

ELECTRONIC STRUCTURE AND PHYSICO-CHEMICAL CHARACTERISTICS OF IMIDAZO[4,5-b]- AND [4,5-c]PYRIDINES AND THEIR PROTONATED AND DEPROTONATED DERIVATIVES

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Dipole moments, diamagnetic permeabilities, 1H , ^{13}C and ^{15}N chemical shifts, and the energies of the lowest singlet-singlet transitions for imidazo[4,5-b]- and [4,5-c]pyridines, the corresponding protonated species and anions have been calculated using the bonding variant of the PPP perturbation method. The aromaticity of the compounds is given based on the results obtained.

Derivatives of [4,5-b]- and [4,5-c]pyridine (1-deazapurine and 3-deazapurine respectively) show a wide range of biological activities. Some of them are used as cardiotonic [1], anti-ulcer [2], antineoplastic [3] and herbicidal [4] substances which explains why these compounds have recently been studied intensively. We have carried out quantum chemical calculations on imidazo[4,5-b]- (IIa-IVa) and -[4,5-c]pyridines (IIb-IVb) and the corresponding anions (Ia, Ib) and cations (Va-VIIIa, Vb-VIIIb) using the PPP method. The results have been compared with experimental data.

Table 1 contains the results of calculations (for method see [5, 6]) of the residual π -electron charge and the bond order of structures Ia-VIIIa and Ib-VIIIb. The numbering of the compounds and their atoms are shown in Table 2. The data show that the maximum π -electron density (maximum negative or minimum positive charge) on the non-junction carbon atoms of the imidazo[4,5-b]pyridine series occurs in position 6, except for compound Va where it occurs at position 7. This agrees with the observation that 3-methylimidazo[4,5-b]pyridine nitrates at position 6 [7]. For the imidazo[4,5-c]pyridines (IIb, IIIb, Vb-VIIIb) maximum electron density is observed at $C_{(7)}$ whereas in compounds Ib and IVb it occurs at position 6. It should be noted that there is negligible change in charge at these positions on going to the corresponding dications.

As a rule the maximum change in electron density for the compounds studied when the nitrogen atom of the imidazole ring is protonated is observed at position 2. Exceptions are the anions (Ia and Ib) and the azulene-like structures (IVa and IVb) where it occurs at position 3. The maximum change in charge on the non-junction carbon atoms occurs at $C_{(5)}$ for the imidazo[4,5-b]pyridines (Ia, IVa) and at $C_{(6)}$ for the corresponding [4,5-c] compounds (Ib, IVb).

As in the case of quinoline and pyridine [8], addition of a hydrogen atom to the nitrogen atom of the pyridine unit leads to maximum change in electron density at $C_{(7)}$ (γ to the protonated nitrogen atom) for derivatives of imidazo[4,5-b]pyridine, whereas it occurs at $C_{(4)}$ (α to the protonated nitrogen atom) for the imidazo[4,5-c]pyridines. The sole exceptions are anion Ib and compound IIIb in the imidazo[4,5-c]pyridine series where the maximum charge is at $C_{(2)}$. Note that the exceptions are observed on protonation of anions and the azulene-like structure. It has been shown previously [9] that changes in the pK_a of unsaturated heterocycles on substitution is proportional to the difference in the residual π -electron charge between the unsubstituted base and its conjugate acid at the point of substitution. Our results on the change in electron density on protonation of imidazopyridines permits the prediction of changes in the pK_a of these molecules on introduction of a substituent.

A deficit of electron density is observed at $C_{(2)}$ in the imidazopyridines, as in benzimidazole [10], but unlike that compound, the six-membered ring of the imidazoles carries a positive charge. In a number of cases other atoms, e.g., $C_{(5)}$ in compounds IIIa and IVa and $C_{(4)}$ in compounds IIb and IVb have even greater positive charges than $C_{(2)}$. The imidazole nitrogen atoms in anions Ia and Ib have practically the same residual π -electron charge (Table 1) which should indicate that

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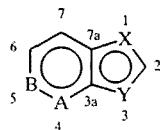
TABLE 1. Residual π -Electron Charges (P_{kk}) and Bond Orders (P_{ik}) for the Imidazopyridines (I-VIII)

