

Resonance Structure of Azaindoles

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Abstract

Contribution of resonance structures of 7-methyl-7*H*-7-azaindole and 4-methyl-4*H*-4-azaindole was examined. It was concluded from multinuclear NMR and MO calculation studies that the nonpolarized 7-methyl-7*H*-7-azaindole or 4-methyl-4*H*-4-azaindole is the major contribution structure. However, they have much larger dipole moments than non-methylated azaindoles. The electronic natures of pyrrole ring and pyridin ring of the methylated azaindoles are exchanged compared with those of 7- and 4-azaindoles, and the directions of the dipole moments were reversed.

Key words: Azaindole, Resonance, Dipole moment, Atomic charge, NMR, MO calculation.

1 Introduction

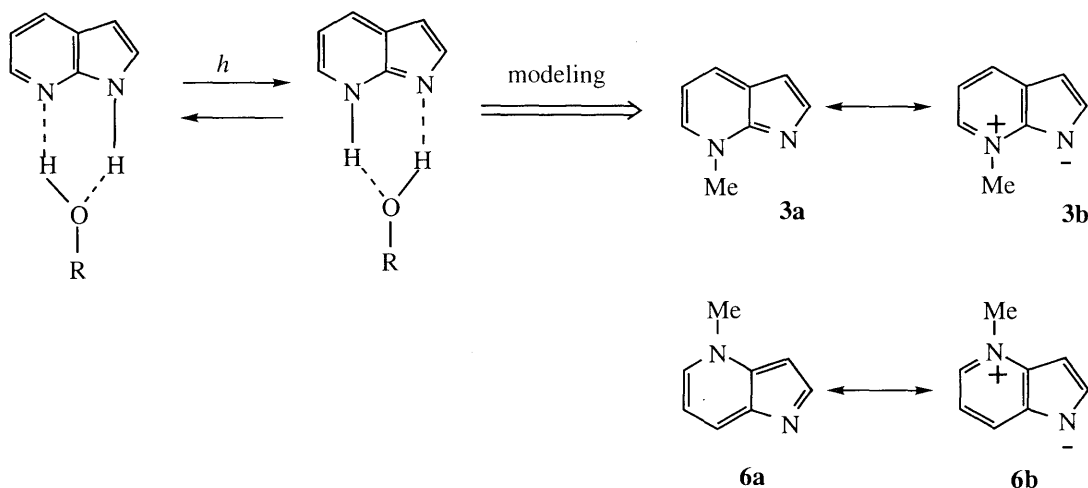
1*H*-Pyrrolo[2,3-*b*]pyridine (7-azaindole : **1**) and its derivatives are much interest in biochemical and physico-chemical studies because of their characteristic ring system, which is consisted with pyridine and pyrrole rings having opposite π -electron densities.^[1] Among them, existence of a basic nitrogen of the pyridine ring and an acidic hydrogen of the pyrrole ring in 7-azaindole is of interest to physico-chemists. While 7-azaindole readily forms various binuclear complexes with metals,^[2] its two nitrogen atoms are located favorably so that this compound interacts with an

alcohol (1:1 adduct formation) or itself (dimerization) through hydrogen bonds.^[3,4] It is known that these 7-azaindole complexes take place a photoinduced double proton transfer reaction to form tautomers.^[5] This behavior was widely investigated by El-Bayoumi and his co-workers who used 7-methyl-7*H*-pyrrolo[2,3-*b*]pyridine (**3**) as the model compound of the tautomer. The structure, charge distribution, dipole moment and basicity of the azaindole **3** were also studied using molecular orbital calculations by comparing with those of the isomer, 1-methyl-7-azaindole (**13**).^[6]

The contribution of the polarized structure **3b** to the azaindole **3** is one of the most important subjects, but it has been only discussed from the standpoints of absorption spectra^[7] and ¹H- and ¹³C-NMR spectra.^[8] The detailed conclusion has not been established.

