

Quantum chemical studies on acidity-basicity behaviors of some bipyridine derivatives

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Abstract

The protonation of six isomeric forms of bipyridine has been investigated by means of different quantum chemical methods (i.e. semi-empirical (PM5), DFT (B3LYP/6-31G(d)) and *ab initio* (HF/6-31G(d))). It is concluded that 2,2'-bipyridine exists as *transoid* isomer, 2,3'-bipyridine as *cisoid* isomer and 3,3'-bipyridine coexist in equal amount of *cisoid* and *transoid* isomeric forms.

Keywords: Bipyridines, acidity constants, nucleophilicity, proton affinities, substituent constant, isomers

Introduction

Many procedures were reported for the synthesis of bipyridine derivatives in the past years. It seems that the substituted bipyridine derivatives have been prepared mostly by reactions of Grignard reagents or organo-lithium derivatives with various sulfur and phosphor containing compounds respectively.¹⁻⁹

Studies on structure of bipyridine derivatives are also indicate an enormous amount of research affords. A low temperature X-ray structure,¹⁰ the theoretical calculations¹¹⁻¹⁵ and spectroscopic studies of bipyridine derivatives have been reported in the literature.¹⁶

Chemical reaction studies of the various bipyridines are numerous. Among the other isomers the chemistry of the 2,2'-bipyridine is the most studied because of its ability to complex with metals.¹⁷⁻²¹ This compound usually acts as a chelating ligand.²²⁻²⁶

Much of the chemistry carried out on the bipyridines has been for their incorporation as structural motifs in large molecules and supramolecular species.²⁷⁻³³

Following our previous work on alkyl and halogen substituted pyridines³⁴⁻³⁹ and bipyrazoles,⁴⁰ we now are reporting on the semi empirical (PM5) and *ab initio* (HF and DFT) calculated structural and thermodynamic parameters of six isomeric bipyridine derivatives (Scheme 1). Any possible parallelism with reported and available experimental data were searched. The parallelism and discrepancies between the experimental and computed data were

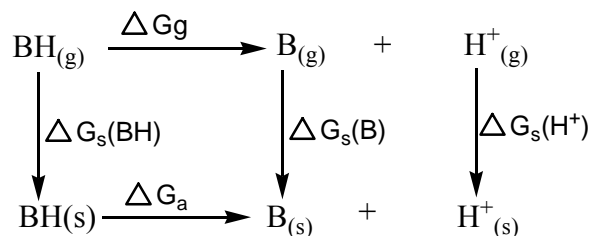
attempted to be interpreted.

Computational methods

Theoretical calculations were carried out at the restricted Hartre-Fock level (RHF) using PM5, method in the MOPAC 2002 program^{41a} implemented in an Intel Pentium IV computer. All the structures were optimized to a gradient norm of and 0.1 – 1.0 in the aqueous phase, using the eigenvector method following (EF). The initial estimates of the geometry of all the structures were obtained by a molecular mechanics program of CS Chem. Office pro for Windows⁴², followed by full optimization of all geometrical variables (bond lengths, bond angles and dihedral angles), without any symmetry constraint, using the semi-empirical PM5 quantum chemical methods in the MOPAC 2002 program.

Nowadays both microscopic and macroscopic theoretical methods are available for the estimation of solvation free energies. Therefore it is possible, in principle, to determine theoretical relative or absolute acidity constants, pK_a values, the thermodynamic cycle using the Equation 1.

Scheme 1 explains the interrelationship between the thermodynamic parameters of gas and solution phases.



Scheme 1. Interrelationship between the gas phase and solution thermodynamic parameters.

The acidity constant, pK_a , can be computed by using Equation 1 and Equation 2. The Equation 2 is an rearranged form of Equation 1.

$$\Delta G = -RT \ln K_a \quad (1)$$

$$pK_a = \Delta G_a / 2.303RT \quad (2)$$

The *ab initio* calculation of the absolute pK_a values can be made by using Equation 3 in which ΔG_g and $\Delta G_a = \Delta G_s(\text{B}) - \Delta G_s(\text{BH}) + \Delta G_s(\text{H}^+)$ are the gas phase and solvation free energies of the ionization and ΔG_s 's are solvation free energies respectively.^{43,44}

$$pK_a = [\Delta G_g + \Delta G_a] / 2.303 RT \quad (3)$$

In the present work *ab initio* Hartree-Fock (HF) and density functional geometry (DFT) optimizations were performed using the Gaussian 03 program.^{41b} The calculation of solvation free energies was carried out using at HF/6-31G(d) and B3LYP/6-31G(d) respectively. The value of $\Delta G_s(H^+)$ -271.2 kcal mol⁻¹ was used as suggested in the literature.⁴⁴