<i>i-k</i>	Imidazo[4,5-b]pyridines							
	Ia	IIa	IIIa	IVa	Va	VIa	VIIa	VIIIa
1-1	-0,290	0,330	-0,253	-0,273	0,373	0,346	-0,254	0,375
2-2	-0,031	0,073	0,063	0,082	0,244	0,203	0,144	0,338
3-3	-0,286	-0,248	0,336	-0,295	0,377	-0,285	0,342	0,362
4-4	-0,178	-0,177	-0,238	0,322	-0,236	0,337	0,315	0,322
5-5	-0,033	0,066	0,076	0,088	0,166	0,199	0,184	0,287
6-6	-0,109	-0,023	-0,030	-0,065	0,049	-0,005	0,003	0,064
7-7	-0,021	-0,022	0,039	0,114	0,028	0,136	0,198	0,186
7a-7a	-0,011	0,028	0,032	0,039	0,037	0,093	0,078	0,089
3a-3a	-0,042	-0,028	-0,025	-0,013	-0,037	-0,023	-0,104	-0,023
1-2	0,657	0,497	0,760	0,696	0,603	0,537	0,765	0,616
2-3	0,651	0,756	0,490	0,595	0,596	0,706	0,481	0,573
3-3a	0,593	0,526	0,450	0,664	0,422	0,581	0,487	0,443
3a-4	0,536	0,545	0,561	0,403	0,565	0,421	0,424	0,428
4-5	0,717	0,717	0,698	0,498	0,700	0,520	0,500	0,516
5-6	0,597	0,609	0,616	0,724	0,598	0,694	0,703	0,655
6-7a	0,717	0,717	0,720	0,622	0,726	0,655	0,655	0,688
7-7	0,555	0,579	0,557	0,624	0,568	0,606	0,565	0,548
7a-1	0,582	0,430	0,520	0,556	0,408	0,423	0,517	0,404
7a-9	0,453	0,552	0,551	0,401	0,587	0,538	0,553	0,632

<i>i-k</i>	Imidazo[4,5-c]pyridines							
	Ib	IIb	IIIb	IVb	Vb	VIb	VIIb	VIIIb
1-1	-0,287	0,333	-0,253	-0,250	0,370	0,354	-0,257	0,369
2-2	-0,038	0,062	0,074	0,079	0,254	0,166	0,207	0,369
3-3	-0,284	-0,248	0,333	-0,271	0,376	-0,264	0,337	0,363
4-4	0,028	0,090	0,028	0,134	0,088	0,217	0,147	0,220
5-5	-0,227	-0,189	-0,184	0,320	-0,152	0,361	0,351	0,323
6-6	-0,055	0,048	0,040	-0,014	0,131	0,111	0,114	0,221
7-7	-0,053	-0,070	-0,010	-0,004	-0,027	-0,021	0,023	0,011
7a-7a	-0,035	-0,003	0,002	0,027	-0,003	0,081	0,096	0,093
3a-3a	-0,049	-0,024	-0,029	-0,021	-0,037	-0,053	-0,017	-0,028
1-2	0,649	0,490	0,758	0,613	0,596	0,495	0,722	0,587
2-3	0,660	0,761	0,501	0,690	0,608	0,760	0,525	0,611
3-3a	0,583	0,521	0,431	0,554	0,405	0,513	0,416	0,386
3a-4	0,544	0,546	0,573	0,655	0,570	0,610	0,662	0,632
4-5	0,710	0,711	0,703	0,504	0,707	0,540	0,518	0,543
5-6	0,580	0,607	0,610	0,423	0,619	0,472	0,470	0,504
6-7	0,733	0,717	0,720	0,793	0,699	0,760	0,763	0,717
7-7a	0,530	0,567	0,549	0,496	0,587	0,546	0,524	0,583
7a-1	0,595	0,442	0,526	0,652	0,409	0,479	0,566	0,424
7a-9	0,468	0,562	0,560	0,389	0,585	0,517	0,501	0,568

