JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. **12**, 725–733 (1999)

NMR spectroscopic and *ab initio* MO study of sterically hindered 2,3-disubstituted quinoxalines

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Received 18 February 1999; revised 28 May 1999; accepted 28 May 1999

ABSTRACT: A number of quinoxalines substituted in position 2 with the π-electron excess 2′-benzo[*b*]furanyl substituent were studied with respect to the sterically/electronically restricted rotation about the C(2)—C(2′) bond by ^{13}C and ^{15}N chemical shifts (both experimental and calculated by the GIAO method) and *ab initio* MO calculations. Both the barriers to rotation and the preferred ground-state conformers were obtained, which proved strongly dependent on steric hindrance and the balance of π-electron deficiency π-electron excess of the heterocyclic systems involved. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: NMR; barrier to rotation; *ab initio* MO calculation; π-electron resonance; steric hindrance; quinoxalines

INTRODUCTION

NMR spectroscopy together with semi-empirical calculations (PM3) have been employed to determine the dihedral angle about the C(2)—C(2′) bond in a number of quinoxalines substituted in position 2 with π-electron excess heterocycles (2′-benzoxazolyl, 2′-benzthiazolyl, 2′-benzimidazolyl, 2′-indolinyl and 2′-benzo[*b*]furanyl) and thereby the preferred conformation of these compounds.[1] Both the ^{13}C and ^{15}N chemical shifts of N-1, C-2, C-3, C-2′ and C-3′ (Scheme 1) were found to be linearly dependent on this theoretically obtained parameter and proved indicative of the stereochemistry of these unsaturated compounds. However, the corresponding barrier to rotation about the C(2)—C(2′) bond, which could be electronically and/or sterically controlled, could not be studied by dynamic NMR spectroscopy (at −120 °C no broadening of the NMR signals was obtained).

It was the major objective of this paper to study this dynamic process in detail by *ab initio* MO calculations to resolve the latter aspect. In addition, the ^{13}C and ^{15}N chemical shifts involved were calculated with the use of the GIAO method on the basis of the *ab initio* MO calculated absolute structural minima dependent on the frozen C(2)—C(2′) dihedral angle.

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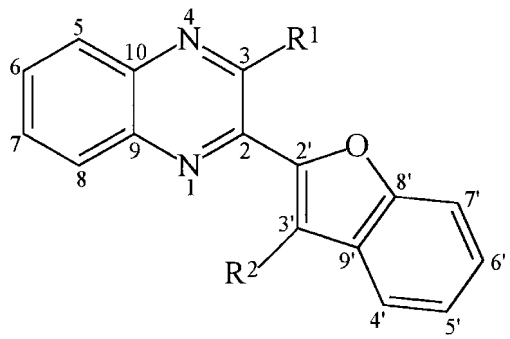
RESULTS AND DISCUSSION

Barrier to rotation about the C(2)—C(2′) bond

The 2,3-disubstituted quinoxalines **1–5** studied (Scheme 1) are interesting compounds from the physical–organic chemistry point of view as there is a π-electron deficient



