GIAO-HF/DFT calculation of ^{13}C and ^{15}N chemical shifts for studying tautomerism and intramolecular hydrogen bonding in 2,3-disubstituted quinoxalines

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ABSTRACT: Both the ^{13}C and ^{15}N chemical shifts of a number of quinoxalines substituted in position 2 with the π-electron excess 2′-benzo[*b*]furanyl substituent which has in position 3′ a hydroxy or amino group could be satisfactorily calculated by the GIAO method on the basis of HF and DFT *ab initio* structures. Thereby both the presence of the intramolecular hydrogen bond —C2=N··H—O—C3′— and —C2=N··H—NH—C3′—, respectively, strongly dominating the common plane of resonance of the two heterocyclic moieties, and the preferred enol tautomer could be studied in detail. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: NMR; *ab initio* MO calculation; tautomerism; intramolecular hydrogen bonding; π-electron resonance; steric hindrance; quinoxalines

INTRODUCTION

If the quinoxaline ring system is substituted in position 2 with π-excess heterocycles (2′-benzoxazolyl, 2′-benzo-thiazolyl, 2′-imidazolyl, 2′-indolinyl and 2′-benzo[*b*]furanyl), the π-electron conjugation between the two moieties proved remarkable.[1] If additional substituents are introduced into position 3 of quinoxaline and position 3′ of the annelated heterocycle, the common plane of resonance between the two ring systems will be more or less sterically hindered, limiting π-electron delocalization at the same time. The ^{13}C and ^{15}N chemical shifts of the nuclei involved readily indicate both the amount of π-electron delocalization and the dihedral angle about the C2—C2′ bond. The corresponding barrier to rotation could not be studied for several reasons: either it is too low to make the dynamic process slow on the NMR time-scale or the population difference of the two rotamers is so strongly different that the minor one could not be detected.[1]

However, this restricted rotation could be studied in detail by *ab initio* MO calculations simulating this rotational process by calculating both the dihedral angle-dependent global minima structures and on their basis (by the GIAO method) the corresponding ^{13}C and ^{15}N chemical shifts of the nuclei involved.[2] Both global minima structures and ^{13}C and ^{15}N chemical shifts

indicate impressively the steric/electronic state of this kind of compound.[2]
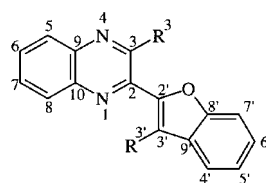
No.	R^3	$R^{3'}$
1	H	H
2	CH$_3$	H
3	Ph	H
4	H	OH
5	CH$_3$	OH
6	Ph	OH
7	H	NH$_2$
8	CH$_3$	NH$_2$
9	Ph	NH$_2$
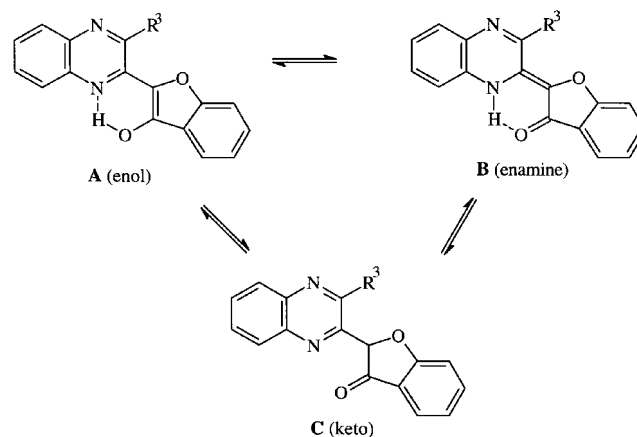
Scheme 1

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Table 1. Most significant geometric features of the global minima structures of **1–9** as calculated *ab initio* at the HF level of theory using the 6–31G** basis set

