DOI: 10.1002/chem.201102272

Computational and Experimental Evidence of Through-Space NMR Spectroscopic *J* Coupling of Hydrogen Atoms

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Abstract: *J* coupling in NMR spectroscopy is conventionally associated with covalent bonds. A noncovalent contribution often called through-space coupling (TSC) has been observed for heavy atoms. In this study, the TSC was detected and analyzed for the more common ^{1}H–^{1}H coupling as well. In synthesized model molecules the hydrogen positions could be well controlled. For several coupling constants the through-space mechanism was even found to be the predominant factor. The nature and magnitude of the phenomenon were also analyzed by density functional computations. Calculated carbon- and hydrogen-coupling maps and perturbed electronic densities suggest that the aromatic system strongly participates in the noncovalent contribution. Unlike covalent coupling, which is usually governed by the Fermi contact, TSC is dominated by the diamagnetic term comprising interactions of nuclei with the electron orbital angular momentum. The computations further revealed a strong distance and conformational dependence of TSC. This suggests that the through-space coupling can be explored in molecular structural studies in the same way as the covalent one.

Keywords: conformations • density functional calculations • NMR spectroscopy • through-space coupling • weak interactions

Introduction

Isotropic spin–spin (scalar) *J* coupling of nuclear magnetic momenta is normally thought of as a proof of a strong covalent link between two atoms. The relationship between the vicinal coupling and the torsion angles in peptides and sugars, for example, became famous as the Karplus equation.[1] But molecular structure, constitution, and configuration can also be elucidated from the coupling information contained in the NMR spectra.[1b,c,2]

J coupling is mediated by electrons, and their covalent distribution is not necessary for the phenomenon. Indeed, measurable scalar couplings of nuclei not connected by conventional chemical bonds have been recently observed in a variety of systems. Typically, such "through-space" coupling (TSC) occurs for nuclei involved in hydrogen bonding, in which the covalent contribution is minor.[3,4]

Intramolecular TSC has been observed as well. The through-space character can be inferred, for example, from an unexpectedly large coupling between two atoms close in space but separated by several bonds.[5] TSC was observed for fluorine–fluorine,[6] fluorine–carbon, fluorine–nitrogen,[7] fluorine–hydrogen,[6d,8] phosphorus–phosphorus,[9] carbon–phosphorus,[10] and rarer metallic nuclear pairs.[11]

Studies of TSC in van der Waals complexes without any covalent interaction are least frequent. It is very difficult to detect the coupling for such systems in the same manner as for the hydrogen-bound case because the lifetime of the dispersion (van der Waals) complexes is usually too short to allow for a conventional measurement. A sizable magnitude of TSC was also predicted in several theoretical studies for xenon[12] and helium[13] dimers; $HF{\cdot}CH_4$ and $HF{\cdot}CH_3F$ complexes;[14] methane–benzene and benzene–benzene dimers;[15] and the $CH_3CN{\cdot}C_6F_6$ complex.[16] Experimentally, to the best of our knowledge, TSC in a van der Waals complex has been confirmed only for dithallium cryptate, with $J(\mathrm{Tl,H}) = 17$ Hz.[17]

The electronic origin of TSC was analyzed by Bagno et al.[15b] Quantum chemical calculations verified that the electronic cloud could produce the spin–spin coupling between two nuclei regardless of whether there was a covalent link or not.[13,14b,18] Similar results were obtained by density functional theory (DFT)[19] and wavefunction methods.[5,14a,19b,20] We chose the DFT methodology with the B3LYP functional as it provides a good balance between computational cost and accuracy, and describes all the main physical factors involved in the coupling.[21]

We studied the TSC effect on model compounds **1**–**7** (Scheme 1), in which the spatial arrangement of interacting nuclei could be controlled. For example, in the [2,2]paracyclophane derivatives **1**–**3** the distance between the pseudo-

