

Theoretical study of spin-spin coupling across the hydrogen (O-H···N) bond in adenosine derivatives

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Abstract The study of spin-spin coupling constants across hydrogen bond provides useful information about configuration of complexes. The interesting case of such interactions was observed as a coupling across an intramolecular hydrogen bond in 8-bromo-2',3'-*O*-isopropylideneadenosine between the -CH₂OH (at 5'' proton) group and the nitrogen atom of adenine. In this paper we report theoretical investigations on the ^{4h}J_{NH} coupling across the H''-C-O-H···N hydrogen bond in adenosine derivatives in various solvent models.

Keywords *Ab initio* calculations · Adenosine derivatives · Coupling across hydrogen bonds · Density functional theory

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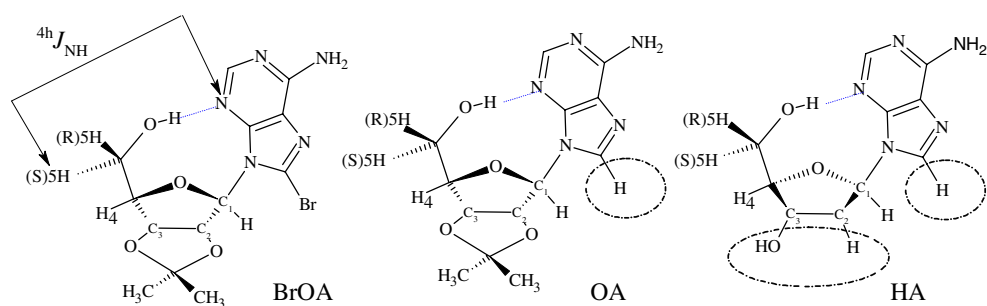
Introduction

NMR spectroscopy has become a valuable tool to study the variety of cases of hydrogen bonding [1]. The analysis of NMR spectra allows us to observe coupling constants across hydrogen bonds (^{nh}J_{XY}) and dihydrogen bonds (ndJ_{XY}). The designation ^{nh}J_{XY} indicates the number of bonds (n) present between coupled atoms (X,Y) across hydrogen (h) or dihydrogen bonds (d) [2]. The analysis allows us to detect inter- and intramolecular interactions and conformational changes in synthetic and natural compounds of variable structures [1]. Nucleotide derivatives are interesting because, apart from their biological function, their small modifications provide compounds which can be applied to anticancer, antibacterial, and antiviral therapies [3].

Majority of measured and described examples of compounds revealing couplings across hydrogen bond involve interactions between purine bases and amino acids [1, 4]. An important development of this scientific area has been done by Dingley and Grzesiek [5] who in 1998 detected a coupling across a hydrogen bond between adenine and uracyl (A:U) and guanine and cytosine (G:C) pairs [5]. The couplings such as: ^{2h}J_{NN'}, ^{1h}J_{NN'}, ^{3h}J_{HH'} (N-H···N) [5–9], ^{4h}J_{NN'}, ^{3h}J_{HC'} (N-H···O=C) [10], ^{2h}J_{FC}, ^{1h}J_{FH} (F-H···N) have been detected and well characterized in nucleic acids, nucleotides, and their derivatives [11].

One of the most interesting interactions observed so far was a coupling across an intramolecular hydrogen bond in 8-bromo-2',3'-*O*-isopropylideneadenosine (BrOA) between the -CH₂OH (at 5'' proton) group and nitrogen atom of adenine. This coupling was detected in 1986 by Koole et al. (^{4h}J_{NH}) in the H''-C-O-H···N fragment of molecule [12] and was found to be considerably dependent on the solvent used. In non-polar solvents, such as chloroform and benzene, the conformation with intramolecular hydro-

Fig. 1 Molecular structures of BrOA (8-bromo-2',3'-*O*-isopropylideneadenosine), OA (2',3'-*O*-isopropylideneadenosine), and HA (2'-hydroadenosine)



gen bond O-H \cdots N dominates, and this allows to observe the $^4hJ_{\text{NH}5'}$ coupling. In polar solvents this intramolecular hydrogen bond does not exist [12].

In this study correlation of calculated geometry of structure and spin-spin coupling across H-bond in the 8-bromo-2',3'-*O*-isopropylideneadenosine with experimental values has been done. Since measured NMR parameters are influenced by solvent, we have focused theoretical modeling on intramolecular hydrogen bond in various solvents.