No.	τ(C2—C2′—C3′)	τ(N1—C2—C2′)	τ(C2′—C3′—O/N)	ϕ(C3—C2—C2′—C3′)	r(X—H)	r(XH···N)	r(C—X)
1	131.36	117.91	—	180.0	—	—	—
2	129.16	114.37	—	179.6	—	—	—
3	130.07	115.20	—	145.0	—	—	—
4	129.56	117.41	128.83	180.0	0.951	2.133	1.328
4a	133.36	118.97	133.36	180.0	0.942	—	1.337
5	128.13	114.61	129.16	180.0	0.952	2.033	1.325
5a	131.32	115.13	127.32	180.0	0.942	—	1.337
6	127.99	114.21	129.29	173.9	0.952	2.039	1.326
6a	131.72	116.12	126.16	138.0	0.942	—	1.342
7	131.42	118.68	128.85	179.6	0.996	2.317	1.375
8	129.89	115.40	129.52	−179.3	0.995	2.224	1.373
9	130.03	115.46	129.16	161.5	0.996	2.297	1.387

If in position 3′ of the 2′-benzoxazolyl substituent (compounds **4–9**, Scheme 1) hydroxyl or amino groups are present, further with intramolecular hydrogen bonding, the common plane of resonance stabilizing structural increment has been introduced. In addition, the opportunity of *tautomerism* arises (Scheme 1, **A–C**). The major objective of this work was to study the influence of the two phenomena on the ground-state structure of a number of 2-(2′-benzoxazolyl)quinoxalines, **4–9** (Scheme 1). For this purpose, not only NMR spectroscopy but also *ab initio MO* calculations were employed. Only these calculations can separate the substituent effect of additional OH/NH$_2$ substituents on ^{13}C and ^{15}N chemical shifts and that of intramolecular hydrogen bonding, thereby indicating both the presence and strength of the corresponding hydrogen bond.

The GIAO method[3,4] has already been employed to study in detail similar structural aspects of simple enamines[5] and amidine derivatives.[6]

RESULTS AND DISCUSSION

Influence of intramolecular hydrogen bonding on the ground state structures of 4–9

The substituted quinoxalines **1–9** were *ab initio* calculated using the 6–31G** basis set at the Hartree–Fock level of theory (in the case of **4–9** tautomers **4–9A** were considered). The most significant geometric features of the global minima structures thus obtained, which are necessary for studying the above topic, are given in Table 1. The ^{13}C and ^{15}N chemical shifts were calculated on the basis of these global minima structures by the GIAO method[3,4] and are given, together with the experimentally obtained values, in Table 2. Owing to the absence of electron correlation, these HF shielding calculations may give only qualitatively correct results because in **1–9** nuclei with lone pairs and multiple bonds are involved.[7] However, even if the DFT methods[8–10] do not provide

systematically better NMR results than HF,[11] electron correlation could be included while being faster. The results thus obtained at the B3LYP/6–31G** level are also given in Tables 1 and 2.

Discussing first the geometric features of **1–9**, the physical-organic conclusions about the ground-state structure of these compounds prove uniform when R^3 = H or CH$_3$ (**1, 2, 4, 5, 7, 8**) the structures are perfectly planar [ϕ(C3—C2—C2′—C3′) *ca.* 180°] (Table 1); if a phenyl substituent is introduced in this position (**3, 6, 9**), steric hindrance due to this bulky substituent increases and the two heterocyclic moieties become twisted from the common plane. This twist is strongest in **3** [ϕ(C3—C2—C2′—C3′) = 145°] but decreases owing to the N···H—N hydrogen bond in **9** [ϕ(C3—C2—C2′—C3′) = 161.5°] and even more with the stronger N···H—O hydrogen bond in **6** (ϕ(C3—C2—C2′—C3′) = 173.9°]. Figure 1 shows the global minima structures of **3, 6** and **9**.

If the intramolecular hydrogen bond is not taken into account, the steric twist returns adequately [**6a**: ϕ(C3—C2—C2′—C3′) = 138°] (Fig. 2).