No.	R^1	R^2
1	H	H
2	CH_3	H
3	CH_3	CH_3
4	CH_3	C_6H_5
5	C_6H_5	H

Scheme 1

CCC 0894–3230/99/090725–09 $17.50

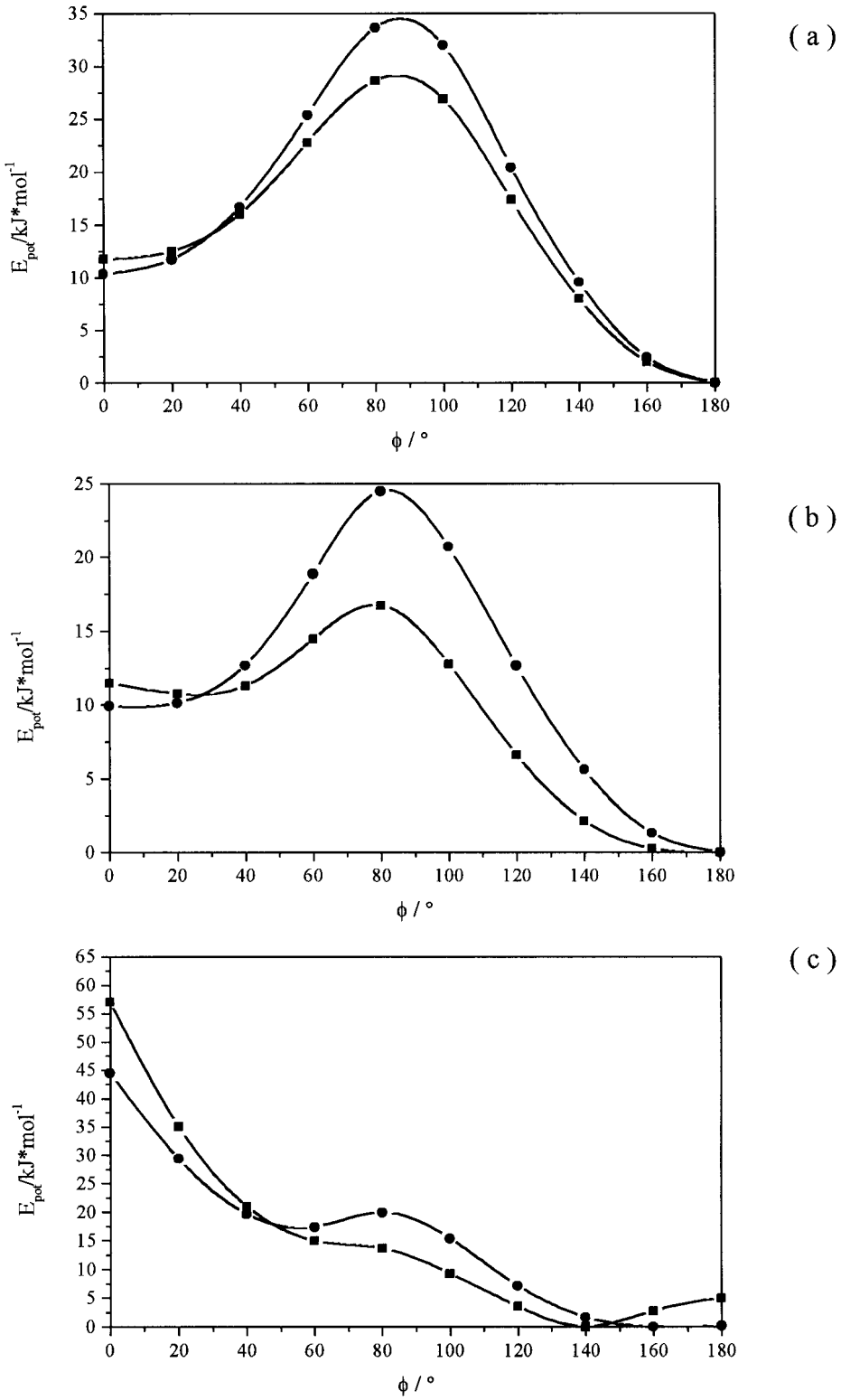


Figure 1. Barrier to rotation about the C(2)—C(2′) bond of compounds (a) **1**, (b) **2** and (c) **3**. (■) HF/6–31G*; (●) B3LYP/6–31G*

heteroaromatic moiety (quinoxalinyl) which is bound to the π-excess heteroaromatic entity 2′-benzo[*b*]furanyl, both parts of the molecules able to undergo mesomerism. For this, a common plane of resonance is a supposition; in the absence of steric hindrance, dihedral angles $\phi = 0°/180°$ will be strived for and π-barriers to rotation will be obtained.

However, if there are substituents in positions 3 and/or

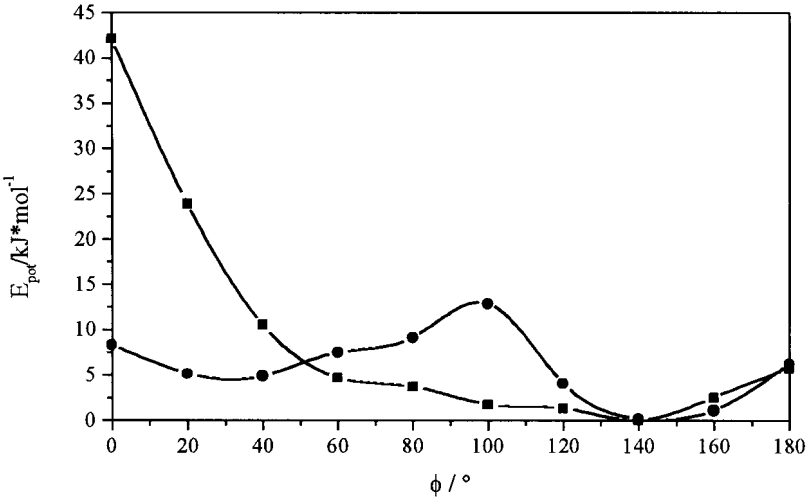


Figure 2. Barrier to rotation about the C(2)—C(2′) bond at the HF/6–31G* level for compounds (■) **4** and (●) **5**

3′, the undisturbed adjustment of the common plane of resonance could be sterically hindered and the corresponding barrier to rotation could be more and more controlled by the latter effect.

Dynamic NMR spectroscopy proved useless; even at the lowest temperatures obtained with the local NMR equipment dynamic exchange phenomena could not be obtained. Therefore, *ab initio* MO calculations were employed using the 6–31G* basis set at both the HF and the B3LYP DFT levels. In both calculation modes, the dihedral angle about the C(2)—C(2′) bond, ϕ [C(3)—C(2)—C(2)—C(3′)], was varied in 20° steps, frozen and the rest of the molecule energetically minimized. The results of these calculations are given in Figs 1 and 2.

In the case of compound **1**, unsubstituted in positions 3 and 3′, a π-barrier to rotation was obtained in both calculation modes [Fig. 1(a)]. The global energy minimum was found at $\phi = 180°$; increasing twist raises the potential energy of the system by increasingly restricting the resonance of the two heterocyclic moieties of **1**. Around $\phi = 90°$, when mesomerism is completly interrupted, the system attains the highest energy on the reaction coordinate, subsequently decreasing again when coming back to more resonance of the two conjugated entities. At $\phi = 0°$ this situation was established; however, the potential energy of the system is higher than at $\phi = 180°$ considering steric hindrance of H-3 and H-3′ being absent at $\phi = 180°$. This result was found at both the HF and the B3LYP levels of *ab initio* MO calculations, the latter giving a higher barrier to rotation.