Computational details

The structures of adenosine derivatives were optimized using the density functional theory (DFT) [13] with the

B3LYP functional [14] and the standard 6-31G(*d,p*) basis of atomic orbitals [15]. The geometry was modeled taking into account the influence of solvent (chloroform) within the polarized continuum model [16]. Additionally, for the 8-bromo-2',3'-*O*-isopropylideneadenosine -BrOA (Fig. 1a) the calculations were performed in benzene, acetonitrile, and dimethyl sulfoxide (DMSO) as solvents. Vibrational frequencies and thermodynamic properties were calculated by applying the ideal gas, rigid rotor, and harmonic oscillator approximations [17]. For all conformers energy minima were confirmed by frequency calculations. The initial structure of BrOA was adopted from the Cambridge Structural Database [18] (refcode BRADOM [19]). Other conformers of BrOA were designed by a modification of glycosyl torsion angle and rotation of a -CH₂OH. The

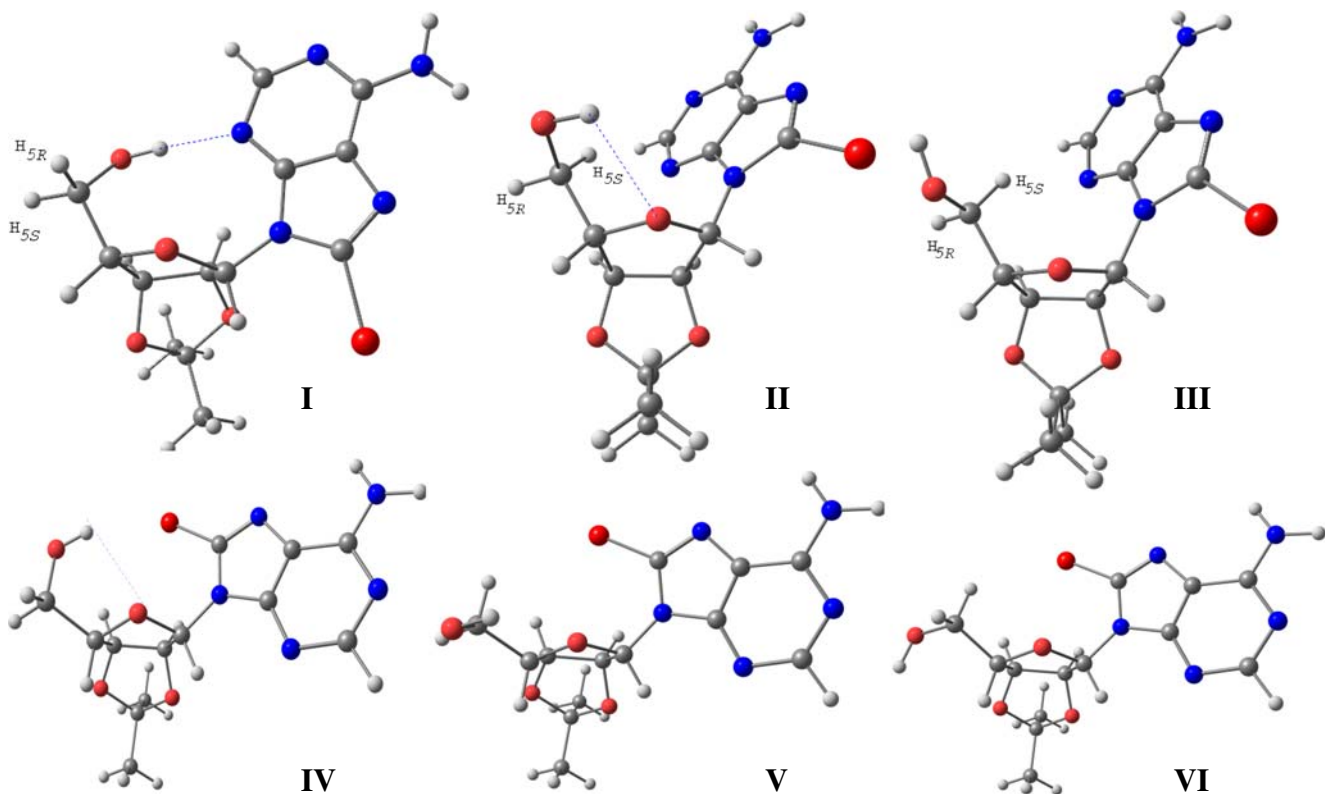


Fig. 2 The structures of low energy conformers of BrOA

Table 1 Values of selected distances (l) in Ångstroms, angles (α), and dihedral angles (τ) in degree for BrOA, OA, HA_N, HA_S of conformers I