The N···H—X bond distances behave similarly (*cf.* Table 1); here another result is significant: the r(N···H—X) values prove that the hydrogen bond in **4** and **7** (*e.g.* **4**, 2.133 Å) is less stable than in **5** and **8** (*e.g.* **5**, 2.033 Å). Obviously, the methyl substituent in position 3 of **5** and **8** forces the two units together establishing a stronger hydrogen bond; this structural variation is corroborated by reduced bond angles τ(C2—C2′—C3′) and τ(N1—C2—C2′) and widened bond angles τ(C2′—C3′—O/N) (Table 1). As a further proof, the present intramolecular hydrogen bond in **4–6** is indicated by strong low-field ^{1}H chemical shifts of the OH proton involved [δ(OH) >12 ppm].

Identically, both the ^{13}C and ^{15}N chemical shifts visualize the ground-state structures of the studied compounds (Table 2)—the chemical shifts calculated are parallel to the experimental values but deviate from the line of identity similarly to that obtained previously.[2]

Table 2. Experimental and theoretical ^{13}C and ^{15}N chemical shifts of the quinoxalines **1–9**[a]

No.	N-1	N-4	C-2	C-3	C-2′	C-3′
1 Exp.	−69.2	−50.7	144.0	142.5	152.9	107.9
HF/6–31G**	−99.0	−76.1	145.8	141.6	149.9	106.6
B3LYP/6–31G**	−64.6	−40.4	140.2	137.6	150.9	105.1
2 Exp.	−61.3	−53.7	144.0	151.6	153.5	109.9
HF/6–31G**	−92.4	−85.1	145.5	151.9	151.7	107.8
B3LYP/6–31G**	−59.9	−44.0	139.9	148.3	152.6	106.6
3 Exp.	−58.4	−50.4	143.1	153.0	152.4	110.8
HF/6–31G**	−79.8	−81.6	146.0	155.0	152.4	106.5
B3LYP/6–31G**	−51.4	−42.7	139.6	149.8	152.3	106.1
4 Exp.	−100.8	—[b]	145.5	141.2	131.8	148.0
HF/6–31G**	−138.7	−68.8	150.2	140.0	125.2	144.9
B3LYP/6–31G**	−113.5	−35.7	142.1	136.5	130.5	146.7
4a[c]						
HF/6–31G**	−96.8	−78.8	146.9	141.0	129.7	136.5
B3LYP/6–31G**	−61.7	−43.2	141.3	137.0	134.4	137.3
5 Exp.	−125.6	−81.1	144.6	151.2	132.2	151.6
HF/6–31G**	−139.2	−60.0	156.5	154.7	130.9	155.9
B3LYP/6–31G**	−115.6	−41.0	142.3	147.5	131.2	147.7
5a[c]						
HF/6–31G**	−88.2	−87.3	146.9	151.0	130.7	137.1
B3LYP/6–31G**	−55.8	−45.7	141.5	147.3	135.4	138.1
6 Exp.	−142.2	−78.2	144.2	150.2	131.6	151.6
HF/6–31G**	−133.7	−69.1	150.1	152.9	125.0	146.0
B3LYP/6–31G**	−113.9	−36.5	141.1	148.8	130.2	148.1
6a[c]						
HF/6–31G**	−73.5	−84.4	145.5	155.2	131.7	133.9
B3LYP/6–31G**	−48.2	−44.6	140.2	149.3	134.9	136.3
7 Exp.[d]	−121.6	−79.6	146.2	141.4	135.5	130.2
HF/6–31G**	−127.5	−73.8	150.1	141.0	126.7	134.5
B3LYP/6–31G**	−96.7	−40.6	142.6	137.5	130.9	131.7
8 Exp.	—[e]	—[e]	147.1	151.4	133.2	134.3
HF/6–31G**	−123.2	−83.5	150.6	151.3	127.2	135.5
B3LYP/6–31G**	−95.1	−44.5	143.0	148.1	131.7	132.5
9 Exp.	−80.9	−51.0	145.5	151.8	133.0	134.0
HF/6–31G**	−115.0	−75.2	149.6	153.9	126.6	133.9
B3LYP/6–31G**	−93.7	−40.2	141.6	148.9	130.3	132.8

[a] ν_0 (^{15}N) = 50.55 MHz; standard 90% formamide in DMSO-d_6, $\delta = -298$ ppm.
[b] Not obtained owing to line broadening.
[c] As calculated for ϕ(C2′—C3′—OH) = 180°.
[d] NH$_2$ at $\delta = -357.4$ ppm.
[e] Not obtained owing to low solubility.