they have similar basicity. At the same time the electron density at these nitrogen atoms is considerably greater than that at the nitrogen atoms of the pyridine units. It follows that the formation of the azulene-like forms IVa and IVb from the anions Ia and Ib is unlikely. Since the values of pK_a are linked to the residual π -electron density at the reaction site [11-13], structures IVa and IVb should provide a negligible contribution to the tautomeric equilibrium in imidazopyridines and this is in agreement with experimental results [14-16] and calculations of the resonance energy. The calculated π -electron energies for the imidazo[4,5-b]pyridines IIa, IIIa, and IVa are 49.9, 50.0 and 49.4 eV and for the imidazo[4,5-c]pyridines IIb, IIIb and IVb are 49.9, 49.9 and 49.2 eV respectively.

TABLE 2. Diamagnetic Permeabilities (χ^I and χ_m), Induced π -Electron Ring Current (I_1) and Position of the Longwave Transition (λ) for the Imidazopyridines I-VIII



Compound	Charge	X	Y	A	B	χ^I	$\chi_m \cdot 10^6$, cm ³ /mole	I_1	I_2	$\lambda_{\text{calc.}}$, nm	$\lambda_{\text{exp.}}$, nm [17, 20]
Imidazo[4,5-b]pyridines											
Ia	-1	N	N	N	CH	1,708	63,14	1,095	1,111	298	
IIa	0	NH	N	N	CH	1,676	74,36	0,886	1,089	287	
IIIa	0	N	NH	N	CH	1,663	74,23	0,886	1,077	286	282; 288
IVa	0	N	N	NH	CH	1,537	72,91	0,886	0,950	364	
Va	+1	NH	NH	N	CH	1,568	84,79	0,784	1,049	286	282
VIa	+1	NH	N	NH	CH	1,408	83,12	0,794	0,882	302	
VIIa	+1	N	NH	NH	CH	1,413	83,18	0,808	0,878	298	
VIIIa	+2	NH	NH	NH	CH	1,300	93,55	0,704	0,834	287	
Imidazo[4,5-c]pyridines											
Ib	-1	N	N	CH	N	1,821	67,32	1,111	1,086	295	
IIb	0	NH	N	CH	N	1,667	74,27	0,895	1,074	279	272
IIIb	0	N	NH	CH	N	1,680	74,40	0,896	1,087	283	284; 286
IVb	0	N	N	CH	NH	1,546	73,01	0,924	0,935	362	
Vb	+1	NH	NH	CH	N	1,587	84,98	0,776	1,073	290	300
VIb	+1	NH	N	CH	NH	1,461	83,67	0,802	0,930	293	
VIIb	+1	N	NH	CH	NH	1,430	83,35	0,770	0,920	294	292; 294
VIIIb	+2	NH	NH	CH	NH	1,345	94,02	0,647	0,917	284	278

It follows from the calculated residual π -electron charges on the nitrogen atoms (see Table 2) that the first proton should be added to the imidazole ring of the more stable tautomeric forms IIa and IIIa to give the cation Va. This agrees with the calculated resonance energies for the monocations Va, VIa and VIIa: 57.3, 56.4 and 57.2 eV respectively. For the imidazo[4,5-c]pyridines IIb and IIIb calculations indicate that the nitrogen atoms with the maximum electron density are in the imidazole unit and consequently addition of a proton should be to the imidazole ring which agrees with calculations of the π -electron energies of the monocations Vb-VIIb (57.2, 55.8 and 56.0 eV) which is lowest for structure Vb. In this connection, it has been shown [17] that in aqueous sulfuric acid 1- and 3-imidazo[4,5-c]pyridines gave monocations of types IVb and VIIb, but not VIb. This phenomenon may be ascribed to a medium effect which was not taken into account in the calculations.

Table 1 contains, in addition to the residual π -electron charges, values for the bond orders, which characterize their strength, and the free valence indexes, which are indexes of reactivity in free radical substitution reactions. For example, the free valency indexes calculated for the most stable monocation of the imidazo[4,5-b]pyridine Va ($F_2 = 0.534$, $F_7 = 0.438$, $F_5 = 0.434$) show that radical methylation in weakly acidic media should occur at position 2 which is in agreement with experiment [18].