Structure/solvent*	Geometrical parameters									
	l_{NH}	l_{NO}	l_{HO}	α_{NHO}	l_{NC5}	$l_{\text{NH(R)}}$	$\tau_{\text{NOC5H(R)}}$	$l_{\text{NH(S)}}$	$\tau_{\text{NOC5H(S)}}$	$\tau_{\text{C(3)C(4)C(5)O(5)}}$
BrOA-I										
Gas-B3LYP	1.885	2.862	0.983	172.1	3.639	3.750	62.3	4.649	-179.7	-42.8
Gas-B3PW91	1.854	2.832	0.983	172.8	3.601	3.706	61.5	4.614	179.5	-43.2
CHCl ₃	1.853	2.833	0.985	173.2	3.608	3.715	62.2	4.620	-179.9	-44.1
CH ₃ CN	1.850	2.828	0.986	173.1	3.614	3.725	62.4	4.624	-179.6	-44.5
DMSO	1.848	2.828	0.985	172.4	3.619	3.737	62.7	4.627	-179.3	-44.5
OA-I										
Gas-B3LYP	1.868	2.847	0.984	172.4	3.618	3.700	59.6	4.630	177.6	-42.3
CHCl ₃	1.849	2.830	0.986	172.9	3.613	3.711	61.0	4.622	179.0	-43.6
HA_S -I										
Gas-B3LYP	1.878	2.856	0.984	172.3	3.609	4.625	-177.4	3.671	-58.9	44.2
CHCl ₃	1.858	2.839	0.986	173.2	3.604	4.617	-177.3	3.678	-60.0	45.8
HA_N -I										
Gas-B3LYP	1.930	2.888	0.981	164.8	3.689	4.642	156.1	4.083	-86.6	41.2
CHCl ₃	1.003	2.865	0.983	165.4	3.695	4.632	153.8	4.116	-89.0	44.4

*Gas-B3LYP (B3LYP/6-31G(*d,p*)); Gas-B3PW91(B3PW91/6-31G(*d,p*)); Solvent: CHCl₃, CH₃CN, DMSO (B3LYP-(PCM)/6-31G(*d,p*)).

structure of BrOA was additionally optimized applying the B3PW91 [14] potential.

The NMR parameters were calculated using the coupled perturbed density functional theory (CP-DFT) method by including the diamagnetic spin-orbit, paramagnetic spin-orbit, Fermi-contact, and spin-dipolar terms [20]. The applied B3LYP functional has usually been found to lead to reasonable agreement with experimental data [21]. The calculations were performed within NMR dedicated IGLOII [22] basis set for H, C, N, O atoms and standard atomic basis set cc-pVTZ [23] (without *f* orbitals) for bromide atom. The same solvent models which were employed for the geometry optimization were also adopted for calculations of scalar couplings [24]. The additional procedure B3PW91/6-31G(*d,p*)/B3PW91/6-311G(*d,p*) applied by Barfield for calculations of ^{3h}J_{NC'} couplings in selected regions of peptides [25] was used to verify the applied methods.

The chemical proton shifts were defined in relation to TMS standard. The shift values for protons in TMS were computed as a mean value of methyl protons. The proton shift calculated within B3LYP/6-31G(*d,p*)/B3LYP/IGLO-II approach amounts to 31.98 ppm, and agree with 31.97 ppm determined within the B3LYP-PCM(CHCl₃)/6-31G(*d,p*)/B3LYP-PCM(CHCl₃)/IGLOII scheme. The computations were carried out using the Gaussian 03 suite of codes [26].

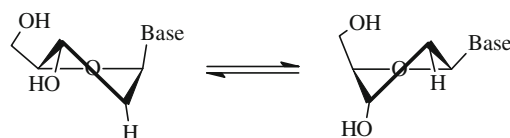
Results and discussion

The investigations of coupling constant ^{4h}J_{NH} in 8-bromo-2',3'-*O*-isopropylideneadenosine -BrOA (Fig. 1a) were

inspired by the experimental study Koole et al. [12], who indicated the predominant existence of molecular conformation characterized by intramolecular hydrogen bond, which is accompanied with the coupling across a hydrogen bond with a H5(*S*) proton. This coupling was estimated to be in a range of 0.2–0.6 Hz. The compound above, was the first moiety analyzed in this work, the further molecules included adenine derivatives: OA and HA (Fig. 1b, c) are studied. The OA (2',3'-*O*-isopropylideneadenosine) molecule differs from the parent molecule in that it contains proton in the place of bromine atom, whereas HA (3'-hydroadenosine) lacks an isopropylidene bridge. The latter modification makes the sugar ring more flexible. The structure of HA also differs from other compounds in chirality, however, this fact should not influence general conclusions.

Conformational analysis

Since in spectroscopic investigations the distribution of conformers plays the crucial role, the detailed conformational analysis was performed for BrOA. Thus, six lowest energy conformations were determined (Fig. 2). First three conformers (I–III) have *syn*-base conformation, whereas the



North sugar (C3-endo-C2-exo) South sugar (C2-endo-C3-exo)

Fig. 3 The dynamic two-state equilibrium of N + S pseudorotamers [27]

Table 2 Values of couplings constants across the hydrogen bond [Hz]