In this paper, the consideration on contribution of the polarized structure **3b** to the azaindole **3** as

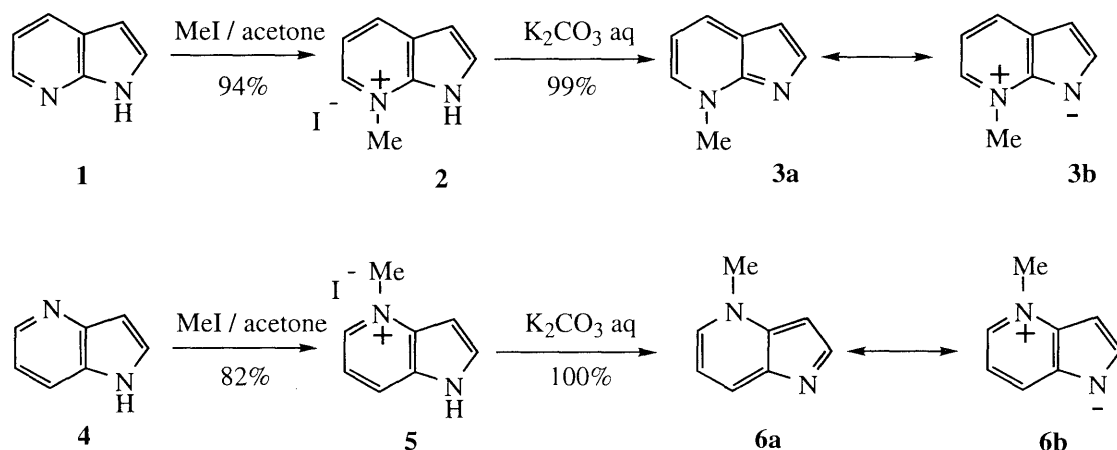
well as of the polarized structure **6b** to 4-methyl-4H-pyrrolo[3,2-*b*]pyridine (**6**) was discussed on the basis of multinuclear magnetic resonances (¹H, ¹³C, and ¹⁵N) and *ab initio* molecular orbital calculations using 6-31G basis set.^[9]



2 Synthesis of *N*-Methylazaindoles and Related Compounds

The 7-azaindole **1** and 1*H*-pyrrolo[3,2-*b*]pyridine (**4**) were quarternarized easily to give 7-methyl-azaindolum iodide (**2**) and 4-methyl-4-azaindolum iodide (**5**), respectively.

On treatment with alkali, the salts gave the yellowish basic substances **3** and **6** which can be readily extracted with diethyl ether or dichloromethane.^[10]



3 ¹⁵N-NMR Chemical Shifts of the Compounds 1-6

To clarify the molecular structures, ^{15}N -NMR spectra in $\text{DMSO-}d_6$ were measured for six compounds and the chemical shifts are shown in Fig.1 accompanying those of primary heterocyclic compounds 7-12.^[11]

Quaternarization of the 7-azaindole **1** to 7-methyl-7-azaindolum iodide (**2**) caused no significant shift on the signal of the pyrrole nitrogen. But upfield shift (about 100 ppm) of the

pyridine nitrogen well agreed with the variation of ^{15}N -chemical shift between pyridine (**7**) and the pyridinium salt **8**.^[12] The deprotonation of the pyrrole hydrogen of the compound **2** to the azaindole **3** caused to considerable downfield shift of the pyrrole nitrogen. This variation was seemed to anion formation of a pyrrole having an electron-withdrawing group such as the compound **10**.^[13]