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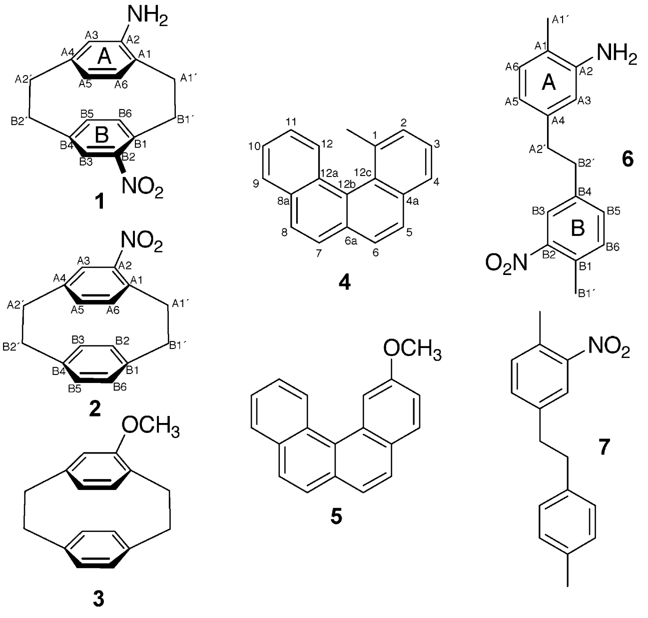
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201102272. It contains further synthetic and computational details, including the compound characterization.



Scheme 1. Structure and atom numbering of the model compounds. Molecules **6** and **7** are formally open forms of compounds **1** and **2** (the structure of which is close to **3**); therefore, analogous numbering is maintained within **1**–**3** and **6** and **7**. TSC was observable in **1**–**5**.

ipso-hydrogen atoms is 3.1 Å.[22] The ring rotations are completely blocked at room temperature. In the benzophenanthrene derivatives **4** and **5** the hydrogen atom at the 12-position is close to the hydrogen atoms of the C-1 methyl group (**4**) or to the H-1 hydrogen atom (**5**). Compounds **6** and **7** were prepared as systems in which the TSC is supposed to be minimal. Otherwise they are chemically similar to and can be thought of as open forms of derivatives **1** and **2**.

Results and Discussion

NMR spectroscopy experiment: As the primary model compound, we investigated the pseudo-*meta*-heteroannular-disubstituted derivative of [2,2]paracyclophane (**1**). The 1D COSY and 1D NOE spectra, in which the signal of hydrogen A3 was selectively irradiated, are plotted in Figure 1. Note that in the COSY experiment (Figure 1b) one can observe signals of hydrogen atoms that couple with the irradiated atom. In the NOE spectra (Figure 1c), the signals correspond to hydrogen atoms close in space to A3.

The spectra in Figure 1 thus reveal significant TSC (formally seven-bond) *J*(A3,B5), in addition to the usual four- and five-bond couplings (*J*(A3,A5), *J*(A3,A6)) in the same benzene ring. These results are in agreement with the previous selective decoupling experiment on compound **1**, which indicated the magnitude of the heteroannular coupling of 0.3–0.4 Hz.[23] Analogous "seven-bond" coupling between hydrogen atoms that are not close in space, such as *J*(A3,B3), is absent. Nor is the seven-bond coupling observable in compound **6** (compare with the spectrum in Figure S1 of the Supporting Information), in which the two benzene rings are not kept together by the covalent link. The same coupling behavior as for compounds **1** and **6** was observed for closed and opened mononitro derivatives **2** and **7**. As an alternate confirmation we performed long-range COSY experiments (e.g., the aromatic region of 2D long-range COSY of compound **2** is shown in Figure S2 in the Supporting Information).

A similar coupling pattern was observed in the benzophenanthrene derivatives **4** and **5** for hydrogen atom H-12, close to the methyl group or H-1, respectively (Figure S3 in the Supporting Information). In **4**, the TSC is detectable between hydrogen atoms that are separated by seven bonds, similarly as for **1**–**3**, whereas no coupling is observed between the methyl-group hydrogen atoms and H-6 or H-7 separated by the same number of covalent bonds. In compound **5** the "six-bond" TSC between H-1 and H-12 is detectable, unlike analogous six-bond couplings *J*(H1,H6) or *J*(H1,H7). The absolute values of the constants were obtained from comparison of off- and on-resonance selective decoupling of the coupled nucleus. Because of their small magnitude, the small TSCs do not result in line splitting, but only in a broadening. The coupling constant thus were evaluated by the usual simulation of spectral shape.[23] Nevertheless, rather long acquisition times, substantial zero filling, and strong windowing had to be applied to obtain sufficient spectral resolution.