In **3** also at $\phi = 180°$ the conjugated system seems sterically disturbed [Fig. 1(c)]; from the HF MO calculation, the π-barrier (now smaller than in **1** owing to the energetically higher rotational ground state) still came out with the corresponding energy maximum near $\phi = 90°$. Subsequently (with further decrease in the dihedral angle) the situation is dominated by steric hindrance between the methyl groups in positions 3 and 3′, increasing considerably the potential energy of the system up to $\phi = 0°$, the point of highest energy on the reaction coordinate. The DFT calculations describe the electronic situation present even better.

If only one methyl substituent is present [**2**, R^1 = Me; Fig. 1(b)], the rotational behaviour is similar: only after passing the π-barrier at $\phi = 90°$ was the potential energy of the conjugated system found to relax with smaller dihedral angles due to the lower steric effects between 3-Me and H-3′ in **2** compared with the 3-Me–3′-Me interaction in **3**. Actually, the rotational behaviour of **2** looks more similar to that of **1**, only the barrier to rotation being *ca*. 10 kJ mol^{-1} lower owing to the two ($\phi = 90°$ and 180°) sterically destabilized ground states.

The behaviour of the quinoxalines involving phenyl substituent(s) proved different. As expected, one phenyl in position 3 sterically destabilizes the in-plane conformations at $\phi = 0°$ and $\phi = 180°$, but the π-barrier to rotation still exists between $\phi = 120°$ and $\phi = 40°$ with the energy maximum at $\phi = 90°$. The steric barriers to rotation at $\phi = 0°$ and 180°, however, proved much higher, again in agreement with general stereochemical requirements.

Finally, in **4**, the quinoxaline with a phenyl substituent in position 3′ and methyl in position 3, the corresponding barrier to rotation about the C(2)—C(2′) bond proved completely sterically controlled (Fig. 2). The steric hindrance of in-plane conformations at $\phi = 0°$ and 180° proved so dramatic that the global minimum of the present conjugated system was obtained at $\phi = 140°$.

As mentioned already, these barriers to rotation could not be experimentally determined by dynamic NMR spectroscopy. Also, this experimental result was corroborated by the MO calculations. Either only one preferred

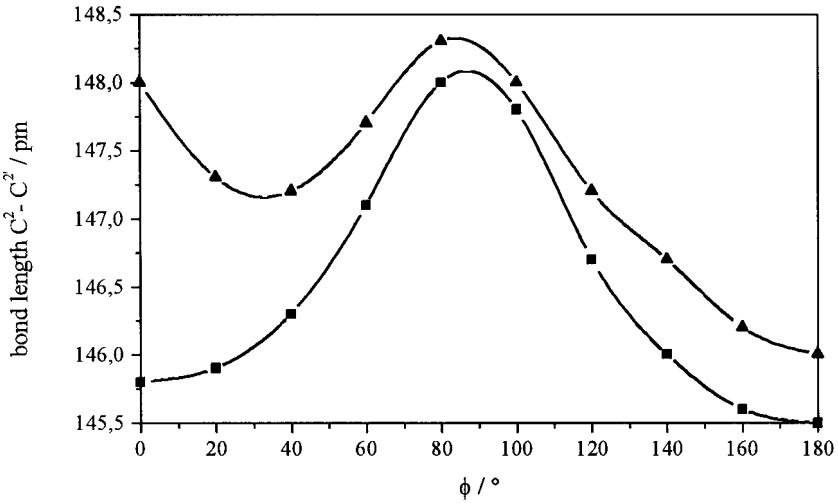


Figure 3. C(2)—C(2′) bond length variation subject to the dihedral angle ϕ [C(3)—C(2)—C(2′)—C(3′)] in the quinoxalines (■) **1** and (▲) **3** as calculated by B3LYP/6–31G* *ab initio* MO calculations

conformer was found (in the case of **1–4**) or, if two seem to be sufficiently populated, the corresponding barrier to rotation was calculated to be too low to be determined experimentally (in the case of **5**).

In Fig. 3, the length of the C(2)—C(2′) bond, as calculated by the DFT method, is correlated with the dihedral angle ϕ about this bond for **1** and **3**. Figures 1 and 3 are almost identical, readily corroborating the generality of the calculation results obtained: in **1** rotational twist from in-plane conformations at $\phi = 0°$ and 180° reduces resonance between the π-electron deficient heterocyclic part of the molecule (quinoxalinyl) and the π-electron excess moiety (benzo[*b*]furanyl), lengthening the interconnecting C(2)—C(2′) bond by 2.3 and 2.6 pm, respectively, and in **3** by 2.3 pm [between $\phi = 180°$ and $\phi = 80°$ (the transition state of the dynamic process)] for the same reason. In the latter case, however, the in-plane conformation at $\Phi = 0°$ is again destabilized by steric hindrance; in this conformation also the C(2)—C2′) bond length is 2.0 pm longer than at $\phi = 180°$), from a different point of view corroborating the reduced π-electron resonance of quinoxaline **3** in this conformation. The bond lengths obtained by the present B3LYP/6–31G* MO calculations are in good agreement with results found for similar compounds by x-ray spectroscopy,[2,3] detailed files of the calculation results are available on request.