The following correlations $\delta_{exp} = a\delta_{calc} + b$ given in Figs 3–5 were obtained. Fig. 3: HF ($r = 0.993$; SD = 1.60; $n = 16$; $a = 0.9533$; $b = 4.933$); DFT ($r = 0.996$; SD = 1.22; $n = 16$; $a = 1.0067$; $b = -5.163$); Fig. 4: **A** ($r = 0.97$; SD = 2.81; $n = 16$; $a = 1.0280$; $b = -7.706$); **B** ($r = 0.60$; SD = 8.67; $n = 16$; $a = 1.1487$; $b = -23.929$); **C** ($r = 0.66$; SD = 8.20; $n = 16$; $a = 1.5559$; $b = -75.052$); Fig. 5: **A** ($r = 0.98$; SD = 1.89; $n = 16$; $a = 1.0260$; $b = -7.655$); **B** ($r = 0.60$; SD = 8.77; $n = 16$; $a = 0.8199$; $b = 18.564$); **C** ($r = 0.51$; SD = 9.43; $n = 16$; $a = 1.0631$; $b = -19.276$).

The ^{15}N chemical shift of N-1 is very indicative; if we compare first **1–3**, the steric twist of the two heterocyclic moieties in **3** shifts N-1 slightly to lower field because the π-electron flow from the π-excess benzo[*b*]furanoyl moiety has been partly reduced. In **7–9** the weak intramolecular hydrogen bond N···H—N shifts N-1 to

higher field [*e.g.* HF, δ (^{15}N) = −115 to −127 ppm], also in line with the expected charge variation due to hydrogen bonding N$^-$···$^+$(H—X). This effect is further strengthened in **4–6** owing to the stronger hydrogen bond N···H—O [*e.g.* HF, δ (^{15}N) = −133 to −138 ppm]. That this progressive high-field shift of N-1 results really from the effect of present hydrogen bonding was proved independently by calculating both the structure and the ^{13}C and ^{15}N chemical shifts of **4a–6a**; in these conformers of **4–6** the OH group was rotated from the position of intramolecular hydrogen bonding by 180° (thus completely interrupting this kind of intramolecular interaction). The result is again significant: the chemical shift of N-1 is calculated to be only −73.5 to −96.9 ppm, so even slightly downfield from **1–3**, probably owing to a larger twist [**6a**, Φ(C3—C2—C2′—C3′) = 138°] and reduced π-electron flow from the benzo[*b*]furanyl

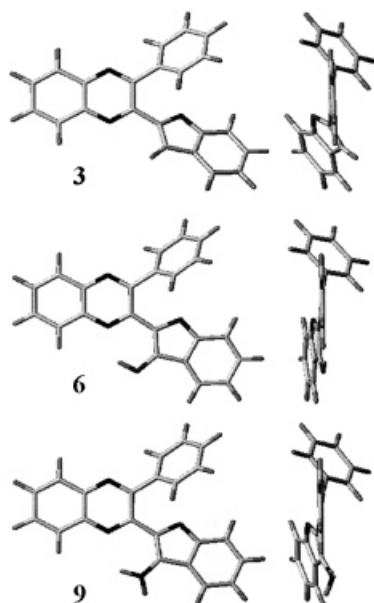**Figure 1.** Global minima structures of the 3-phenyl-substituted quinoxalines **3, 6** and **9** as calculated at the HF/6–31G** level of theory