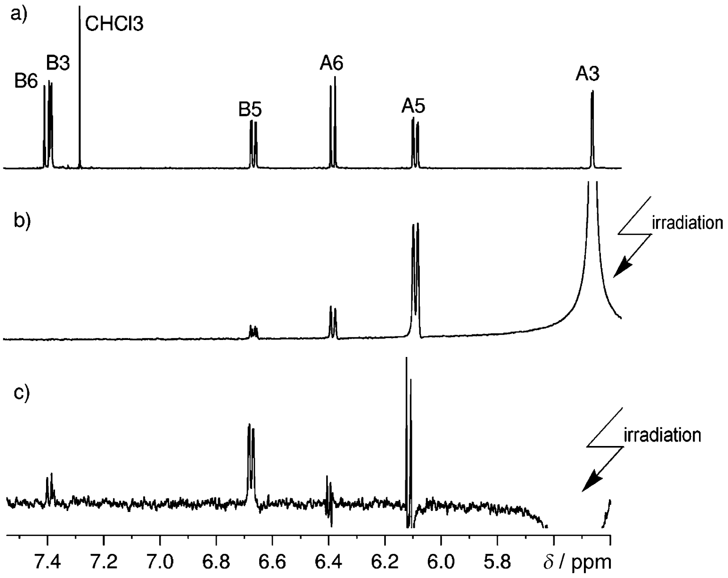


Figure 1. a) The aromatic region of the ^{1}H NMR spectrum of compound **1**, b) selective 1D COSY, and c) selective differential 1D NOE experiments with the irradiation of the signal of hydrogen A3.

Comparison to calculated *J* couplings: The experimental magnitudes of TSC agree very well with the calculated values (Table 1). As discussed before,[24] reliable computa-

Table 1. Calculated (B3LYP/6-311++G(2df,2pd), B3LYP/6-31+G** geometry) and experimental TSC constants (in Hz) for compounds **1**–**7**.

Compound	Coupling	Calcd	Exptl	Compound	Coupling	Calcd	Exptl
1	A3,B5	0.37	0.37	**4**	12,CH_3	0.56	0.38
1	A5,B3	0.34	0.33	**5**	1,12	−0.42	0.55[b]
2	A3,B3	0.36	0.45	**6**	A3,B5	0.13	0
2	A5,B5	0.34	0.54	**6**	A5,B3	0.14	0
2	A6,B6	0.33	–[a]	**7**	A3,B3	−0.03	0
3	A3,B3	0.38	0.34	**7**	A5,B5	−0.04	0
3	A5,B5	0.34	0.60	**7**	A6,B6	−0.05	0
3	A6,B6	0.36	–[a]				

[a] Immeasurable because of signal overlap. [b] Absolute value.

tion of *J* coupling requires a large basis set of atomic orbitals. We noticed that adding polarization or diffuse functions on heavy atoms had a particularly dramatic effect on computed TSC (Table S1 and Figure S4 in the Supporting Information). Also, the double→triple zeta basis change (6-31++G**→6-311++G**) typically caused a significant drop (up to 50%) of the calculated constants. For converged results it was further important to include the f orbitals. The 6-311++G(2df,2pd) basis set finally provided coupling values very close to the supposedly most accurate aug-cc-pVTZ ones, but with significantly less computational effort (Table S2 in the Supporting Information). On the other hand, when the conductor-like polarizable continuum model (CPCM) solvent correction was added, the coupling constants changed less than 0.01 Hz (Table S1 in the Supporting Information). Likewise, inclusion of the DFT dispersion correction (Table S3 in the Supporting Information) for the geometries led to a minor (≈10%) change of the calculated constants. Thus we attribute most of the remaining error to the inaccuracy of the B3LYP method, and a lack of anharmonic and dynamical averaging.[25]

Components of TSC constants: Individual terms contributing to the coupling (Fermi contact (FC), spin dipolar (SD), paramagnetic spin–orbit (PSO), and diamagnetic spin–orbit (DSO))[21,24] ratios are very different from those in the usual through-bond *J* coupling. As exemplified in Figure 2 (and more in Table S4 in the Supporting Information), the Fermi contact term, which usually dominates the covalent coupling,[24,26] is relatively small for TSC, in favor of the PSO and DSO terms. This can be explained by the delocalized character of TSC. The electron spin–nuclear spin interactions (giving the FC and SD terms) are not so important, probably because of an electron-spin pairing within a large part of the molecule. Nevertheless, the PSO and DSO terms have opposite signs and partially cancel. Only the relative contribution of the SD component is consistently minor in both coupling types.