^{13}C and ^{15}N chemical shift variation calculated by the GIAO-CHF method subject to the dihedral angle Φ of the C(2)—C(2′) bond

After theoretically studying the barrier to rotation about the C(2)—C(2′) bond, we were also interested in the

Table 1. Experimental and theoretically calculated ^{13}C and ^{15}N chemical shifts of quinoxalines **1–5**

		Chemical shift, δ (ppm)							
Compound	Method	N(1)	N(4)	C(2)	C(3)	C(2′)	C(3)	R^1	R^2
1	Expt.	−69.2	−50.7	144.0	142.5	152.9	107.9	—	—
	HF/6–31G*	−90.0	−77.1	144.2	140.8	148.3	105.9	—	—
	B3LYB/6–31G*	−64.7	−43.1	132.4	130.7	143.1	98.4	—	—
2	Expt.	−61.3	−53.7	144.0	151.6	153.5	109.9	25.2	—
	HF/6–31G*	−92.5	−84.9	144.0	150.5	149.9	107.1	25.8	—
	B3LYB/6–31G*	−60.0	−43.0	132.3	140.9	144.9	99.8	21.5	—
3	Expt.	−55.0	−53.7	145.7	153.4	148.6	118.8	24.4	9.5
	HF/6–31G*	−81.7	−88.5	145.8	152.8	144.8	115.4	24.9	10.8
	B3LYB/6–31G*	−55.3	−44.1	134.5	142.3	139.8	112.7	21.5	7.7
4	Expt.	−50.6	−53.4	147.0	153.4	145.8	122.4	23.1	—
	HF/6–31G*	−73.1	−90.0	145.1	152.7	145.8	120.1	24.4	—
5	Expt.	−58.5	−50.4	143.1	153.0	152.4	110.8	—	—
	HF/6–31G*	−80.0	−81.6	144.6	153.6	150.7	105.8	—	—

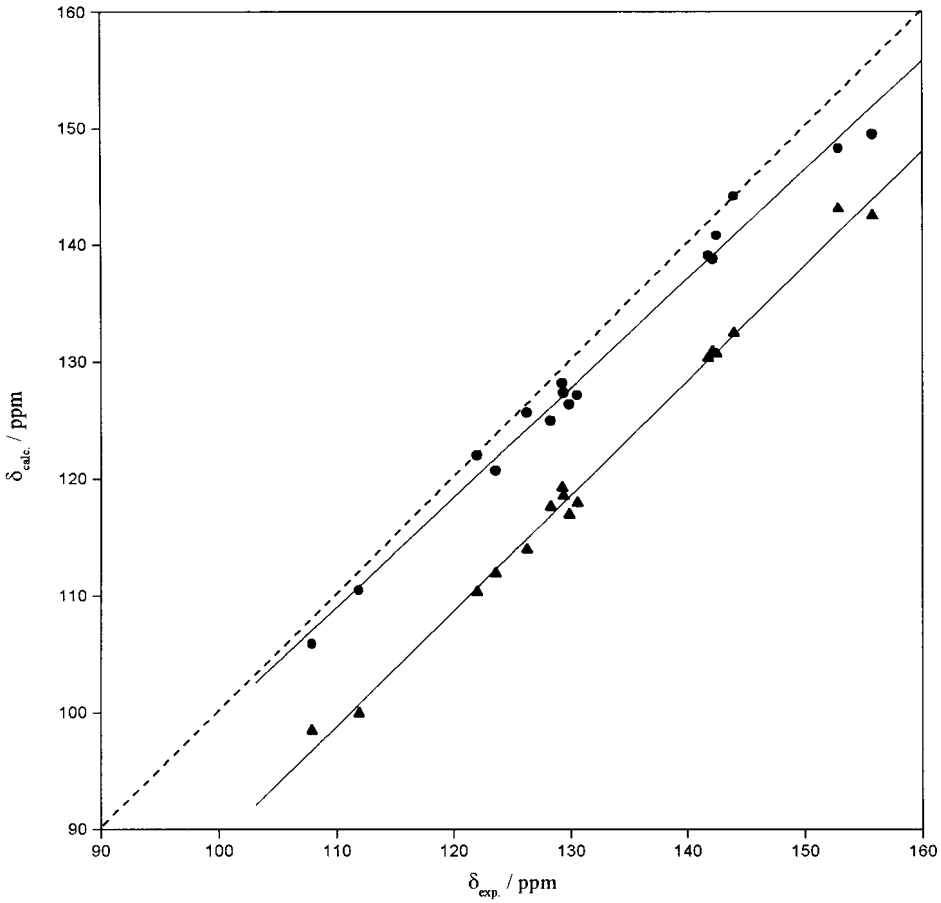


Figure 4. Correlation of experimental and theoretically calculated ^{13}C chemical shifts of compound **1**. (●) HF/6–31G* ($r = 0.9931$; SD = 1.531; $n = 16$); (▲) B3LYP/6–31G* ($r = 0.9967$; SD = 1.112; $n = 16$); The dashed line is the line of identity