Structure and conformers	Solvent*	Coupling across hydrogen bond**				
		$^1J(^{14}\text{NH})$	$^2J(^{14}\text{NO})$	$^3J(^{14}\text{NC5})$	$^4J(^{14}\text{NH5R})$	$^4J(^{14}\text{NH5S})$
BrOA-I	Gas-B3LYP	-2.76	-3.99	-0.05	-0.04	0.33
	Gas-B3PW91	-2.53	-3.60	-0.06	-0.03	0.30
	CHCl ₃	-2.77	-4.60	-0.06	-0.05	0.33
	CH ₃ CN	-2.74	-4.75	-0.05	-0.05	0.34
	DMSO	-2.75	-4.81	-0.05	-0.05	0.34
OA-I	Gas	-2.79	-4.20	-0.05	-0.07	0.33
	CHCl ₃	-2.76	-4.81	-0.06	-0.06	0.34
HA _S -I	Gas	-2.77	-4.06	-0.07	0.32	-0.05
	CHCl ₃	-2.75	-4.54	-0.06	0.33	-0.05
HA _N -I	Gas	-2.59	-3.47	0.04	0.29	-0.01
	CHCl ₃	-2.59	-4.08	0.06	0.31	-0.08

*Gas-B3LYP (B3LYP/6-31G(*d,p*)); Gas-B3PW91(B3PW91/6-31G(*d,p*)); Solvent: CHCl₃, CH₃CN, DMSO (B3LYP-(PCM)/6-31G(*d,p*)).

** The calculated value of coupling constant was on ^{14}N isotope. The isotope ^{15}N (spin 1/2) is more useful nuclei in NMR measure than isotope ^{14}N (spin 1). The couplings $J(^{14}\text{NX})$ constant is smaller value than $J(^{15}\text{NX})$. The dependence is described by the equation: $J(^{14}\text{NX})/J(^{15}\text{NX}) = \gamma_{14\text{N}}/\gamma_{15\text{N}} = 0.713$ (where γ means gyromagnetic coefficients of appropriate nucleus).

Table 3 ΔE (kcal mol⁻¹) and ΔG (kcal mol⁻¹) for conformers of BrOA, OA, and HA

Compound	Solvent		I	II	III	IV	V	VI	
BrOA	gas	ΔE	0.00	4.82	6.94	3.42	5.69	7.34	
		ΔG	0.00	4.25	6.24	2.72	4.68	6.13	
		%	98.9	0.1	0.0	1.0	0.0	0.0	
	chloroform	ΔE	0.00	4.23	5.01	2.71	3.35	4.52	
		ΔG	0.00	3.23	3.76	1.82	2.08	3.34	
		%	92.1 (100)*	0.4	0.2	4.2	2.8	0.3	
	CH ₃ CN	E	0.00	3.13	3.92	1.99	2.06	2.82	
		G	0.00	1.18	1.89	0.87	0.02	1.48	
		%	40.7(82)*	5.5	1.7	9.3	39.5	3.3	
	DMSO	E	0.00	3.79	3.90	1.91	2.01	2.83	
		G	0.37	1.79	2.16	1.48	0.00	1.46	
		%	30.2(22)*	2.7	1.5	4.6	56.1	4.8	
OA	gas	ΔE	0.00	5.35	7.4	5.68	7.65	9.44	
		ΔG	0.00	5.22	6.67	4.98	5.33	7.39	
		%	100.0	0.0	0.0	0.0	0.0	0.0	
	chloroform	ΔE	0.00	4.00	5.09	4.14	5.13	7.11	
		ΔG	0.00	3.17	3.89	2.34	2.78	3.81	
		%	96.5	0.5	0.1	1.9	0.9	0.2	
HA _S	gas	ΔE	0.00	5.55	6.63	6.92	7.38	8.2	
		ΔG	0.00	4.34	5.23	5.04	5.26	5.94	
		%	97.5	0.1	0.0	0.0	0.0	0.0	
HA _N	gas	ΔE	2.81	6.41	5.81	5.69	8.05	7.45	
		ΔG	2.26	4.69	4.45	4.25	5.06	6.11	
		%	2.2	0.0	0.1	0.1	0.0	0.0	
HA _S	chloroform	ΔE	0.00	4.42	5.09	3.92	5.45	5.41	
		ΔG	0.00	3.55	3.76	2.87	3.44	3.34	
		%	94.9	0.2	0.2	0.8	0.3	0.3	
	HA _N	chloroform	ΔE	2.91	5.38	5.94	4.56	5.74	6.77
			ΔG	2.67	3.86	2.54	3.32	3.18	5.33
			%	1.0	0.1	1.3	0.4	0.5	0.0

*measured values ref. [12].

Boltzman distributions (%) for BrOA and OA were determined assuming six structures, while for HA assuming the existence of two pseudoconformers

remaining (IV–VI) are *anti*-base. They also differ from each other regarding the position of $-\text{CH}_2\text{OH}$ group, mainly *g*+ (I, IV), *g*- (II, V), *ap* (III, VI). The conformer I exhibits single intramolecular hydrogen bond of $\text{O}-\text{H}\cdots\text{N}$ type (Table 1). Conformers II and IV possess an intramolecular hydrogen bond of $\text{O}-\text{H}\cdots\text{O}$ type, in which oxygen atom of the sugar ring acts as an acceptor of proton. In conformers III, V, and VI the hydroxyl group does not form any intramolecular hydrogen bond.