As for radical methylation of imidazo[4,5-c]pyridine in acid solutions, N-methylimidazo[4,5-c]pyridine occurs as a mixture of mono- and dicitations in 10% aqueous sulfuric acid [17] so it is necessary to estimate the reactivity of both these cations.

The free valency indexes of cations VIb and VIIb are respectively $F_2 = 0.553$, $F_4 = 0.581$, $F_6 = 0.500$ and $F_2 = 0.485$, $F_4 = 0.553$, $F_6 = 0.500$, and for the dication VIIb $F_2 = 0.534$, $F_4 = 0.556$, $F_6 = 0.511$, i.e., the radical methylation reaction should occur preferentially at position 4, which is in agreement with experiment [19]. According to the calculations, the second methyl group should be inserted in position 2 for the cation VIIb and at position 6 for the monocations VIb and

TABLE 3. ^1H NMR Spectra of Imidazopyridines, δ , ppm

Compound	Solvent*	$\text{H}_{(2)}$	$\text{H}_{(4)} / \text{H}_{(5)}$	$\text{H}_{(6)}$	$\text{H}_{(7)}$
1H-Imidazo[4,5-b]pyridine (IIa)		8.42	8.56	7.18	7.46
3H-Imidazo[4,5-b]pyridine (IIIa)		8.40	8.57	7.15	7.85
4H-Imidazo[4,5-b]pyridine (IVa)		9.33	7.51	7.18	7.89
Experimental [28]	a	8.34	8.47	7.29	8.16
[28]	b	8.46	8.60	7.25	8.07
[28]	c	8.50	8.62	7.32	7.93
[14]	d	8.01	7.93	6.68	7.51
1-CH ₃ -Imidazo[4,5-b]pyridine		8.40	8.63	7.25	7.46
Experimental [28]	a	8.07	8.56	7.23	7.72
	b	8.34	8.45	7.23	7.93
	c	8.47	8.46	7.28	8.03
3-CH ₃ -Imidazo[4,5-b]pyridine		8.34	8.63	7.24	7.94
Experimental [28]	a	8.05	8.40	7.21	8.06
	b	8.38	8.32	7.25	8.05
	c	8.47	8.42	7.31	8.13
4-CH ₃ -Imidazo[4,5-b]pyridine		8.75	7.39	7.43	8.24
Experimental [28]	a	8.43	7.79	7.08	8.24
	b	8.26	8.15	7.18	8.15 8.40
	c	8.30	8.40	7.23	8.22
Imidazo[4,5-b]pyridinium cations					
Va		8.40	9.34	7.94	8.24
VIIa		9.19	8.29	7.95	8.30
VIIa		8.31	7.96	8.70	9.10
Experimental [10]	d	8.92	8.46	7.60	8.39
Imidazo[4,5-b]pyridinium dication (VIIIa)		9.12	9.08	8.70	8.97
Experimental †	e	9.33	9.00	8.07	9.00
1-CH ₃ -Imidazo[4,5-b]pyridinium dication		9.42	9.06	8.71	8.88
Experimental [28]	e	9.15	8.94	8.01	8.81
3-CH ₃ -Imidazo[4,5-b]pyridinium dication		9.30	9.08	8.74	9.02
Experimental [28]	e	9.42	9.06	7.96	8.68
4-CH ₃ -Imidazo[4,5-b]pyridinium dication		9.34	7.49	7.35	8.21
Experimental [28]	e	9.11	8.72	7.98	8.89
1H-Imidazo[4,5-c]pyridine (IIa)		8.44	8.82	8.51	7.77
3H-Imidazo[4,5-c]pyridine (IIIb)		8.40	9.20	8.59	7.38
5H-Imidazo[4,5-c]pyridine (IVc)		9.35	8.12	7.32	7.72
Experimental [10]	d	7.96	8.37	8.85	7.14
Imidazo[4,5-c]pyridinium cations					
Vb		8.44	9.62	9.31	8.18
VIIb		9.13	8.52	8.23	8.20
VIIb		9.18	9.56	8.19	8.53
Experimental [10]	d	8.67	9.13	8.43	8.04
1-CH ₃ -Imidazo[4,5-c]pyridinium dication		9.31	9.42	9.12	8.95
Experimental *	f	9.50	9.80	8.90	8.43
3-CH ₃ -Imidazo[4,5-c]pyridinium dication		9.41	9.27	9.09	9.05
Experimental *	f	9.84	9.81	9.02	8.68

*a) CDCl₃, b) acetone-D₆, c) DMSO-D₆, d) D₂O, e) CF₃COOH, f) 30% D₂SO₄ in D₂O.