corresponding behaviour of both ^{13}C and ^{15}N chemical shifts; ^{1}H chemical shifts proved less useful owing to the much smaller chemical shift range and heavy inter-/intramolecular influences on the latter parameter.[4] Similarly to the barrier calculations, the dihedral angle ϕ [C(3)—C(2)—C(2′)—C(3′)] was varied in 20° steps (near $\phi = 90°$ in 10° steps), frozen and the rest of the molecule energetically minimized by *ab initio* MO calculations at the HF/6–31G* and B3LYP/6–31G* levels. These basic structures of varying dihedral angle ϕ were employed to calculate the corresponding chemical shifts of the two nuclei by the 'gauge including' atomic orbital method (GIAO),[5] which is implemented in the Gaussian 94 program,[6] as the difference in the ^{13}C and ^{15}N chemical shifts in the compounds studied and in a reference compound (TMS for ^{13}C and nitromethane for ^{15}N).

When the values obtained in this way are compared with experimental ^{13}C and ^{15}N chemical shifts, it should be considered that the theoretically obtained values are related to the molecules in vacuum at 0 K from interactions with the lattice; the experimental chemical shifts, however, are subject to various inter-intramolecular interactions with the solutes, solvent, concentration, temperature, etc. In Table 1, both experimental and theoretically calculated ^{13}C and ^{15}N chemical shifts for the global minima structures of quinoxalines **1–5** are given; in Fig. 4, the ^{13}C chemical shifts of **1** are correlated with each other and in Fig. 5 the ^{15}N chemical shifts of N(1) of the quinoxalines **1–5** (the lines of identity are included in both correlations). The correlations of the ^{13}C chemical shifts were good; the ^{13}C chemical shifts obtained at the HF level are practically on the line of identity. The DFT values deviate from this line but systematically (*ca* 12 ppm to higher field). The opposite result was obtained for the ^{15}N chemical shifts; in this case the DFT values are nearer to the line of identity and the HF values deviate systematically (*ca* 25 ppm to higher field from this line). Hence both the ^{13}C and ^{15}N chemical shifts proved to be a good estimate of the real structural situation in the quinoxalines studied even when taking into account that they were calculated for the gaseous state at 0 K.

Chemical shift GIAO calculations have been employed

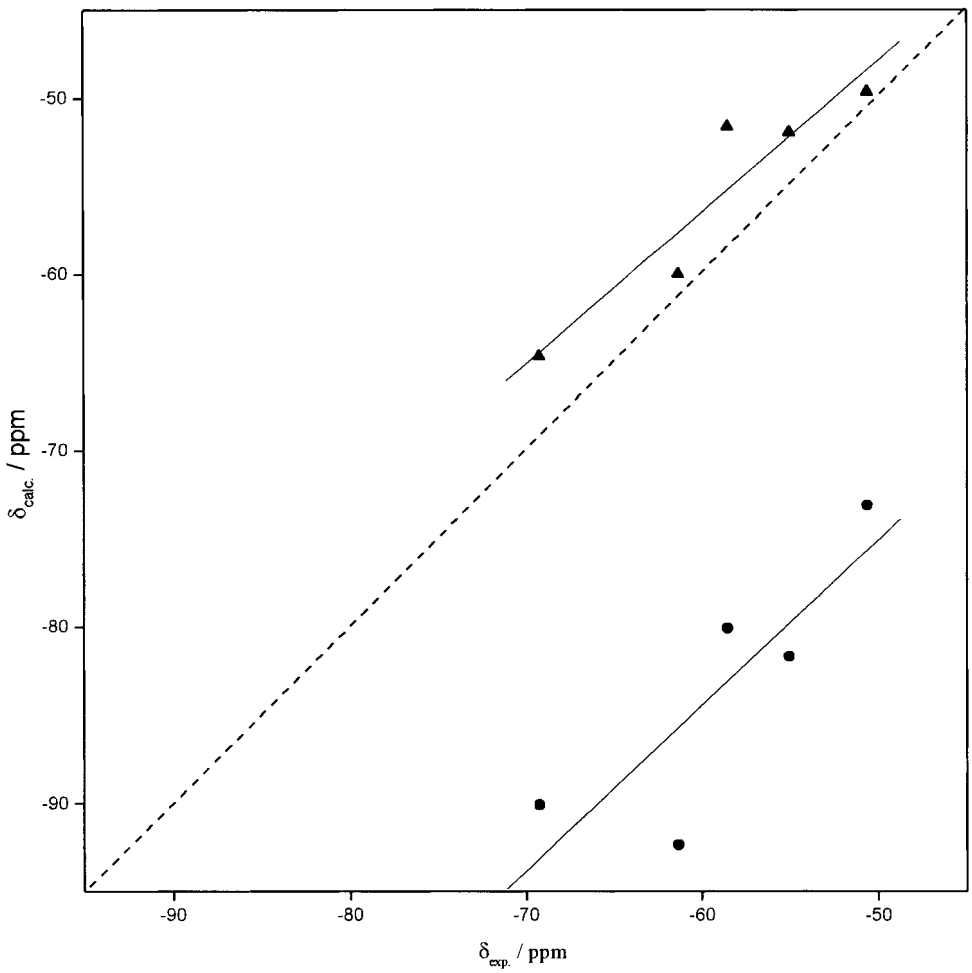


Figure 5. Correlation of experimental and theoretically calculated ^{15}N chemical shifts of N(1) of the quinoxalines **1–5**. (▲) B3LYP/6–31G* (r = 0.9374; SD = 2.587; *n* = 5); (●) HF/6–31G* (r = 0.8387; SD = 4.924; *n* = 5). The dashed line is the line of identity