moiety. Similar consideration apply to the ^{13}C chemical shifts; the most sensitive is C-3′. With the introduction and (later) increased strength of the intramolecular hydrogen bond N···H—X, it shifts from 107–110 ppm (in **1–3**) to 130–134 ppm (in **7–9**) and finally to 148–152 ppm (in **4–6**). That also this low-field shift of C-3′ [in line with the expected charge variation due to hydrogen bonding N$^-$···$^+$(H—X)], which is mainly dependent on the substituent X, was caused by hydrogen bonding was also corroborated by the results calculated for **4a–6a**. Only 134–137 ppm was obtained for the chemical shift of C-3′; the chemical shift difference from the values in **1–3** results from the OH substituent effect, which will be about 20 ppm.[12] The chemical shifts of N-4, C-2, C-3 and C-2′ are less characteristically influenced.

Tautomerism of 4–9

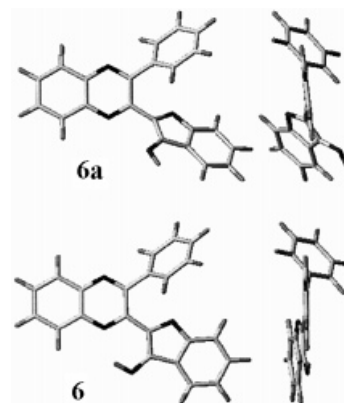In addition to the enol form **A** of **4–9** the substituted

Figure 2. Optimized structures of the 3′-OH-3-phenyl-substituted quinoxaline with (**6**) and without (**6a**) an intra-molecular N1···H—O—C3′ hydrogen bond as calculated at the HF/6–31G** level of theory

quinoxalines could also prefer both the enamino form **B** and the keto form **C** (Scheme 1). The tautomeric equilibria **A** ⇌ **C** and **B** ⇌ **C** which were expected to be slow on the NMR time-scale have been studied already by examining the chemical shift of C-2′, which should be strongly shifted to high field due to sp^3 hybridization in **C**; thus **C** was excluded from the tautomeric equilibrium present.[1,13] The tautomeric equilibrium **A** ⇌ **B**, however, which is expected to be fast on the NMR time-scale, cannot be examined adequately by NMR spectroscopy because there is no unequivocal proof. Only chemical shifts, *e.g.* of C-3′,[1,13] and substituent effects could be related to reference compounds with frozen tautomerism. That is why also both the enamino form **B** and the keto form **C** (Scheme 1) in addition to **A** were calculated for **4–9** in the same way as mentioned earlier. The results are given in Tables 3 and 4. Only the DFT results are given because only here could electron correlation be considered.

Evaluating first the formation energies (Table 4), as expected **A** proved to be more stable than **B** and **C**, which was already ruled out for several experimental reasons just mentioned. For the calculations, molecules in vacuum were considered; if the solvent had been taken into account, the coincidence of experimental and

Table 3. ^{13}C and ^{15}N chemical shifts (δ ppm) of **4–9** in tautomeric forms **B** and **C** as calculated *ab initio* at the B3LYP/6–31G** level of theory

No.	B						C					
	N-1	N-4	C-2	C-3	C-2′	C-3′	N-1	N-4	C-2	C-3	C-2′	C-3′
4	−263.4	−34.4	124.2	141.4	126.4	173.1	−49.9	−39.4	145.2	136.6	88.8	188.1
5	−256.5	−49.3	122.3	154.2	129.6	168.3	−39.2	−43.3	146.0	149.6	91.8	190.3
6	−257.7	−35.5	125.1	152.0	125.9	172.8	−36.9	−38.8	145.8	153.1	91.9	191.9
7	−268.8	−48.2	119.9	145.4	129.1	156.5	−61.2	−51.8	141.4	131.7	68.2	162.1
8	−253.3	−49.9	124.8	151.5	127.2	157.1	−39.9	−44.1	147.3	150.1	92.1	172.4
9	−252.1	−41.9	123.7	152.5	126.1	157.5	−48.6	−36.6	145.5	151.8	89.7	171.0

Table 4. Formation energies ΔE (kJ mol^{-1}) as calculated *ab initio* on the B3LYP/6–31G** level of theory of **4–9** in the tautomeric forms **A–C**