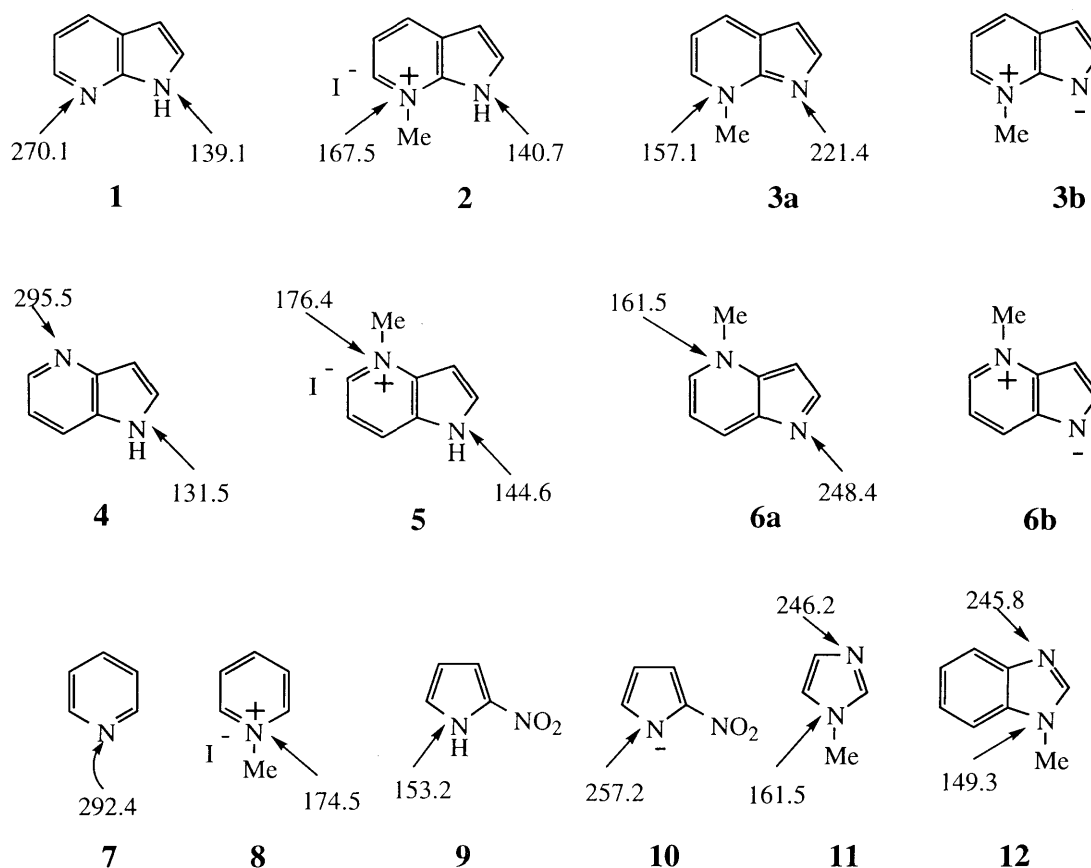


Fig. 1 ^{15}N -NMR Chemical Shifts of the Compounds 1-6
(in $\text{DMSO-}d_6$, ppm from anhydrous liq. NH_3)

This result predicts that the contribution of the structure **3b** is larger than that of the structure **3a**. On the other hand, the chemical shifts of the two nitrogens of the azaindole **3** were similar to those of the *N*-methylimidazoles **11** and **12**,^[14] and did not shift either in a polar solvent ($\text{DMSO-}d_6$) or in a non-polar solvent (CDCl_3). This result is in conflict with the above assumption that the

contribution of the structure **3b** is predominant. A similar tendency of chemical shift variation was also observed for 4-azaindole derivatives. Therefore, we could not conclude whether the major contributing structure is the nonpolarized structure **3a** or the polarized structure **3b**.

4 ¹H- and ¹³C-NMR Chemical Shifts of the Compound 1-6

In addition to the ¹⁵N-NMR results, the contribution of the polarized structure **3b** to the azaindole **3** was examined by means of ¹H- and ¹³C-NMR spectra. The chemical shifts of the compound **1-6** are given in Table 1.