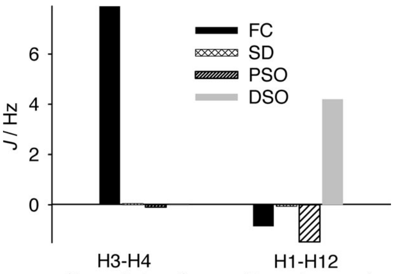


Figure 2. A typical composition of the through-bond (FC-term-dominated) and through-space (DSO-term-dominated) couplings, obtained for compound **5** at the 6-311++G(2df,2pd) level.

Another insight into the spatial coupling provides visualization of the diamagnetic coupling density, and Fermi contact and paramagnetic perturbations (Figure S5 in the Supporting Information), obtained using the sum-over-states (SOS) approximation.[26] The density plots indicate that the aromatic system enhances TSC by providing many electrons that interact with the nuclei. Nucleus-free TSC maps (Figure S6 in the Supporting Information) indicate a significant role of the benzene ring, and a strong directional, geometrical dependence of the phenomenon.

Molecular dynamics and conformational dependence of the coupling: Starting from the DFT-optimized geometry of compound **1**, we performed Born–Oppenheimer (BO) molecular dynamic runs to investigate the influence of molecular flexibility on TSC. The linear distance dependence of the constants simulated during the MD run (Figure 3) is somewhat surprising because of the much steeper r^{-3} term in the conventional magnetic dipole–dipole interaction operator.[21a] However, a similar dependence was previously found in the simpler systems and covalent *J* coupling.[27] Clearly, for larger distances, the coupling quickly disappears.[15b] The large dispersion of TSC (≈0.4–1.2 Hz, Figure 3) suggests that the correlation with the distance can be potentially used in structural studies, in a same way as the NOE.

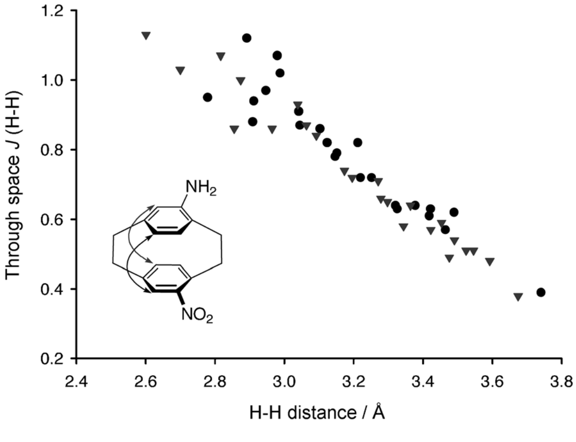


Figure 3. Calculated (B3LYP/6-31+G**) dependence of the through-space *J*(H,H) coupling on the distance, obtained from 24 BOMD snapshots for compound **1**. The dynamics was performed at 300 K. ● = A5–B3; ▼ = A3–B5.

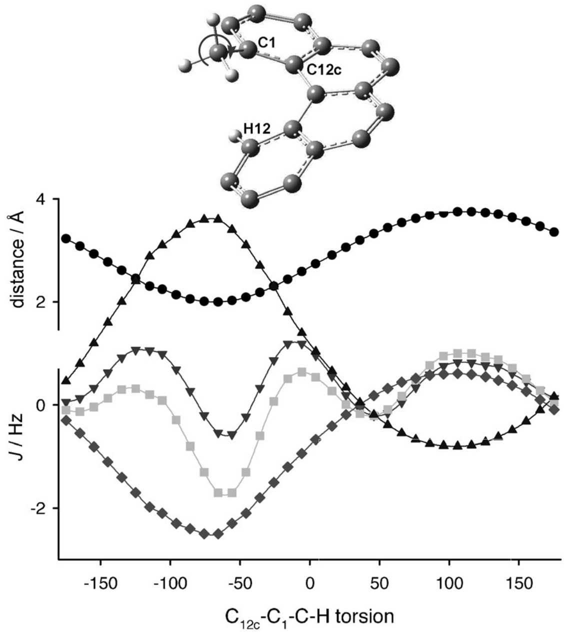


Figure 4. Calculated (B3LYP/6-31+G**) dependence of the H–H distance, and components of the H12–methyl hydrogen TSC on the CH_3-group rotation in compound **4**. ● = H–H distance in Å; ▼ = *J* (H–H) in Hz; ■ = FC; ◆ = PSO; ▲ = DSO.