No.	A	B	C
4	0.0	7.5	30.9
5	0.0	38.1	30.5
6	0.0	5.0	29.3
7	0.0	72.4	70.3
8	0.0	41.0	64.4
9	0.0	42.2	59.4

calculated results was expected to be even better.[14] The ^{13}C and ^{15}N chemical shifts also proved very useful (Tables 2 and 3). Experimental and theoretically calculated ^{13}C and ^{15}N chemical shifts of all atoms involved in the six-membered ring fragment of the intramolecular hydrogen bond moiety (N1—C2—C2′—C3′—XH) are only in conformity in case of tautomer **A** (Table 2). In the case of **B** the deviations are dramatic; N-1 is calculated to be more than 150 ppm upfield, *e.g.* C-2 *ca* 20 ppm upfield and C-3′ *ca* 30 ppm downfield, ruling out completely the latter conformer from participating in the present tautomeric equilibrium. Figures 3–5 show a comparison of experimental and calculated ^{13}C chemical shifts for **1, 4** and **7**; in Fig. 3 there is fair coincidence of the two calculation methods employed in reproducing the ^{13}C NMR spectrum of **1**. Figure 4 and 5 for **4** and **7**, respectively, impressively corroborated that only tautomer **A** dominates the present tautomeric equilibria. Only in the case of these ^{13}C chemical shifts is there fair

coincidence between theory and experiment (identical results were obtained for **2, 3, 6, 8** and **9**).

EXPERIMENTAL

The *ab initio* calculations were carried out with the Gaussian 94 program[15] using the 6–31G** basis set[16] at the Hartree–Fock and the B3LYP DFT level.[17,18]

The NMR chemical shifts were calculated using the 'gauge-including' atomic orbital (GIAO) method[3,4] as the difference in the NMR chemical shifts of the carbon and nitrogen atoms in the molecules and a reference compound. The GIAO method is implemented in the Gaussian 94 program.[15] The calculations of the chemical shifts of the reference compound (TMS for ^{13}C and nitromethane for ^{15}N) and the quinoxalines were carried out at the same level of theory in order to make valid comparisons.

The chemical shifts of **1–9** were calculated with the 6–31G** basis set at the HF level and using the DFT-B3LYP method[17,18] in order to find the best fit of the theoretical and experimental results. Especially the large deviations of the ^{15}N chemical shifts from the line of identity and the insensitivity of N-4 ^{15}N chemical shifts on hydrogen bonding and tautomerism of **1–9** induced us to extend the calculations to the DFT method because electron correlation effects are probably important.[19]

The quantum-chemical calculations were processed on SGI Octane (2 × R 12000) and SGI ORIGIN (24 × R 10000) computers at Potsdam University.
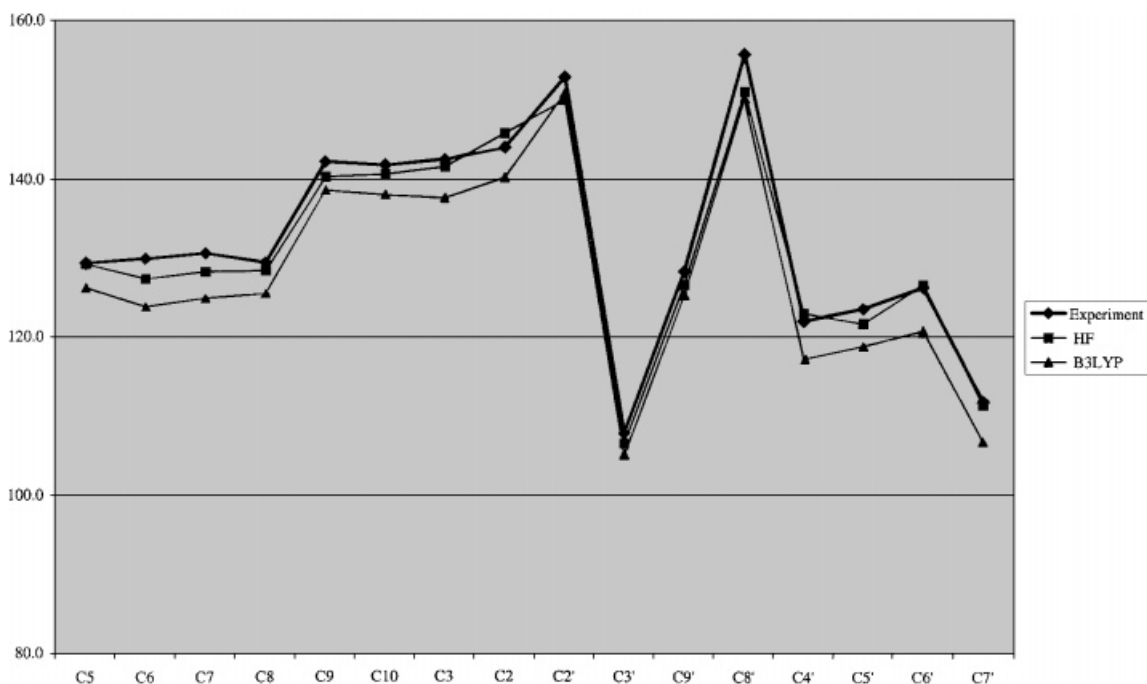