†Data recorded on a Tesla-467C (67 MHz) with TMS as internal standard for CF₃COOH and tert-butanol as internal standard for 30% D₂SO₄ in D₂O.

VIIb. Experimental results show substitution of a second methyl group at position 2 which may indicate the greater activity of the dication and agrees with predictions of the nucleophilic nature of the methyl radical [20]. Taking the effect of the N-methyl group into account (by use of perturbation theory [10]) did not change the conclusions.

It is not difficult to calculate the dipole moments of these systems on the basis of the calculated charges. As in previous work [6, 21, 22] the influence of the σ -framework, which contributes the calculated moments via the unshared pairs of electrons and the moments of the C–H and N–H bonds, is described with the aid of additive parameters. The additive parameters which characterize the dipole moment arising in the σ -framework on substituting a CH unit by a nitrogen atom of pyridine or imidazole type are $\vec{\mu}_N^g = -1.37$ and $\vec{\mu}_{NH}^g = 0.6$ D and are directed along the bisector of the angle formed by the C–N bonds. The calculated dipole moments for compounds IIa-IVa are 4.90, 1.43 and 6.83 D and for compounds IIb-IVb are 6.51, 5.68 and 8.02 D respectively. As expected the azulene-like structures IV have the largest dipole moments. If the low stability and small contribution of this structure to the tautomeric equilibrium are taken into account, it would be expected that the dipole moment of imidazo[4,5-b]pyridine should lie in the range 1.4–5.0 D, whereas that of imidazo[4,5-c]pyridine should be about 6 D. The experimental value of the dipole moment of imidazo[4,5-b]pyridine in benzene is 1.99 D [16]. Using these results and the calculated values of the dipole moments for the tautomers IIa and IIIa, it is not difficult to estimate the percentage composition of tautomers IIa and IIIa in the mixture, using the additivity of the squares of the dipole moments of the individual molecules which arises from the additivity of polarization [13]. The calculation gives a 91% content of tautomer IIIa which agrees with other data [14–16] and paper [24] in which the value is 98%. It is to be expected that our results would give only a qualitative estimate of the tautomeric equilibrium since, for example, solvation effects were not taken into account in the calculations. Contributions to the π -electron ring current in the five and six membered rings, I_1 and I_2 respectively, calculated by a previously described method [5] are cited in Table 2 (relative to the ring current of benzene, $I(C_6H_6) = 1$). Comparing the current distribution with the π -electron ring currents of imidazole ($I = 0.772$), its anion ($I = 0.795$), pyridine ($I = 1.01$), its cation ($I = 0.835$) [8], and benzimidazole ($I_1 = 0.707$ and $I_2 = 1.060$) [5], it is seen that annelation with a pyridine leads to an increase in the ring current in both the imidazole and pyridine parts of the molecule. In the azulene-like structures IVa and IVb the ring currents are comparable with the ring currents in the pyridine cation and the imidazole anion. Note the uniform value of the current in the five membered ring of the imidazo[4,5-b]pyridines IIa-IVa in contrast to the imidazo[4,5-c]pyridines IIb-IVb where compound IVb has $I_1 = 0.924$, considerably greater than for the other imidazopyridines, which indicates aromaticity of the imidazole ring in this azulene-like structure. It should be emphasized that while substitution of carbon atom by a pyridine nitrogen in indole decreased the π -electron ring current in both the heterocycle and the benzene ring [5], transition from benzimidazole to imidazopyridine had the reverse effect. Going to the cations VIIa, VIIa, Vb-VIIb and the dication VIIIa and VIIIb caused a decrease in the π -electron ring current in both the five and six membered rings.