already to solve dihedral angle problems in cases where dynamic NMR spectroscopy proved useless, e.g. for the conformational analysis of hydrocarbons,[7] especially *n*-octanes,[8] and also for the conformational analysis of glycines[9,] glycinamides[9] and peptides.[10] The dihedral angle ϕ dependences of the chemical shifts of N(4), C(3), C(2), N(1), C(2′) and C(3′) of the quinoxalines **1** and **3**, calculated at the DFT level, are depicted in Figs 6 and 7; characteristic values at $\phi = 0°$ and 180° and also $\phi = 90°$ are given in Table 2. First in **1** [Figs 6(a) and 7(a)], the sterically less hindered reference compound, the ^{13}C chemical shifts of C(3), C(2) and N(1) move to lower field on leaving the in-plane conformations at $\phi = 0°$ and 180°. Here the ^{15}N chemical shift variation proved much more sensitive than ^{13}C chemical shifts. The chemical shift of C(3′), on the other hand, similarly goes to higher field; C(2′) and N(4) proved less characteristically dependent. These chemical shift variations could be readily understood in terms of present π-electron delocalization between the π-electron deficient quinoxalinyl moiety and the π-electron excess heteroaromatic moiety of benzo[*b*]furanyl and are parallel to previous NMR spectroscopic studies:[1] with increasing steric twist, the corresponding delocalization of the π-electrons will be increasingly hindered. Thereby in the quinoxalinyl moiety less π-electron density will be available and the $^{13}C/^{15}N$ chemical shifts involved are shifted to low field. In the 3,3′-dimethyl-substituted quinoxaline **3** [Figs 6(b) and 7(b)], practically identical chemical shift variations were obtained; however, the effects are less marked. Obviously owing to the larger steric hindrance between the two heterocyclic molecule parts, contributions to chemical shifts different from the π-electron effects just mentioned have some influence and mask the aforementioned dependences. The opposite happens in the π-electron excess part of the molecule; the ^{13}C chemical shift of C(3′) moves to higher field. Again, the ^{15}N chemical shift variation proved much more sensitive to the dihedral angle variation than all the ^{13}C chemical shifts.

Also, the ^{13}C chemical shift variations of the methyl substituents in **3** corroborate fundamental stereochemical