Figure 3. Comparison of experimental and theoretical ^{13}C chemical shifts of **1** as calculated at the HF/6–31G** and B3LYP/6–31G** levels of theory
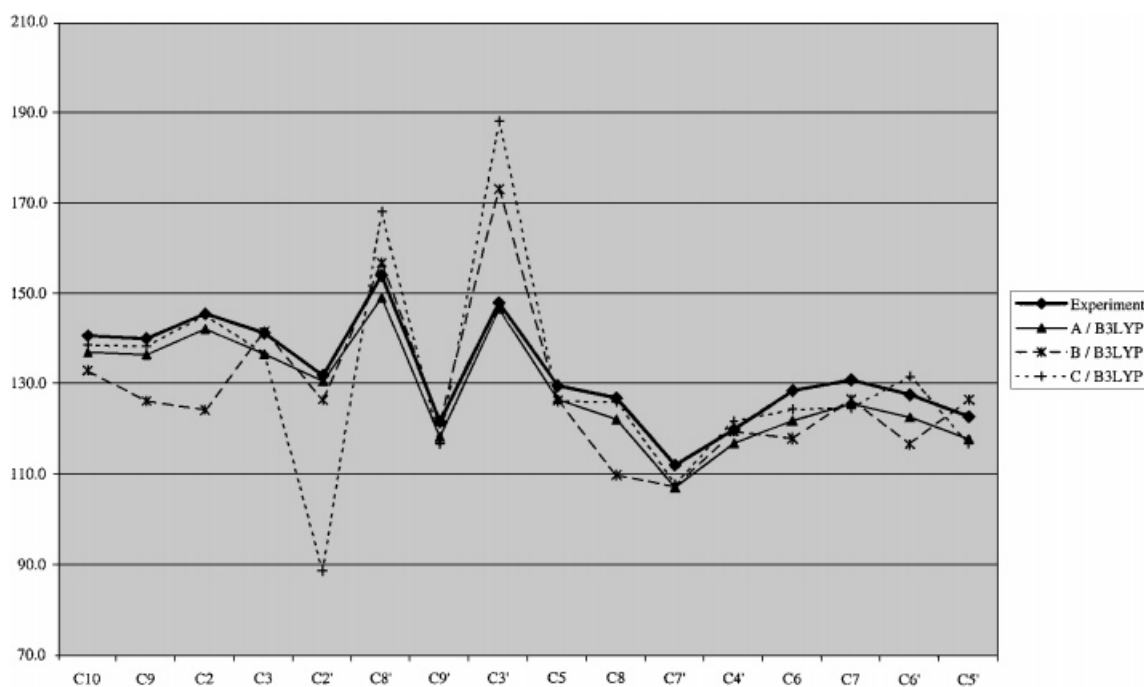
Figure 4. Comparison of experimental and theoretical ^{13}C chemical shifts of **4A–C** as calculated at the B3LYP/6–31G** level of theory