Similar conformers were observed in the case of OA. In both BrOA and OA the sugar ring is almost planar as a result of the presence of bridging isopropylidene group. The structure of HA exhibits an additional effect, which results in the presence of two major conformers: north ($\text{C}3'$ -endo- $\text{C}2'$ -exo) and south ($\text{C}2'$ -endo- $\text{C}3'$ -exo) (Fig. 3) [27].

The structure of conformers of the HA were computed for pseudorotamers north HA_N and south HA_S analogously to BrOA. The images of conformers OA, HA_N and HA_S are shown in the [supplementary materials](#).

^4J_N coupling constants

In BrOA, coupling constants across the hydrogen bond were observed in ^1H NMR and $^1\text{H}\{^{14}\text{N}\}$ NMR spectra. Thus, two multiplets resulting from the presence of diastereotopic protons $\text{H}5'$ and $\text{H}5''$ were observed in ^1H NMR spectrum by Koole et al. [12]. The doubled doublets result from spin interactions between $\text{H}5'$ and $\text{H}5''$ protons ($^2J_{\text{H}5'\text{H}5''}=9.4$ Hz) and spin interaction between $\text{H}4'$, $\text{H}5'$, and $\text{H}5''$ protons ($^2J_{\text{H}4'\text{H}5'}=1.5$ Hz and $^2J_{\text{H}4'\text{H}5''}=1.8$ Hz). Additionally, in ^1H NMR spectrum the broadening of signals for $\text{H}5''$ protons was caused by the coupling with ^{14}N nitrogen across a hydrogen bond. With regard to the significant signal broadening caused by the quadrupole relaxation of ^{14}N nucleus, the low resolution of detection (the frequency of apparatus being 200 MHz) and signal overlap, it was impossible to determine this coupling constant and thus it was estimated to lay in the range of 0.2 to 0.6 Hz.

For all the compounds studied ^4J_NH coupling constant across a hydrogen bond was calculated for the conformer I (Table 2). Theoretical values, which took into account various solvent models (gas phase, chloroform), are similar to each other and differ by 0.04 Hz. Calculated values for BrOA fit well to the experimentally estimated range of 0.2–0.6 Hz.

Coupling constants calculated for BrOA, OA, and HA are similar to each other and thus indicate that the substitution has no meaningful effect. The pseudoconformation of the ring also has little influence on the coupling. The similarity is therefore due to small structural differences in geometry of the hydrogen bond $\text{O}-\text{H}\cdots\text{N}$ (Table 1).

The comparison of computed coupling constants found for $\text{H}5(\text{S})$ and $\text{H}5(\text{R})$ protons indicates that only one proton leads to the measurable effect. Koole et al. deduced that

only for $\text{N}\cdots\text{H}-\text{O}-\text{C}-\text{H}$ atoms lying in the same plane such a coupling may occur. Theory nicely supports this finding.

^1J_NH , ^2J_NO and ^3J_NC coupling constants

The ^1J_NH coupling for OH proton was not described, however, similar $^1J_\text{NH}'$ was detected by Giedroc et al. [28]