Result and Discussion

The computed physical and thermodynamic parameters for studied compounds were depicted in Tables 1-3. We have attempted to evaluate the obtained results as follows:

Acidity- basicity

The acidity of a given base, B, for the protonation reaction (Equation 4) can be calculated using the Equation 5, where ΔG is the standard free energy.⁴⁵



$$\delta\Delta G_{(BH^+)} = [\Delta G_{(B)} + \Delta G_{(AH^+)}] - [\Delta G_{(BH^+)} + \Delta G_{(A)}] \quad (5)$$

In Equation 1, B and BH⁺ are neutral and protonated species of base B, and A and AH⁺ are H₂O and H₃O⁺ respectively. The computed thermodynamic data were used in predicting the pK_a values of various species, using Equation 6 in which the $\delta\Delta G_{(BH^+)}$ is the standard free energy change for protonation reaction (Equation 4, Table 4 and 5).

$$pK_{a(BH^+)} = \delta\Delta G_{(BH^+)} / 2.303RT \quad (6)$$

Table 1. Aqueous phase PM5 calculated thermodynamic data for studied molecules for *cisoid* and *transoid* forms (ϵ : 78.4)

Compo und	ΔH_f (kcal/mol)	ΔS (cal/molK)	ΔG_f (kcal/mol) ^a	Compo und	ΔH_f (kcal/mol)	ΔS (cal/molK)	ΔG_f (kcal/mol) ^a
1s	51.77	88.55	25.38	1t	51.67	88.39	25.33
1sN'p	153.33	90.40	126.39	1tN'p	155.15	90.60	128.15
1sNp	153.29	90.37	126.36	1tNp	155.14	90.33	128.22
1sN''p	260.144	95.79	231.59	1tN''p	263.05	89.78	236.30
2s	50.19	89.80	23.43	2t	50.37	89.87	23.59
2sN'p	151.57	90.56	124.58	2tN'p	151.84	90.32	124.92
2sNp	153.71	90.89	126.62	2tNp	153.43	90.60	126.43
2sN''p	257.57	90.82	230.50	2tN''p	257.60	90.80	230.54

Table 1. Continued

Compo und	ΔH_f (kcal/mol)	ΔS (cal/molK)	ΔG_f (kcal/mol) ^a	Compo und	ΔH_f (kcal/mol)	ΔS (cal/molK)	ΔG_f (kcal/mol) ^a
3	50.81	90.05	23.98				
3N'p	151.23	90.41	124.29				
3Np	154.49	90.43	127.54				
3N''p	253.24	96.32	224.53				
4s	49.78	88.68	23.35	4t	49.79	88.70	23.36
4sN'p	150.92	90.35	124.00	4tN'p	150.90	90.36	123.97
4sNp	151.00	90.27	124.10	4tNp	150.91	90.34	123.99
4sN''p	253.55	89.47	226.88	4tN''p	253.54	90.08	226.69
5	49.64	89.97	22.83				
5N'p	149.68	90.55	122.70				
5Np	151.30	90.45	124.35				
5N''p	252.70	90.85	225.62				
6	50.07	87.26	24.07				
6N'p	150.57	89.15	124.00				
6Np	150.59	89.17	124.02				
6N''p	252.30	88.29	225.99				

^a from $\Delta G_f = \Delta H_f - T \Delta S$ **Pyridine (PM5)** : ΔH_f (kcal/mol) = 22.99, ΔS (cal/molK) = 68.10, ΔG_f (kcal/mol) = 2.70.**Pyridinium (PM5)** : ΔH_f (kcal/mol) = 121.92, ΔS (cal/molK) = 68.67, ΔG_f (kcal/mol) = 101.46.**H₂O (PM5)** : ΔH_f (kcal/mol) = -59.47, ΔS (cal/molK) = 44.99, ΔG_f (kcal/mol) = -72.88.**H₃O⁺ (PM5)** : ΔH_f (kcal/mol) = 46.51, ΔS (cal/molK) = 45.88, ΔG_f (kcal/mol) = 32.84.**Table 2.** Aqueous phase *ab initio* calculated thermal and solvation free energies, investigated compounds at 298K

Comp ound	Thermal free energy Gg kcal/mol	Solvation free energy G _{s(B)} kcal/mol	Total solvation free energy ^a $\Delta G_{s(B)}$ kcal/mol	Thermal free energy Gg(BH ⁺) kcal/mol	Solvation free energy G _{s(BH⁺)} kcal/mol	Total solvation free energy ^b $\Delta G_{s(BH^+)}$ kcal/mol
HF/6-31G(d)						
1s	- 308884.02	- 308893.22	-9.20			
1sNp				-309135.34	-309181.87	-46.53
1sN'p				-309135.34	-309181.87	-46.53