For the ¹H-NMR chemical shifts, remarkable variations were observed between the 7-azaindole **1** and the azaindole **3**, and the downfield shift of H-2 of the pyrrole ring and upfield shifts of H-5 and H-6 of the pyridine ring were observed. If the contribution of the pyridinium salt **3b** is larger than that of the azaindole **3a**, the δ -hydrogen of the pyridine ring (H-6) would not show an upfield shift.

In ¹³C-NMR measurements, the relation of chemical shifts between C-2 and C-6 was reversed when the azaindole **1** was converted into the azaindole **3**. This result suggested that the electronic natures of the pyrrole ring and the pyridine ring of 7-azaindole skeleton may be exchanged. Hence, it is assumed that the contribution of the structure **3a** becomes larger than that of the structure **3b**. The 4-azaindole derivatives **4-6** indicated similar changes also in chemical shifts, which indicates a major contribution of the resonance structure **6a**.

Table 1 ¹H- and ¹³C-NMR Chemical Shifts of the Compound **1-6**

Compound	¹ H-NMR Chemical Shift ^a						¹³ C-NMR Chemical Shift ^a					
	H-2	H-3	H-4	H-5	H-6	H-7	C-2	C-3	C-4	C-5	C-6	C-7
1 ^b	<u>7.37</u>	6.50	7.95	<u>7.10</u>	<u>8.32</u>	---	<u>125.4</u>	100.4	129.0	115.6	<u>142.1</u>	---
2 ^c	7.99	7.00	8.74	7.65	8.76	---	129.7	103.5	136.8	116.0	137.4	---
3 ^b	<u>7.89</u>	6.66	8.08	<u>6.79</u>	<u>7.52</u>	---	<u>145.4</u>	101.4	130.5	108.8	<u>129.6</u>	---
4 ^b	<u>7.50</u>	6.70	---	<u>8.49</u>	<u>7.12</u>	7.70	<u>128.7</u>	102.3	---	<u>142.6</u>	116.5	119.0
5 ^c	8.33	7.06	---	8.76	7.68	8.54	123.9	92.8	---	134.9	113.4	132.2
6 ^b	<u>8.27</u>	6.39	---	<u>7.50</u>	<u>6.87</u>	8.11	<u>152.6</u>	91.7	---	<u>130.0</u>	109.6	127.5

a: ppm from TMS

b: in CDCl₃

c: in DMSO-*d*₆

5 Effect of Concentration on ¹H-NMR Chemical Shifts

It has been reported that the signals of H-2 and H-6 of the azaindole **1** shift toward downfield with increasing concentration in CCl₄ because of a formation of a dimer through hydrogen bond.^[7] Therefore, chemical shifts depending on concentration were estimated for azaindoles **3** and **6**.

The effects of concentration on the chemical shifts of H-2, H-6 and H-5 of the compounds **3**, **13**, **6** and **14** are shown in Figs.2 and 3. The signals

of the azaindole **3**, 7-methyl-7-azaindole, were shifted slightly toward upfield with increasing concentration. If the variation due to the intermolecular interaction is notable, we may assume that the betaine structure **3b** is the major contributing form. However, the variation for the azaindole **3** was resemble to that of the compound **13**, which could not dimerize. The 4-azaindole derivatives **6** and **14** also showed the same tendency.

Therefore, it is reasonable to consider that the nonpolarized resonance structure **3a** or **6a** is

predominantly for the azaindole **3** or **6**, respectively.

6 Bond Lengths of the Azaindoles **1**, **3**, **4** and **6**

Recently, J. Catalan et. al. have studied the gas-phase basicity of heterobicyclic compounds including 7-azaindole derivatives using experimental measurement and *ab initio* calculations at the STO-3G and 4-31G levels.^[15] In order to clarify the contribution of the polarized structure **3a** or **6a** to 7-methyl-7*H*-pyrrolo[2,3-*b*]pyridine (**3**) or 4-methyl-4*H*-pyrrolo [3,2-*b*]pyridine (**6**) more precisely, we carried out molecular orbital calculations for the compounds **1**, **3**, **4** and **6** using the *ab initio* 6-31G method. So far as we know, no report on molecular orbital calculation of 4-azaindole derivatives has appeared.