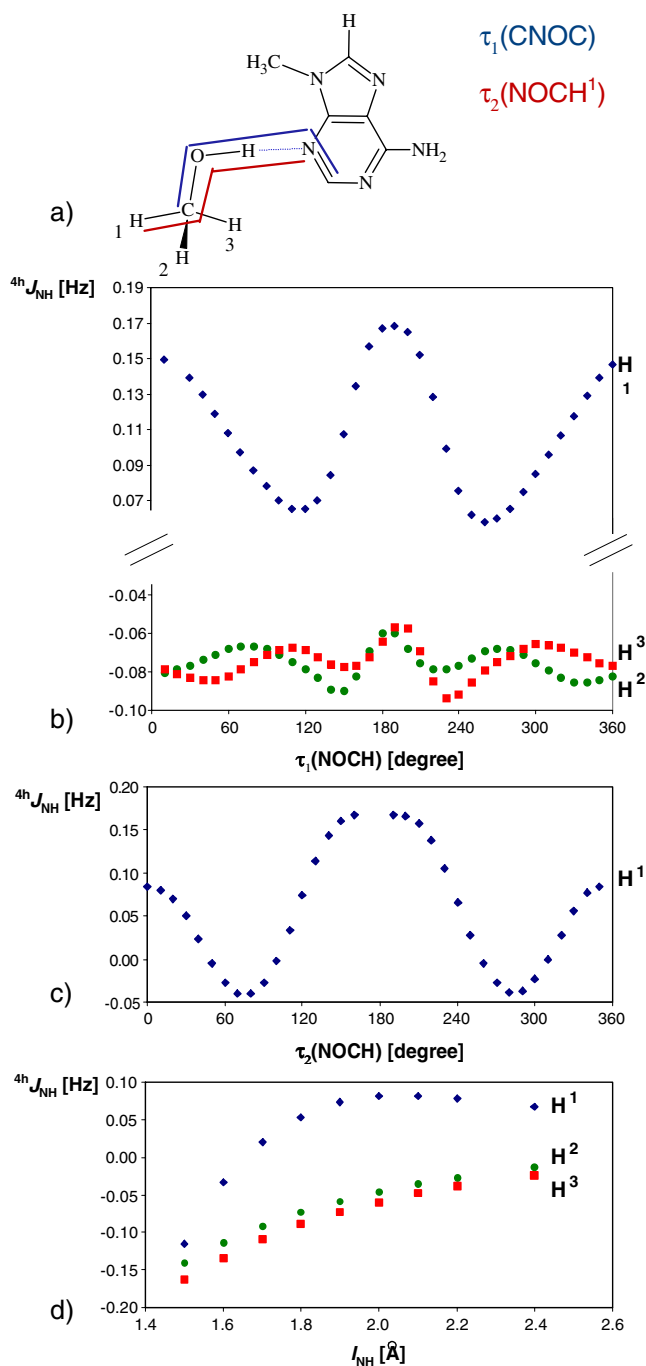


Fig. 4 The molecular complex of 9-N-methyladenine and methanol (a). The coupling constants ^4J_NH as functions: of the $\tau_1(\text{CNOC})$ - b, $\tau_2(\text{NOCH}_1)$ - c, and of the distance l_NH (B3LYP/IGLOII)

as an example of couplings across intramolecular hydrogen bond (O-H \cdots N) between sugar hydroxyl and nitrogen ^{15}N atom in adenosine of pseudoknot mRNA structure motif stimulating the frameshifting in ribosome. Determined coupling constant values 1.7 ± 0.1 Hz, while computed value for adenosine derivatives was found to be ca. 2.7 Hz. Other possible couplings are $^2J_{\text{NO}}$ and $^3J_{\text{NC}}$, with theoretical constants $^2J_{\text{NO}}$ and $^3J_{\text{NC}}$ being in the range of -3.60 to -4.81 and 0.06 to -0.07 Hz, respectively. The $^2J_{\text{NO}}$ should be observable although oxygen may cause difficulties (abundance 0.037%, spin 5/2). The calculated $^3J_{\text{NC}}$ constant possesses very low value, and therefore was not observed by NMR techniques.

Solvent effect

The analysis of coupling constants determined in various solvents relates to the conformation of molecule. It was indicated that the existence of intramolecular O-H \cdots N bond formation is more probable in non-polar solvents. Therefore, calculations were carried out for gas phase and in chloroform, acetonitrile, benzene, and DMSO (Table 3).

The data presented in Table 3 show that conformation I dominates in gas phase and in non-polar solvents. Polar solvents ensure the existence of higher population of other structures, with lack of hydrogen bonding. Calculations confirm the experimental findings. Although, the agreement is not perfect the theory well reproduces the main trends.

Structural effect

The coupling constant $^4J_{\text{NH}}$ reflects the position of hydrogen atoms of methyl group with regard to the adenine ring. The problem was studied using simplified structure as a model (Fig. 4a).

The rotation of methoxy group involving the $\tau_1(\text{CINOC})$ angle indicates that the planar arrangement of N \cdots H-O-C-H 1 atoms results in the highest value of $^4J_{\text{NH}}$ (Fig. 4b). For H 2 and H 3 atoms this correlation is more complex because hydrogens are out-of-plane of the ring. The conclusion is additionally confirmed by the analysis of the coupling variation upon the rotation of methyl group ($\tau_2(\text{NOCH}^1)$) (Fig. 4c). The coupling constant is the highest for τ_2 equal to 180 or 0° . Obviously the coupling constant depends on the distance between proton and acceptor of hydrogen bond. For H 1 proton the coupling constant initially increases and then subsequently decreases. The maximum lies in the range similar to a typical length of hydrogen bond (Fig. 4d).

Scalar coupling constants

Couplings across covalent bonds provide valuable information about conformation of the molecules. The investigation was based on experimental coupling constants measured in various solvents. The comparison of experimental and theoretical values found for vicinal couplings constants $^2J_{\text{H4H5(R)}}$, $^2J_{\text{H4H5(S)}}$, $^3J_{\text{H3H4}}$, $^3J_{\text{H1H2}}$ is reported in a Table 4.