The relative π -electron contribution to the diamagnetic permeability, $\chi^1 = \chi^\pi / \chi_{C_6H_6}^\pi$, calculated from the ring currents, is one of the indexes of aromaticity (see, e.g., [25, 26]). The average values of the molar diamagnetic permeability tensor χ_m calculated according to [5] are cited in Table 2. It should be noted that there are no experimental values yet for χ_m for the compounds studied here. A scale of aromaticity for the compounds studied can be constructed for the compounds studied and, by comparing these values with published data [5, 6], it is not difficult to determine their positions among a series of similar compounds. All of the imidazo[4,5-b]pyridines (IIa-IVa) and imidazo[4,5-c]pyridines (IIb-IVb) are more aromatic than benzimidazole ($\chi^1 = 1.529$), comparable in aromaticity to azaindole ($\chi^1 = 1.60$ –1.62) and indole ($\chi^1 = 1.619$) and less aromatic than thienopyridines ($\chi^1 = 1.78$). It is also seen that the imidazo[4,5-c]pyridines are more aromatic than the corresponding imidazo[4,5-b]pyridines, the azulene-like structures having the lowest aromaticity. Protonation decreases and deprotonation increases the diamagnetic permeability and consequently the aromaticity of the systems. We emphasize that while the diamagnetic permeability characterizes the aromaticity as a whole, the π -electron ring current characterizes the aromaticity of each ring in the molecule and the scale of overall aromaticity may not coincide with the scale of aromaticity of rings taken separately, for example the imidazole ring. For example, the dication VIIb is more aromatic than the dication VIIIa, while the imidazole ring in the latter is more aromatic than that in the former.

It is possible to calculate proton chemical shifts, cited in Table 3, on the basis of the induced π -electron currents (Table 2) and the residual π -electron charges (Table 1) (see [5, 6, 21]). The contribution of the σ -framework to the magnetic shielding is described via an additivity scheme [5, 6, 21, 22]. The contribution of N-methyl groups to the proton magnetic shielding was calculated via the bonding variant of the polyparametric perturbation theory as described in [21] (see also [6]. Table 3 shows that calculation of the proton chemical shifts gave a qualitatively correct picture on the whole of the experimental spectra [14, 28]. Comparison again confirms that imidazo[4,5-b]pyridine exists predominantly in the IIIa form. An analogous picture was observed for imidazo[4,5-c]pyridine.

Similar results were obtained in calculating ^{13}C chemical shifts. For example, the following values were obtained for the tautomers of imidazo[4,5-c]pyridine: IIb 147.7 ($\text{C}_{(2)}$); 150.9 ($\text{C}_{(4)}$); 144.4 ($\text{C}_{(6)}$); 116.2 ($\text{C}_{(7)}$); 131.4 ($\text{C}_{(8)}$); 139.2 ($\text{C}_{(9)}$); IIIb 149.5 ($\text{C}_{(2)}$), 141.8 ($\text{C}_{(4)}$), 143.2 ($\text{C}_{(6)}$), 124.8 ($\text{C}_{(7)}$), 142.9 ($\text{C}_{(8)}$), 127.5 ($\text{C}_{(9)}$); IVb 160.5 ($\text{C}_{(2)}$), 147.3 ($\text{C}_{(4)}$), 125.1

(C₍₆₎), 126.4 (C₍₇₎), 146.9 (C₍₈₎), 140.0 (C₍₉₎) ppm. The experimental values for the chemical shifts of imidazo[4,5-c]pyridine [14] are: 148.1 (C₍₂₎), 140.8 (C₍₄₎), 142.8 (C₍₆₎), 112.5 (C₍₇₎), 144.0 (C₍₈₎), 139.1 (C₍₉₎) ppm.