The calculated bond lengths of these compounds are shown in Fig.4. It was found that the N1-C7a, C3a-C4 and C5-C6 bonds of the azaindole **3** are shorter than the corresponding ones of the azaindole **1**. In the case of 4-azaindole derivatives, the N1-C2, C5-C6 and C7-C7a bonds of the azaindole **6** are shorter compared to the azaindole **4**. As one of the characteristics of these azaindoles, the bridged bonds (C3a-C7a) of the azaindoles **3** and **6** were longer compared to those of the azaindoles **1** and **4**. These results suggest that the structures **3** and **6** are resemble to the structures **3a** and **6a**, respectively.

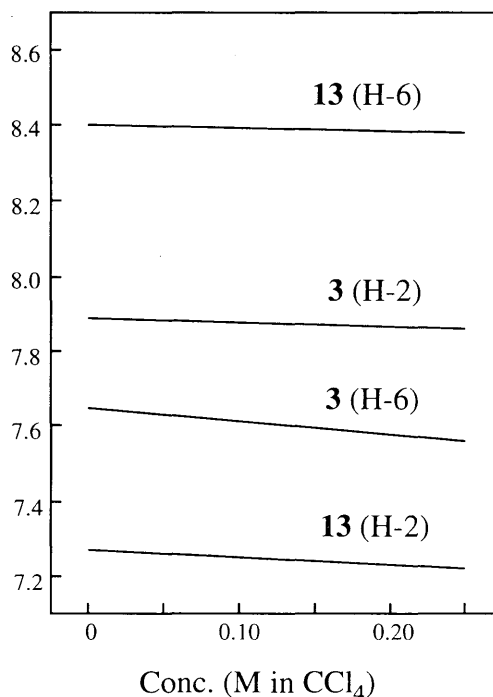
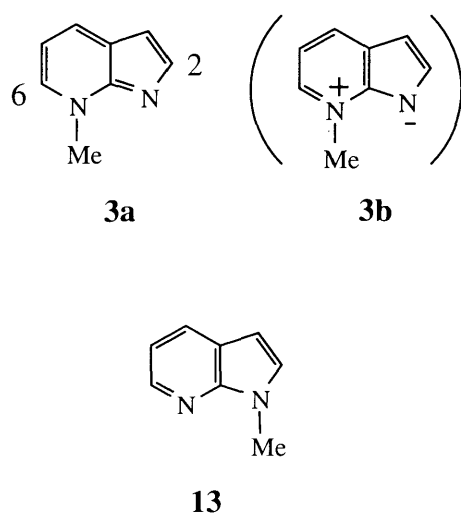


Fig. 2 Effect of Conc. on ¹H-NMR Chemical Shift of the Compounds **3** and **13**