Table 4 Values of selected couplings constants [Hz] measured [12] and calculated by means of various methods

Solvent /Structure	Vicinal coupling constants			
	$^2J_{\text{H4H5(R)}}$	$^2J_{\text{H4H5(S)}}$	$^3J_{\text{H3H4}}$	$^3J_{\text{H1H2}}$
CHCl $_3$				
I	1.24	2.30	0.49	5.21
II	3.26	10.19	2.01	0.94
III	2.29	1.49	6.11	2.48
IV	2.17	8.76	6.29	1.94
V	9.99	4.57	5.02	2.17
VI	11.0	4.61	1.18	0.91
Exp**	1.50	1.80	1.20	5.40
DMSO				
I	1.32	2.25	0.44	5.35
II	2.84	10.01	2.02	0.89
III	2.45	1.38	6.25	2.38
IV	1.79	8.54	6.27	2.01
V	10.02	4.80	5.04	2.21
VI	11.07	4.57	1.24	0.82
Exp**	5.80	5.80	3.00	2.60
weighted-average***	6.75	4.28	3.46	3.05

*Solvent: CHCl $_3$, DMSO (B3LYP-(PCM)/6-31G(d,p)//B3LYP-(PCM)/IGLOII)** ref. [12], *** weighted-average coupling is quotient coupling (J_{XY}) and Boltzman distribution of conformers (Table 3).

In non-polar solvents, such as chloroform, experimental values of coupling constants ${}^2J_{\text{H4H5}(R)}$, ${}^2J_{\text{H4H5}(S)}$, ${}^3J_{\text{H3H4}}$, ${}^3J_{\text{H1H2}}$ are best reproduced for that calculated for structures I. On the other hand, in the case of polar solvent (e.g., DMSO) the best agreement was found for structure V. The best agreement was observed in the case of the coupling constant ${}^3J_{\text{H1H2}}$. This result may be a consequence of rigidity of the system imposed by the isopropylidene group. The comparison of experimental and theoretical values of coupling constants in various solvents indicates that preferred conformations in polar and non-polar solvents are different. The values determined within B3PW91/6-31G(*d,p*)/B3PW91/6-311G(*d,p*) approach for the first conformer are: ${}^2J_{\text{H4H5}(R)}=1.01$, ${}^2J_{\text{H4H5}(S)}=2.14$, ${}^3J_{\text{H3H4}}=0.29$, ${}^3J_{\text{H1H2}}=4.67$ Hz and are similar to results provided by B3LYP/6-31G(*d,p*)/B3LYP/IGLOII calculation.

Location of diastereotopic protons – correlation with experimental results

The analysis of location of diastereotopic protons– H5(*R*) and H5(*S*) was carried out in order to assess the correctness of the determination of signals and to verify the ability of theory to predict the chemical shift for this type of protons [29]. The chemical shifts were determined for structures of molecules in their global minimum in the gas phase and chloroform. The calculated values in gas phase were found to be: $\delta_{\text{H5}(R)}=3.90$ and $\delta_{\text{H5}(S)}=3.54$, whereas in solvent: $\delta_{\text{H5}(R)}=3.96$, and $\delta_{\text{H5}(S)}=3.66$ ppm. Corresponding experimental values are $\delta_{\text{H5}(R)}=3.95$ and $\delta_{\text{H5}(S)}=3.76$ ppm [1]. A difference between theoretical and experimental values for structure I and proton H5(*R*) is equal to 0.01 whereas for H5(*S*) - 0.10 ppm. The results obtained from computations for conformer A-II are different. H5(*R*) proton exhibits smaller shift compared to H5(*S*) (in gas phase $\delta_{\text{H5}(R)}=3.36$ and $\delta_{\text{H5}(S)}=3.72$, in chloroform $\delta_{\text{H5}(R)}=3.47$ and $\delta_{\text{H5}(S)}=3.73$ ppm). The findings above indicate that it is possible to distinguish between diastereotopic protons only when the conformation is in the global minimum.

Conclusions

The theoretical studies indicated the possibility to observe the coupling constants ${}^4J_{\text{NH}}$ in adenine derivatives characterized by the (H-C-O-H \cdots N) hydrogen bond. This coupling can be even detected in systems possessing sufficient number of possible stable conformations characterized by intramolecular hydrogen bond.

The ${}^4J_{\text{NH}}$ coupling constant was detected in BrOA and it can be detected in systems appearing in conformations characterized by intramolecular hydrogen bond of the H-C-O-H \cdots N type. Such conditions exist in gas phase and in

non-polar solvents. As expected, the ${}^4J_{\text{NH}}$ coupling constant depends on the structural arrangement of H-C-O-H \cdots N fragment of the molecule. The constant has the highest value when atoms lay in the same plane and additionally in the plane of aromatic ring, or at least the relevant C-H bonds are parallel to the ring. Additionally, this study has shown that applied solvent models and Boltzman distribution of conformers allow reliable predictions of coupling constants in solutions.