CONCLUSIONS

The global minima conformations of a number of differently substituted 2-(2′-benzo[*b*]furanyl)quinazolines (**1–9**) were calculated *ab initio* using the 6–31G** basis set at the HF and B3LYP DFT levels of theory. On the basis of the global minima structures the ^{13}C and ^{15}N chemical shifts of the nuclei involved were also calculated using the GIAO method. On the basis of the results of these calculations (formation energies, geo-
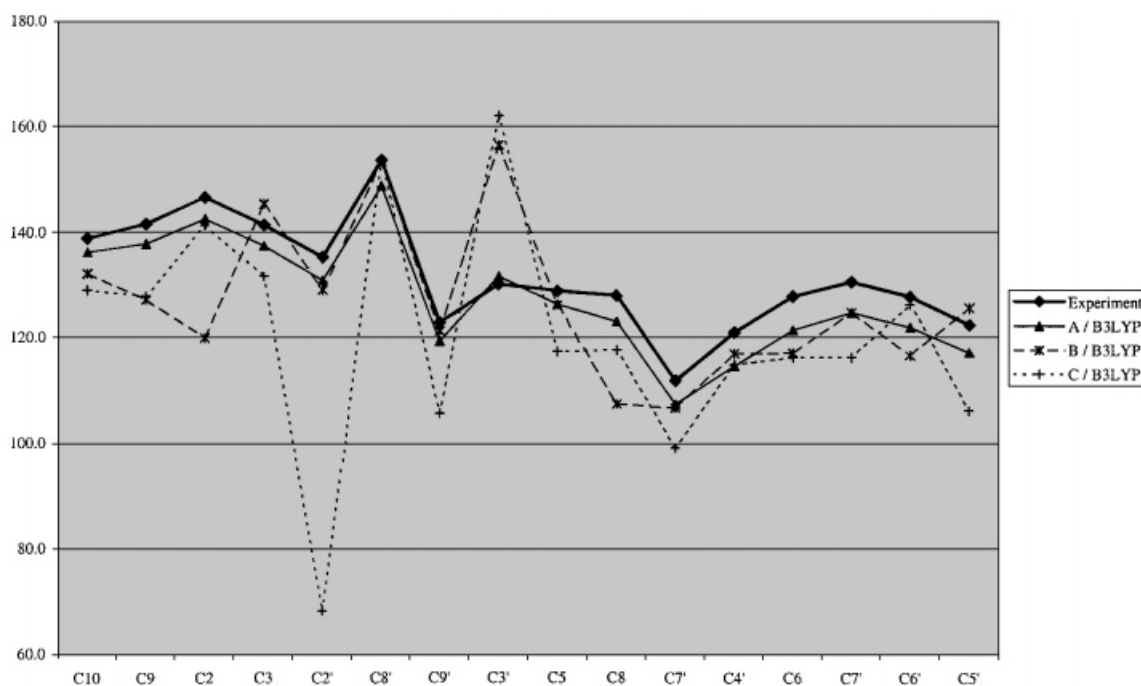

Figure 5. Comparison of experimental and theoretical ^{13}C chemical shifts of **7A–C** as calculated at the B3LYP/6–31G** level of theory

metric features, chemical shifts) in comparison with experimental NMR parameters, both intramolecular hydrogen bonding within and tautomerism of the present molecules could be studied in detail. Intramolecular hydrogen bonding between the two heterocyclic moieties, additionally to π-electron delocalization, stabilizes the molecules by reducing the dihedral angle about the C2—C2′ bond; the enol form is the preferred tautomer of these compounds.

Especially the calculated ^{13}C and ^{15}N chemical shifts prove very valuable estimates for elucidating the presence of intramolecular hydrogen bonding and tautomerism.

Acknowledgements

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