Table 2. Continued

Comp ound	Thermal Free Energy Gg kcal/mol	Solvation Free Energy G _{s(B)} kcal/mol	Total Solvation Free Energy ^a ΔG _{s(B)} kcal/mol	Thermal Free Energy Gg _(BH⁺) kcal/mol	Solvation Free Energy G _{s(BH⁺)} kcal/mol	Total Solvation Free Energy ^b ΔG _{s(BH⁺)} kcal/mol
HF/6-31G(d)						
1t	- 308890.59	- 308895.81	-5.21			
1tNp				-309128.56	-309179.72	-51.16
1tN'p				-309128.56	-309184.42	-55.85
2s	- 308886.42	- 308893.93	-7.51			
2sNp				-309123.87	-309178.15	-54.27
2sN'p				-309127.66	-309179.22	-51.55
2t	- 308887.06	- 308893.84	-6.78			
2tNp				-309123.54	-309177.55	-54.01
2tN'p				-309126.25	-309178.81	-52.55
3	- 308886.77	- 308898.03	-11.26			
3Np				-309121.38	-309177.46	-56.07
3N'p				-309128.99	-309179.92	-50.93
4s	- 308884.51	- 308900.95	-16.44			
4sNp				-309119.88	-309176.90	-57.02
4sN'p				-309119.88	-309181.47	-61.59
4t	- 308884.65	- 308901.09	-16.44			
4tNp				-309119.67	-309181.09	-61.42
4tN'p				-309119.67	-309181.09	-61.42
HF/6-31G(d)						
5	- 308885.03	- 308893.12	-8.09			
5Np				-309118.31	-309176.60	-58.28
5N'p				-309123.12	-309178.01	-54.89

Table 2. Continued

Comp ound	Thermal Free Energy G _g kcal/mol	Solvation Free Energy G _{s(B)} kcal/mol	Total Solvation Free Energy ^a ΔG _{s(B)} kcal/mol	Thermal Free Energy G _{g(BH⁺)} kcal/mol	Solvation Free Energy G _{s(BH⁺)} kcal/mol	Total Solvation Free Energy ^b ΔG _{s(BH⁺)} kcal/mol
	HF/6-31G(d)					
6	- 308885.17	- 308893.62	-8.45			
6Np				-309120.48	-309177.41	-56.92
6N'p				-309120.48	-309177.41	-56.92

$$^a\Delta G_{s(B)} = G_{s(B)} - G_g \quad ^b\Delta G_{s(BH^+)} = G_{s(BH^+)} - G_{g(BH^+)}$$

Table 3. Aqueous phase *ab initio* calculated thermal and solvation free energies, investigated compounds at 298K

Comp ound	Thermal Free Energy G _g kcal/mol	Solvation Free Energy ^a ΔG _{s(B)} kcal/mol	Total Solvation Free Energy ^a ΔG _{s(B)} kcal/mol	Thermal Free Energy G _{g(BH⁺)} kcal/mol	Solvation Free Energy G _{s(BH⁺)} kcal/mol	Total Solvation Free Energy ^b ΔG _{s(BH⁺)} kcal/mol
	B3LYP/6-31G(d)					
1s	-310853.47	-310868.95	-15.48			
1sNp				-311105.14	-311154.23	-49.08
1sN'p				-311105.14	-311154.23	-49.08
1t	-310860.44	-310866.68	-6.24			
1tNp				-311097.79	-311150.30	-52.51
1tN'p				-311097.79	-311149.05	-51.26
2s	-310856.23	-310864.90	-8.67			
2sNp				-311092.66	-311146.05	-53.39
2sN'p				-311097.21	-311150.72	-53.50
2t	-310856.93	-310865.66	-8.73			
2tNp				-311092.27	-311145.57	-53.30
2tN'p				-311095.65	-311148.90	-53.24