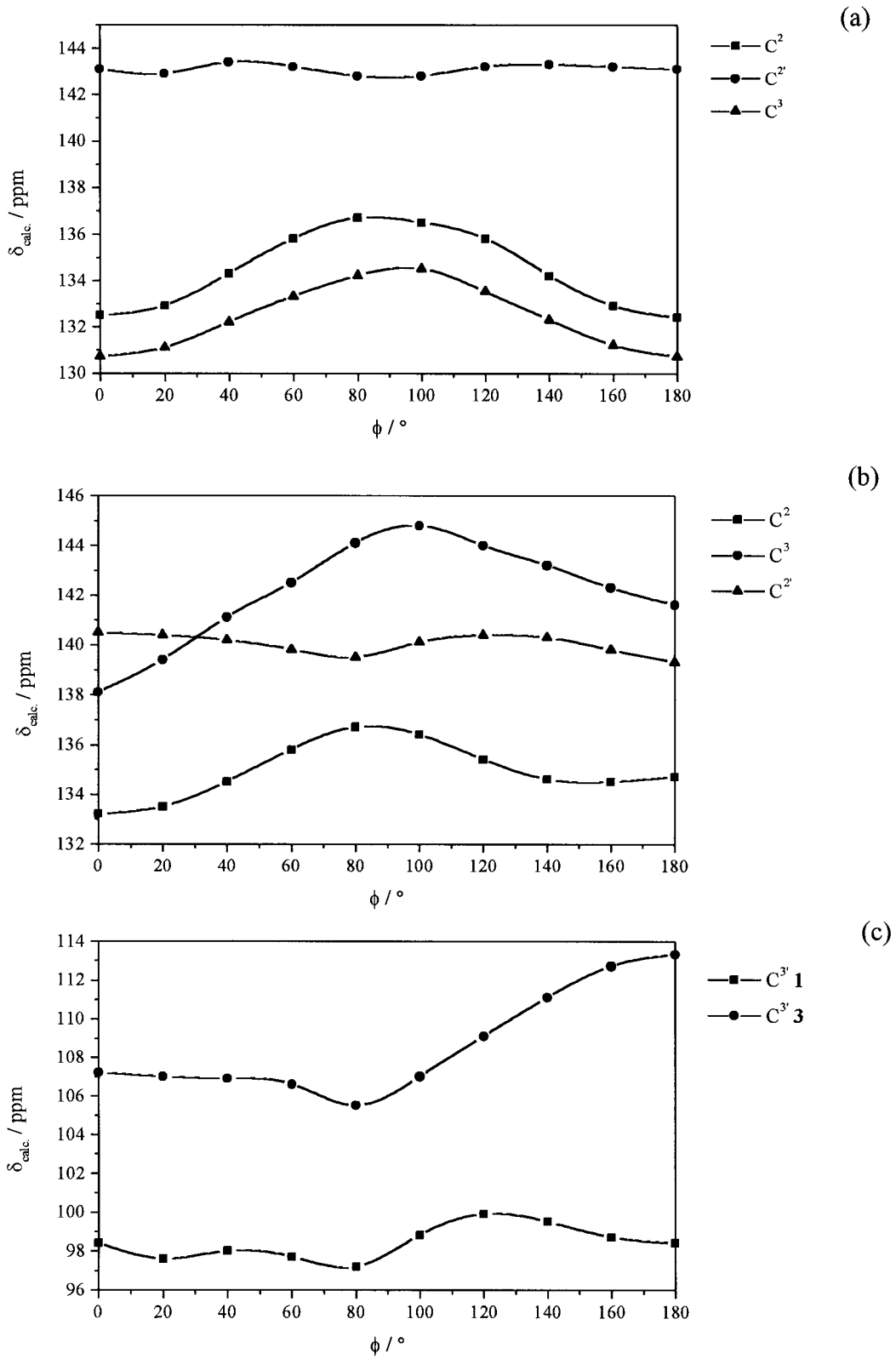


Figure 6. Dependence of the ^{13}C chemical shifts of the quinoxalines **1** and **3** (theoretically calculated by the GIAO method at the B3LYP/6–31G* level) on the dihedral angle ϕ about the C(2)—C(2′) bond. (a) Compound **1**; (b) compound **3**; (c) only C(3′) in both **1** and **3**

principles[11] (Table 2); in line with the δ-substituent effect, both R^1 and R^2 (= Me) are 4.9/4.0 ppm and 3.6/3.5 ppm, respectively, at lower field in the in-line conformations ($\phi = 0°$ and 180°, respectively) compared with the sterically relaxed perpendicular analogue ($\phi = 90°$).