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References

- Grzesiek S, Cordier F, Jaravine V, Barfield M (2004) Progress Nuclear Magnetic Resonance Spectroscopy 45:275–300, doi:10.1016/j.pnmrs.2004.08.001
- Del Bene JE, Perera SA, Bartlett RJ, Alkorta I, Elguero J, Mó O, Yanez M (2002) J Phys Chem A 106:9331–9337, doi:10.1021/jp021160v
- Sponer J, Lankas F (2006) Computational studies of RNA and DNA Vol. 2. Springer, Dordrecht
- Dingley AJ, Cordier F, Grzesiek S (2001) Concept Magn Reson A 13:103–127, doi:10.1002/1099-0534(2001)13:2<103::AID-CMR1001>3.0.CO;2-M
- Dingley AJ, Grzesiek S (1998) J Am Chem Soc 120:8295–8297, doi:10.1021/ja981513x
- Dingley AJ, Masse JE, Peterson RD, Barfield M, Feigon J, Grzesiek S (1999) J Am Chem Soc 121:6019–6027, doi:10.1021/ja9908321
- Pervushin K, Ono A, Fernandez C, Szyperski T, Kainosho M, Wüthrich K (1998) Proc Natl Acad Sci USA 95:14147–14151
- Luy B, Richter U, DeJong ES, Sørensen O, Marino JP (2002) J Biol NMR 24:133–142
- Majumdar A, Gosser Y, Patel DJ (2001) J Biomol NMR 21:289–306
- Liu A, Majumdar A, Hu W, Kettani A, Skripkin E, Patel DJ (2002) J Am Chem Soc 122:3206–3210, doi:10.1021/ja994255s
- Mele A, Salani G, Viani F, Bravo P (1997) Magn Reson Chem 35:168–174, doi:10.1002/(SICI)1097-458X(199703)35:3<168::AID-OMR58>3.0.CO;2-2
- Koole LH, Boer H, Haan JW, Haasnoot CAG, Dael P, Buck HM (1986) J Chem Soc, Chem Commun 4:362–364, doi:10.1039/C39860000362
- Parr RG, Yang W (1994) Density-Functional Theory of Atoms and Molecules. Oxford University Press, New York
- Becke AD (1993) J Chem Phys 98:5648–5652, doi:10.1063/1.464913
- Petersson GA, Bennett A, Tensfeldt TG, Al-Laham MA, Shirley WA, Mantzaris J (1988) J Chem Phys 89:2193–2218, doi:10.1063/1.455064
- Cammi R, Mennucci B, Tomasi J (2000) J Phys Chem A 104:9874–9879, doi:10.1021/jp001749z
- Davidson N (1962) Statistical Mechanics. McGraw-Hill, New York
- Allen FH (2002) Acta Cryst B58:380–388, doi:10.1107/S0108768102003890

19. Fujii S, Fujiwara T, Tomita K (1985) *Nucl Acids Res* 3:1985–1996
20. Sychrovsky V, Sponer J, Trantirek L, Schneider B (2006) *J Am Chem Soc* 128:6823–6828, doi:[10.1021/ja0551180](https://doi.org/10.1021/ja0551180)
21. Sychrovsky V, Grafenstein J, Cremer D (2000) *J Chem Phys* 113:3530–3547, doi:[10.1063/1.1286806](https://doi.org/10.1063/1.1286806)
22. Kutzelnigg W, Fleischer U, Schindler M (1990) *The IGLO-Method: Ab Initio Calculation and Interpretation of NMR Chemical Shifts and Magnetic Susceptibilities*, Vol. 23. Springer, Heidelberg
23. Wilson A, Mourik T, Dunning Jr TH (1996) *J Mol Struct (Theochem)* 388:339–349
24. Ruud K, Frediani L, Cammi R, Mennucci B (2003) *Int J Mol Sci* 4(3):119–134, doi:[10.3390/i4030119](https://doi.org/10.3390/i4030119)
25. Barfield M (2002) *J Am Chem Soc* 124:4158–4168, doi:[10.1021/ja012674v](https://doi.org/10.1021/ja012674v)
26. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery JA Jr, Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA (2004) *Gaussian 03*. Gaussian Inc, Pittsburgh, PA
27. Thibaudeau C, Plavec J, Chattopadhyaya J (1994) *J Am Chem Soc* 116:8033–8037, doi:[10.1021/ja00097a010](https://doi.org/10.1021/ja00097a010)
28. Giedroc DP, Cornish PV, Hennig M (2003) *J Am Chem Soc* 125:4676–4677, doi:[10.1021/ja029286t](https://doi.org/10.1021/ja029286t)
29. Doskocz M, Malinowska B, Lejczak B, Kafarski P (2009) *J Mol Struct.* 920:103–109, doi:[10.1016/j.molstruc.2008.10.027](https://doi.org/10.1016/j.molstruc.2008.10.027)