one linear set of equations to be solved per atom (while the non-FC terms require a total of nine equations), we find it is a good idea to use a large basis set for only the FC term. For example, by using the pcJ-1 basis set for the FC term and the pcJ-0 basis set for the remaining terms, we increase the RMS deviation only slightly, from 0.18 to 0.20 Hz, while reducing the cost by almost an order of magnitude.

Moreover, because the FC term often (but not always) dominates the coupling constants,[21] we may reduce the cost by an order of magnitude by omitting the non-FC terms entirely (perhaps after a small basis pilot study to confirm FC dominance). Retaining only the FC term for strychnine, we obtain RMS deviations of 0.41, 0.27, 0.54, and 0.51 Hz for the pcJ-0, pcJ-1, 6-31G-J, and 6-311G-J basis sets, respectively. These calculations take 3.2 h (CPU) for the smallest pcJ-0 basis set and 9.9 h for the largest pcJ-1 basis set, compared with 4.4 h for the RFF in the DU8 basis set.[3]

The quality of our pcJ-0 and pcJ-1 results is illustrated in Figure 1. A linear fit of the 122 J(CH) constants computed with the pcJ-0 basis set gives $J_{\text{exp}} = 1.0016J_{\text{calc}} + 0.2474$ Hz and $R^2 = 0.9828$. A significant improvement is observed with the pcJ-1 basis set, yielding $J_{\text{exp}} = 0.9798J_{\text{calc}} + 0.0955$ Hz and a noticeably higher R^2 of 0.9986. The good agreement of the pcJ-1 results with experiment indicates that the procedure chosen by KM to optimize molecular geometries provides a sufficiently accurate structure for strychnine.

As seen from Table 1, the DFT results can easily be used to identify conformer A as the dominant one. For conformer B, the deviations relative to experiment are largest for the three ^3J(C−O−C−H) constants; when these are omitted, the RMS deviation for conformer B is reduced significantly. In the pcJ-1 basis set, for example, it is reduced from 1.23 to 0.78 Hz, which is still higher than the corresponding deviation of 0.18 Hz for conformer A. In fact, the difference between the two conformers is primarily related to the C−O−C geometry, and a calculation of the three constants in Table 2 is sufficient to confirm A as the experimentally observed conformer (see Figure 2).

Table 3. Signs of J(C18−H17b) in Strychnine

		KM		pcJ-0		pcJ-1		6-31G-J		6-311G-J	
±exp		J	Δ^2	J	Δ^2	J	Δ^2	J	Δ^2	J	Δ^2
−1.44		−0.56	0.77	0.70	4.57	1.25	7.23	1.05	6.19	1.05	6.22
	rms		0.68		0.60		0.30		0.55		0.50
	max		5.90		5.86		7.23		6.19		6.22
+1.44		−0.56	4.00	0.70	0.55	1.25	0.04	1.05	0.15	1.05	0.15
	rms		0.70		0.57		0.18		0.51		0.45
	max		5.90		5.86		0.31		1.68		1.37

DFT calculations allow the determination of the signs of coupling constants, which are not always available from experiment. We illustrate this in Table 3, having selected the J(C18−H17b) constant (the sign of this constant is different in refs 20 and 3, which is presumably a typo). If −1.44 Hz (rather than the experimental value of 1.44 Hz) is taken as the value for this constant, then the corresponding constant calculated with the pcJ-1, 6-31G-J, or 6-311G-J basis set exhibits the largest deviation among all 122 J(CH) constants (see Table 3). Moreover, in the pcJ-1 basis set, the RMS deviation is noticeably smaller if 1.44 Hz is taken as the correct value.

We have also computed the J(CC) and J(HH) coupling constants of strychnine. For the 22 available ^1J(CC) constants,[22] we obtain $J_{\text{exp}} = 0.8881J_{\text{calc}} + 1.3996$ Hz and $R^2 = 0.9909$ in the pcJ-1 basis set. This overestimation is expected: the B3LYP functional typically gives 8% too large one-bond CC coupling constants.[23] For the three-bond CC constants, we reproduce the earlier DFT values of ref 22. KM have not presented values for these constants.

The DFT calculation of J(HH) constants was recently discussed by Bally and Rablen.[24] Fitting the 27 J(HH) constants (see Table 3 of ref 1) computed in the pcJ-1 basis set, we obtain $J_{\text{exp}} = 0.9141J_{\text{calc}} - 0.1141$ Hz and $R^2 = 0.9948$, in perfect agreement with the slope of 0.912 Hz in ref 24. As for the ^1J(CC) constants, the B3LYP functional overestimates the J(HH) constants. The RMS deviation of 0.86 Hz is reduced to 0.35 Hz when, following the work of Bally and Rablen, the results are scaled linearly according to the expression given above (the corresponding RFF value is 0.19 Hz). For selected constants in the pcJ-2 basis set, we have verified that the polarizable continuum model (PCM) does not affect results significantly; these results thus properly illustrate the performance of the B3LYP method in a large basis set.

In summary, full DFT calculations of indirect nuclear spin−spin coupling constants are practicable for molecules such as strychnine, providing within reasonable CPU time results comparable with those of the RFF. In their DFT comparison with the RFF method, KM quoted the large 6-311++G(d,p) basis set, not suited for spin−spin coupling constants. We obtain significantly better J(CH) values with the large pcJ-1 basis set and equally good results with the much smaller pcJ-0 basis set, making it possible to perform DFT calculations of spin−spin coupling constants for very large molecules.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02157.

Results (experimental data, KM, and our values) for 122 J(CH) constants for conformer A of strychnine (PDF)

Geometries and total energies of conformers A and B (PDF)

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Notes

The authors declare no competing financial interest.

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