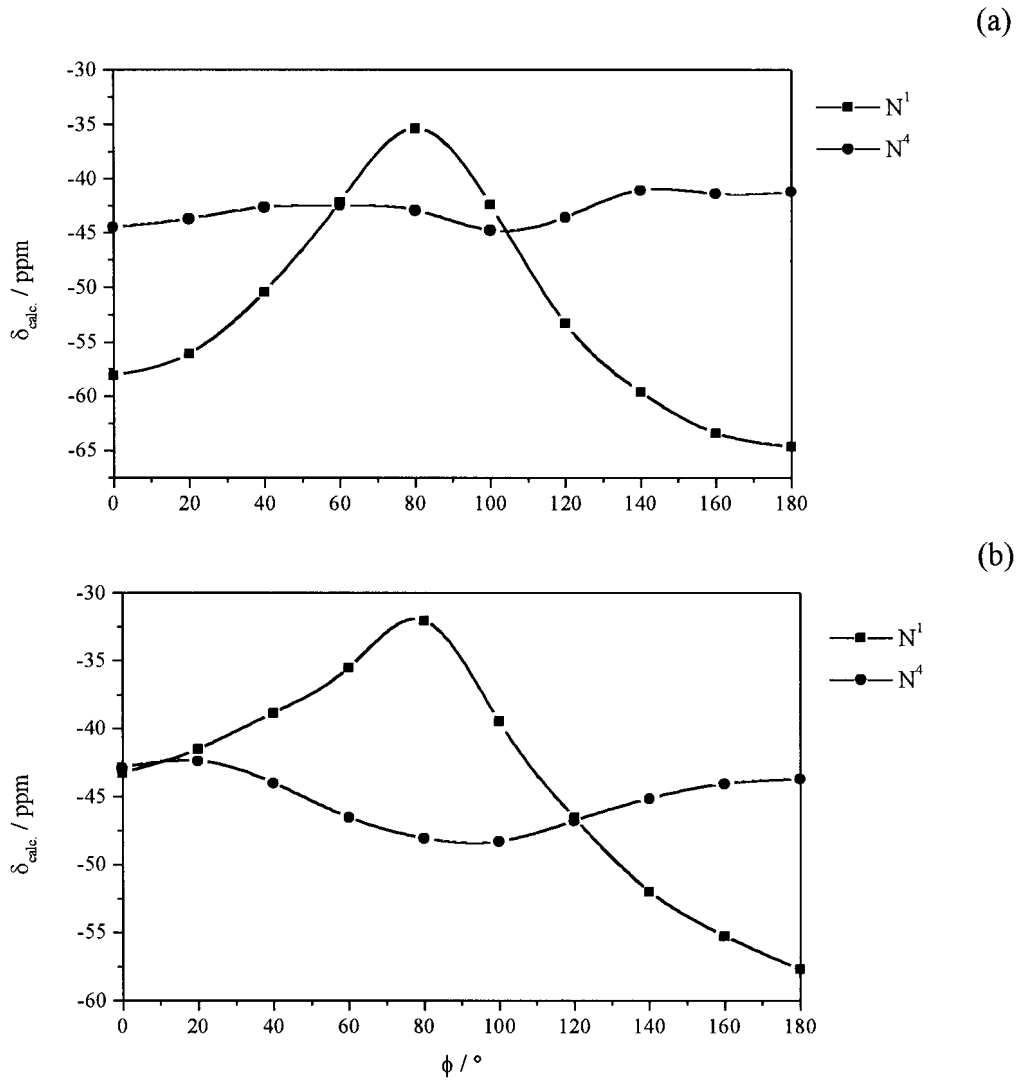


Figure 7. Dependence of the ^{15}N chemical shifts of the quinoxalines **1** and **3** (theoretically calculated by the GIAO method at the B3LYP/6–31G* level) on the dihedral angle ϕ about the C(2)—C(2′) bond. (a) Compound **1**; (b) compound **3**

EXPERIMENTAL

Ab initio calculations were carried out with the Gaussian 94 program[6] using the 6–31G* basis set[12] at the Hartree–Fock and the B3LYP DFT levels.[13]

NMR chemical shifts were calculated using the 'gauge-including' atomic orbital (GIAO) method[5] 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.[6] 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 for comparison.

The chemical shifts of **1–5** were calculated with the 6–31G* basis set at the HF level and using the DFT–Becke3LYP method[13] 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 complete insensitivity of N(4) ^{15}N chemical shifts to the present torsional and structural variations of **1–5** induced us to extend the calculations to the DFT method because electron correlation effects are probably important.[4]

The quantum-chemical calculations were processed on IBM RS/6000 and SGI ORIGIN (24R 10000) computers at Potsdam University.

CONCLUSIONS

The barrier to rotation about the C(2)—C(2′) bond in a number of 2-benzo[*b*]furanyl substituted quinoxalines (**1–5**), the corresponding global minima conformations and the variations of the involved ^{13}C and ^{15}N chemical shifts subject to the dihedral angle ϕ [C(3)–C(2)—

Table 2. ^{13}C and ^{15}N chemical shifts of quinoxalines **1–5** as calculated at the HF/6–31G* and DFT/6–31G* levels of theory[a]

Compound	Dihedral angle, ϕ (0)	Chemical shift, δ (ppm)							
		C(2)	C(3)	C(2′)	C(3′)	N(1)	N(4)	R^1	R^2
1	0	143.0	140.3	148.5	104.6	−90.5	−79.8	—	—
	90	146.5	144.3	150.1	104.1	−70.7	−81.0	—	—
	180	144.2	140.8	148.3	105.9	−90.0	−77.1	—	—
	0	*132.2*	*130.5*	*142.6*	*97.3*	−58.2	−44.5	—	—
	180	*132.4*	*130.7*	*143.1*	*98.4*	−64.7	−41.3	—	—
2	0	142.8	149.4	148.3	106.8	−79.0	−87.0	25.7	—
	90	146.6	152.9	150.4	103.2	−67.5	−92.0	22.6	—
	180	144.0	150.5	149.9	107.1	−92.5	−84.9	25.9	—
	0	*132.1*	*139.4*	*142.8*	*100.3*	−49.6	−45.4	*21.3*	—
	180	*132.3*	*140.9*	*144.9*	*99.8*	−60.0	−43.0	*21.5*	—
3	0	144.6	148.8	144.2	112.2	−69.4	−87.0	27.5	13.4
	90	146.5	153.4	145.2	110.7	−66.2	−92.5	22.6	9.8
	180	146.5	151.2	143.2	118.5	−90.7	−85.4	26.6	13.3
	0	*133.2*	*138.1*	*140.5*	*107.2*	−43.3	−42.9	*22.3*	*9.5*
	180	*134.7*	*141.6*	*139.3*	*113.3*	−57.7	−43.7	*22.2*	*9.2*
4	0	143.9	150.1	144.2	120.6	−68.7	−86.4	26.0	—
	180	144.3	151.1	144.1	122.0	−84.5	−86.0	26.7	—
5	0	143.3	152.9	147.2	108.6	−81.9	−77.8	—	—
	90	145.9	155.3	150.6	103.7	−63.1	−86.8	—	—
	180	144.0	153.1	148.9	107.4	−94.1	−73.5	—	—

[a] Data in roman type, HF/6–31G* level; data in italic type, B3LYP/6–31G* level.

C(2′)—C(3′)] could be studied in detail by semi-empirical (PM3) *ab initio* MO calculations at the HF/6–31G* and B3LYP/6–31G* levels and the corresponding GIAO calculations. Both the barrier to rotation and the preferred ground-state conformers of these compounds proved strongly dependent on the interplay of the present π-electron delocalization between the heterocyclic parts of the molecules and steric hindrance subject to the dihedral angle ϕ; the variation of $^{13}C/^{15}N$ chemical shifts corroborates the latter conclusions and proves these values, calculated by the GIAO method, to be very valuable estimates to represent and to understand electronically/sterically torsional processes if dynamic NMR spectroscopy fails.

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