The following calculated ¹⁵N chemical shifts were obtained for 1H-imidazo[4,5-b]pyridine (IIa) using a known method [6, 27]: 266.0 (N₍₁₎), 122.3 (N₍₃₎), 64.3 (N₍₄₎), for the 3H tautomer IIIa 126.3 (N₍₁₎), 260.9 (N₍₃₎), 113.6 (N₍₄₎), and for the 4H tautomer IVa 142.6 (N₍₁₎), 160.0 (N₍₃₎), 272.3 (N₍₄₎) ppm. The experimental results for this compound at pH 5.7 are: 175.7 (N₍₁₎), 202.3 (N₍₃₎), 113.0 (N₍₄₎) ppm. Comparison of the experimental data with the calculated results do not oppose the view noted above that imidazo[4,5-b]pyridine exists primarily in the 3H form.

The ratio of the tautomers can be determined from the ¹⁵N chemical shifts. The 4H form can be excluded since the experimental value for the N₍₄₎ chemical shift is markedly different from the calculated value. Moreover, calculation of the resonance energy of the tautomers (see above) showed that tautomer IVa is 12.2 kcal/mol less stable than tautomer IIIa whereas tautomer IIa is only 2.7 kcal/mol less stable. These data explain the rearrangement of 4-benzylimidazo[4,5-b]pyridine into a mixture of 1- and 3-benzyl derivatives [29]. Calculation of the ratio of the 3H- and 1H-tautomers from ¹⁵N NMR data using a standard method gave a value of 58-65% for the 3H form IIIa under the experimental conditions described [14]. This agrees qualitatively (since the measurements were made under different experimental conditions) with the results from a study of dipole moments [16].

As for imidazo[4,5-c]pyridine, calculation of the ¹⁵N chemical shifts gave the following values: for the 1H form IIb 264.0 (N₍₁₎), 122.0 (N₍₃₎), 73.6 (N₍₅₎), for the 3H tautomer IIIb 126.0 (N₍₁₎), 263.5 (N₍₃₎), 70.2 (N₍₅₎); and for the 5H form IVb 123.6 (N₍₁₎), 140.5 (N₍₃₎), 274.2 (N₍₅₎) ppm. Comparison with experiment (168.7 (N₍₁₎), 205.2 (N₍₃₎), 126.1 (N₍₅₎) ppm [14]) shows that at pH 6.5 the 3H form IIIb predominates with a negligible amount of the 1H form IIb. In contrast the calculated resonance energies of the two forms are very similar ($\Delta E^{\text{res}} = 0.31$ kcal/mol). As in the case of imidazo[4,5-b]pyridine, the least stable tautomer (by 15.6 kcal/mol) is the azulene-like structure IVb which is even less stable than 4H-imidazo[4,5-b]pyridine. This may probably explain the observation that 5-methyl-5H-imidazo[4,5-c]pyridine isomerizes in vacuum, whereas 4-methyl-4H-imidazo[4,5-b]pyridine, unlike the 4-benzyl derivative, remains unchanged under these conditions [29]. The large chemical shift for N₍₅₎ may be ascribed either to partial protonation of the base at this nitrogen in water [17] or to formation of a dimer, and also the possibility of the 5H tautomer IVb as an impurity. Our tautomer ratios agree with those of Lindon et al. [14] obtained by a comparison of ¹⁵N NMR data for imidazopyridines and N-methyl derivatives of purine.

The energies of the lowest singlet-singlet transitions, determined as eigen functions of the stability matrix for the Hartree-Fock ground state [30], are cited in Table 2 where they are compared with experimental results [17, 21]. The longwave transitions are those of the N-methyl derivatives with structures analogous to compounds I-VIII. Unfortunately UV spectroscopic data are absent for 4-methylimidazo[4,5-b]pyridine and 5-methylimidazo[4,5-c]pyridine (the analogs of tautomers IVa and IVb) as a result of their high hydrophilicity. Clearly there is a reasonable agreement with experiment. The considerable bathochromic shift (~80 nm) for the azulene-like forms IVa and IVb relative to the other tautomers should be noted. Protonation led to negligible shifts in the longwave absorption bands. This phenomenon was noted in an experimental study [17] of the position of protonation of imidazo[4,5-c]pyridine.

In conclusion we note that the excellent agreement between the calculated and experimental physico-chemical characteristics of imidazo[4,5-b]- and imidazo[4,5-c]pyridines indicates the reliability of the currents and charges obtained which underlie the calculations. It also permits the explanation of chemical reactions of the systems studied.

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