Even more surprising is the conformational dependence of the TSC modeled for compound **4** plotted in Figure 4. The coupling does weakly correlate with the distance of coupled atoms; however, it is much more dependent on the torsion angle. For example, *J*(H,H12) = −0.7 Hz for the distance of 2 Å (torsion angle −60°) is smaller than *J*(H,H12) = 1.1 Hz obtained for the larger distance of 2.3 Å (torsion angle of −10°), and so forth. Clearly, the sole FC term is responsible for most of the angular dependence. A more detailed analysis (Figure S7 in the Supporting Information) reveals that the measurable average *J* coupling between the three methyl and H12 hydrogen atoms is dependent on the rotation in a similar manner, and that the aromatic residue attached to the CH_3 group is not so important for this dependence.

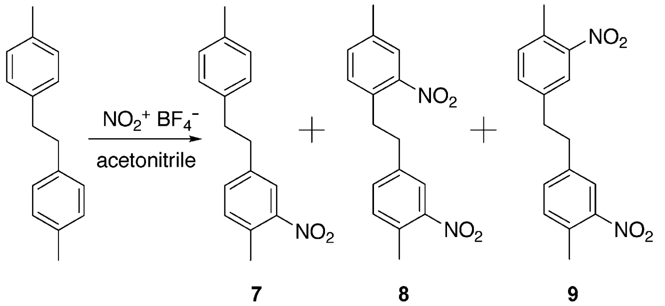
Conclusion

The NMR spectroscopy experiments on model compounds confirmed the presence of TSC for spatially closed hydrogen atoms. The obtained coupling constants could be well reproduced by the density functional calculations. Unlike for the covalent case, the Fermi contact term is relatively small in TSC, whereas the DSO term is unusually large, followed by the PSO interaction.

The analysis of the distant and torsional dependence additionally revealed that the through-space coupling, similarly to the covalent one, provides very specific information about local molecular geometry. As the precision of NMR spectroscopy instruments grows, we thus suppose that TSC effects will play an increasing role in structural studies of molecules and their complexes. Similarly to NOE, for example, TSC can monitor noncovalent contacts in molecules and their complexes.

Experimental Section

Synthesis: Compounds **1**, **3**–**5**, and 1,2-di-*p*-tolylethane were obtained from Sigma Aldrich. To synthesize **6**–**9**, a solution of 1,2-di-*p*-tolylethane (420 mg, 2 mmol) in acetonitrile (100 mL) was purged with argon and cooled with an ice bath. Nitronium tetrafluoroborate (265 mg, 2 mmol) was slowly added at 0 °C and the reaction mixture was stirred without further cooling for 5 h. After evaporation, the products were separated by column chromatography (silica gel, hexane/ethyl acetate). Phases containing the desired products were purified on preparative TLC sheets. After evaporation, 1-methyl-4-(4-methylphenethyl)-2-nitrobenzene (**7**; 37 mg), 1-methyl-4-(4-methyl-2-nitrophenethyl)-2-nitrobenzene (**8**; 46 mg), and 1,2-bis(4-methyl-3-nitrophenyl)ethane (**9**; 114 mg) of a high purity were isolated (Scheme 2).



Scheme 2. The synthesis of compound **7**.

The preparation of **7** by nitration of 1,2-di-*p*-tolylethane appeared to be very challenging. In the beginning we used various nitration reagents such as nitric acid, acetyl nitrate, a mixture of nitric and sulfuric acid, or a mixture of acetic and nitric acid. As verified by GC-MS, these reagents produced mixtures containing dinitro isomers and other byproducts, typically with molecular weights smaller by 2 or 4 than the dinitro compounds. We explain this by the oxidation of the ethane bridge, which forms double or triple bonds between two benzene rings. The nitronium tetrafluoroborate, however, suppressed the oxidation, in accord with the known properties of this mild nitration reagent.[28] Reaction of 1,2-di-*p*-tolylethane with nitronium tetrafluoroborate (Scheme 2) afforded a mixture of three major products, which were isolated by repeated chromatographic purifications, and were identified as **7**, **8**, and **9**.

Nitro[2,2]paracyclophane (**2**) was obtained by the reaction of [2,2]paracyclophane (416 mg, 2 mmol) and nitric acid (1.94 g, 65 %, 20 mmol) in acetic acid (50 mL) at reflux for 10 min. After evaporation, the product was purified by column chromatography (silica gel, hexane/ethyl acetate) to give the nitro[2,2]paracyclophane (246 mg, 49 %).