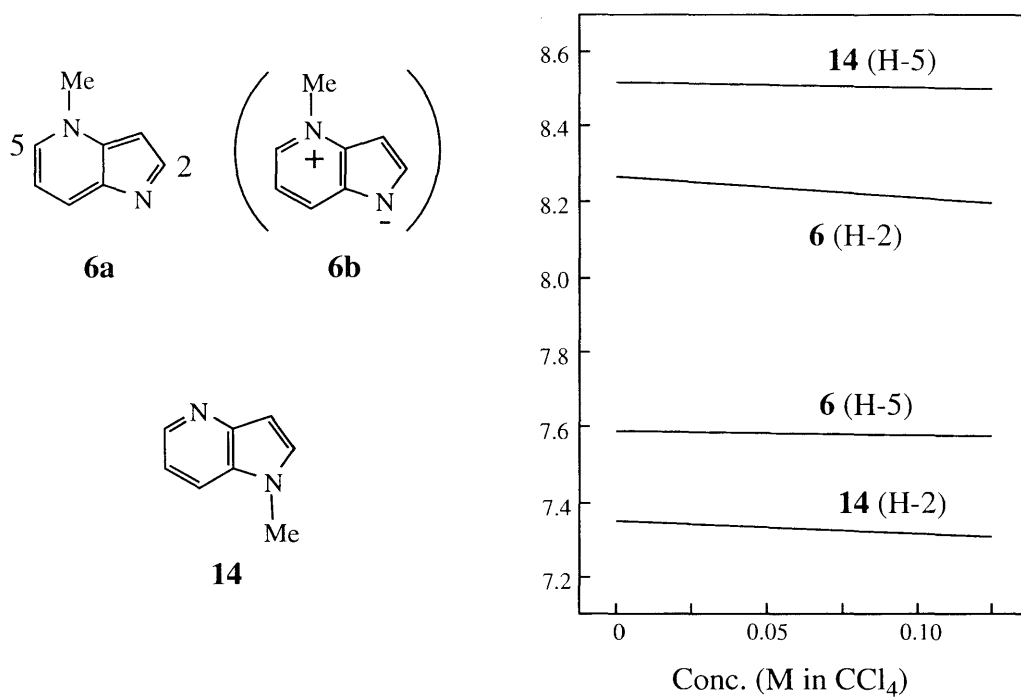


Fig. 3 Effect of Conc. on ¹H-NMR Chemical Shift of the Compounds **6** and **14**

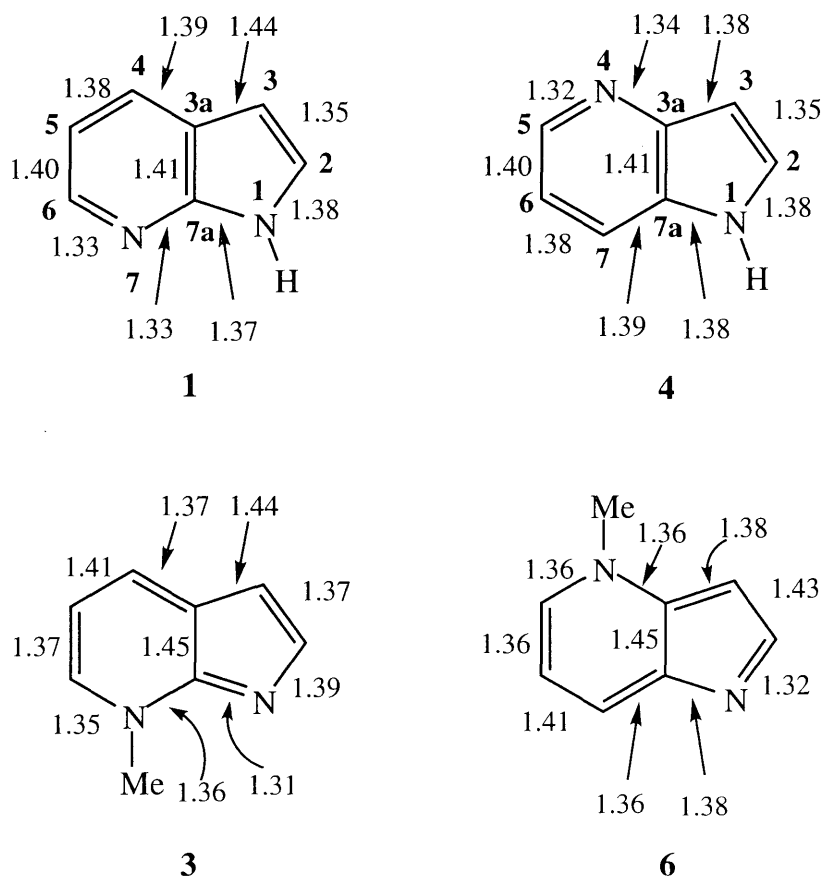


Fig. 4 Bond Lengths of the Compounds **1**, **3**, **4** and **6**
(calculated by the *ab initio* 6-31G Method)