2-Methyl-5-(4-methyl-3-nitrophenethyl)aniline (**6**) was prepared by the selective reduction of compound **9**. The hydrazine hydrate (2 mg, 0.04 mmol) in methanol (5 mL) was added with cooling and vigorous stirring to a mixture containing **9** (12 mg, 0.04 mmol), charcoal (100 mg), and $FeCl_3$ (1 mg, 0.06 mmol) in methanol (20 mL) under argon for 2 h. The temperature was maintained at 20–25 °C. The reaction mixture was then vigorously stirred at room temperature for an additional 4 h. The crude product was purified by preparative TLC (silica gel, hexane/ethyl acetate) to give the desired product **6** (8 mg, 75 %). It may be useful to note that a selective reduction of one of the two nitro group in **9** was successful only under particular conditions, previously described also for a

1,3,5-trinitrobenzene reduction by hydrazine hydrate in the presence of iron chloride and charcoal.[29] An alternative procedure using $SnCl_2$ in HCl[30] failed in this case.

NMR spectroscopy experiments: NMR spectra were measured on a Bruker Avance II 500 and/or Avance II 600 spectrometer (500 or 600 MHz for ^{1}H and 126 or 151 MHz for ^{13}C). All spectra were acquired for samples in $CDCl_3$ and referenced to TMS. Signals of all hydrogen and carbon atoms were assigned by using a combination of 1D and 2D (H,H-COSY, H,C-HSQC, H,C-HMBC, and H,H-ROESY) techniques. The long-range COSY (LR COSY) experiment was recorded by using the standard magnitude-mode COSY sequence and setting the delay for evolution of long-range couplings to 500 ms. The small through-space couplings were obtained from selective 1D homonuclear decoupling experiments, in which the data were reproduced iteratively by simulations with different constant values.

Density functional computations: The geometries of compounds **1**–**7** were optimized at the DFT level of theory, using the Gaussian 09 program,[31] B3LYP functional,[32] and 6-31+G** basis set. Harmonic vibrational frequencies were calculated for all of the optimized structures to confirm a minimum at the potential-energy surface. For the equilibrium geometries and selected atoms, *J* coupling constants were calculated by using Gaussian with the 6-31G, 6-31G*, 6-31G**, 6-31+G**, 6-31++G**, 6-311++G**, 6-311++G(2df,2pd), and aug-cc-pVTZ standard Gaussian basis sets. The IGLOIII[33] basis set, and the COSMO[34] solvent correction with the 6-311++G(2df,2pd) basis set were also tested; for some derivatives, the BPW91[35] and B97D[36] functionals, and IGLOII[33] basis were tried. The nuclear selection appeared extremely important for savings of computer time, especially for the larger basis sets. By using our program interfaced to Gaussian, the diamagnetic coupling density, Fermi contact, and paramagnetic perturbations of the electronic density were visualized within the SOS approximation.[26] The B3LYP hybrid functional was chosen as it has provided very reliable *J* coupling constants on similar systems in the past.[37]

Born–Oppenheimer molecular dynamics (BOMD): By using the DFT-optimized structure of compound **1** as the starting geometry, we performed BOMD[38] runs to investigate the influence of molecular flexibility on the through-space coupling. Note that we used the periodic boundary conditions and the GGA/plane wave methodology[38] for a single molecule to save computer time. For example, BOMD with Gaussian and the B3LYP functional would be unreasonably slow. Within the Car–Parrinello molecular dynamics (CPMD)[39] software (which enables one to perform the Born–Oppenheimer dynamics, apart from the default CPMD) the molecule was placed in a cubic box of $15\times15\times15$ Å^3 and left to develop for 10 ps, using a time step of 0.38704 fs, energy cutoff of 25 Rydberg, the BLYP[32a] functional, Vanderbilt ultra-soft pseudopotentials,[40] and the fictitious electron mass of 600 atomic units. A temperature of 300 K was maintained by using a Nosé–Hoover bath.[41] Trajectory snapshots were saved every 1000 time steps (within 0.39 ps intervals), and the coupling constants were calculated by Gaussian at the B3LYP/6-31+G** level.

Acknowledgements

This study was performed with support from the Academy of Sciences (M200550902, KJB400550903), MSMT (LH11033), Grant Agency of the Czech Republic (P208/11/0105); and Metacentrum and University of Tromsø computer facilities.

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Received: July 23, 2011