7 Dipole Moments and Total Atomic Charges of the Azaindoles

The total atomic charges and the dipole moments of the compounds **1**, **3**, **4** and **6** are shown in Fig.5. Comparison of the calculated atomic charges of the compounds **3** and **6** with those of the azaindoles **1** and **4** indicated that some atomic charge migrates from the pyrrole ring to the pyridine ring by methylation at pyridine nitrogen. These atomic charges on carbons explain well the aforementioned chemical shifts in ^{13}C -NMR spectra of the azaindoles **3** and **6**. The remarkable changes in the direction of the dipole moments also supported the charge migration. Thus, the dipole moments of the azaindoles **1** and **4** were directed toward the pyrrole ring from the pyridine ring, but

the directions were reversed of the methylated azaindoles **3** and **6**.

The results of the calculation suggested that the anionic charge on N-1 of the betaine structures **3b**. and **6b** migrated to the pyridine ring to form the nonpolarized structures **3a** and **6a**.

As a consequence, the electronic natures of the pyrrole ring and the pyridine ring of the azaindole skeleton were exchanged by quarternarization of pyridine nucleus. The experimental and calculated results predicted that the contribution of the nonpolarized structure **3a** or **6a** for the azaindoles **3** or **6** is more predominant than that of the polarized structure **3b** or **6b**.

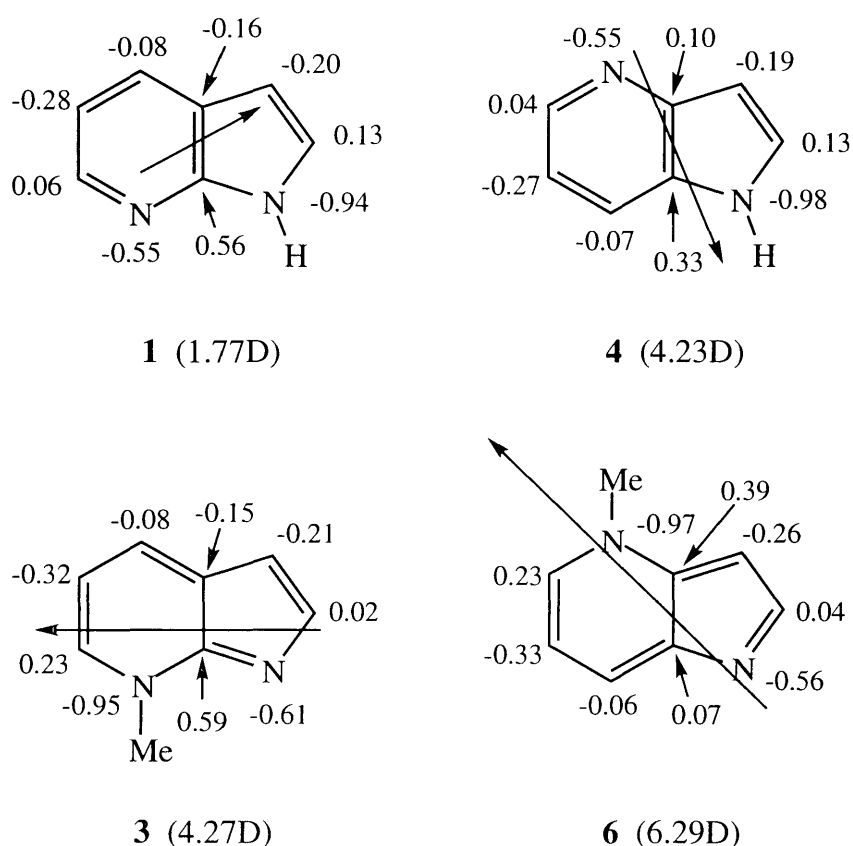


Fig. 5 Dipole Moment and Total Atomic Charge of the Compounds **1**, **3**, **4** and **6** (calculated by the *ab initio* 6-31G Method)

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