Table 3. Continued

Comp ound	Thermal Free Energy Gg kcal/mol	Solvation Free Energy ^a ΔG _{s(B)} kcal/mol	Total Solvation Free Energy ^a ΔG _{s(B)} kcal/mol	Thermal Free Energy Gg(BH ⁺) kcal/mol	Solvation Free Energy G _{s(BH⁺)} kcal/mol	Total Solvation Free Energy ^b ΔG _{s(BH⁺)} kcal/mol
B3LYP/6-31G(d)						
3	-310856.78	-310868.51	-11.72			
3Np				-311090.43	-311149.70	-59.27
3N'p				-311098.66	-311149.39	-50.72
4s	-310854.58	-310869.79	-15.21			
4sNp				-311089.32	-311144.54	-55.22
4sN'p				-311089.32	-311144.54	-55.22
4t	-310854.72	-310870.24	-15.52			
4tNp				-311089.09	-311148.73	-59.64
4tN'p				-311089.09	-311148.72	-59.64
5	-310854.87	-310859.15	-4.28			
5Np				-311087.55	-311141.45	-53.89
5N'p				-311092.12	-311143.24	-51.11
6	-310854.93	-310871.68	-16.75			
6Np				-311089.76	-311148.65	-58.88
6N'p				-311089.76	-311148.65	-58.88

$$^a\Delta G_{s(B)} = G_{s(B)} - G_g \quad ^b\Delta G_{s(BH^+)} = G_{s(BH^+)} - G_g(BH^+)$$

Table 4. Aqueous phase PM5 and *ab initio* calculated pK_a values for the investigated molecules

Protonation pattern	ΔΔG _{R(BH⁺)} (kcal/mol) ^a	pK _a ^b	pK _a ^c	pK _a ^d	pK _a (exp.) ^e
1s↔1sN'p	4.71	3.45	12.80	10.32	4.44
1s↔1sNp	4.74	3.48	12.80	10.32	
2s↔2sN'p	4.57	3.35	10.33	10.71	4.42
2s↔2sNp	2.52	1.85	9.54	7.30	
3↔3N'p	5.41	3.97	7.84	7.10	4.77
3↔3Np	2.15	1.58	6.03	7.33	
4s↔4sN'p	5.08	3.72	6.83	2.60	4.60
4s↔4sNp	4.97	3.65	3.48	2.60	
5↔5N'p	5.85	4.29	10.04	9.45	4.85

Table 4. Continued

Protonation pattern	$\delta\Delta G_{f(BH^+)}^a$ (kcal/mol) ^a	pK _a ^b	pK _a ^c	pK _a ^d	pK _a (exp.) ^e
5↔5Np	4.20	3.08	9.00	8.13	
6↔6N'p	5.78	4.24	9.23	4.22	4.82
6↔6Np	5.77	4.23	9.23	4.22	

^a $\delta\Delta G_{f(BH^+)} = [\Delta G_{f(B)} + \Delta G_{f(H_3O^+)}] - [\Delta G_{f(BH^+)} + \Delta G_{f(H_2O)}]$. ^b $pK_a = \delta\Delta G_{f(BH^+)} / (2.303RT)$. ^c pK_a calculated HF /6-31G(d) *cisoid* and *transoid* form. ^d pK_a calculated B3LYP /6-31G(d) *cisoid* and *transoid* form. ^e pK_a (expt.) were taken from ref. 45, PM5 Calculated pK_a value for pyridine is 5.10

Table 5. Aqueous phase PM5 and *ab initio* calculated pK_a values for the investigated molecules

Protonation pattern	$\delta\Delta G_{f(BH^+)}^a$ (kcal/mol) ^a	pK _a ^b	pK _a ^c	pK _a ^d	pK _a (exp.) ^e
1t↔1tN'p	2.90	2.13	12.77	8.19	4.44
1t↔1tNp	2.83	2.07	9.33	9.11	
2t↔2tN'p	4.38	3.21	10.09	8.82	4.42
2t↔2tNp	2.88	2.11	9.17	6.39	
3↔3N'p		<i>No cisoid or transoid form</i>			
3↔3Np					
4t↔4tN'p	5.10	3.74	6.45	5.35	4.60
4t↔4tNp	5.09	3.73	6.45	5.35	
5↔5N'p		<i>No cisoid or transoid form</i>			
5↔5Np					
6↔6N'p		<i>No cisoid or transoid form</i>			
6↔6Np					

^a $\delta\Delta G_{f(BH^+)} = [\Delta G_{f(B)} + \Delta G_{f(H_3O^+)}] - [\Delta G_{f(BH^+)} + \Delta G_{f(H_2O)}]$. ^b $pK_a = \delta\Delta G_{f(BH^+)} / (2.303RT)$. ^c pK_a calculated HF /6-31G(d) *cisoid* and *transoid* form. ^d pK_a calculated B3LYP /6-31G(d) *cisoid* and *transoid* form. ^e pK_a (expt.) were taken from ref. 45, PM5 Calculated pK_a value for pyridine is 5.10

Possible protonation patterns for the studied molecules were depicted in Scheme 2. The aqueous phase calculated acidity constants, pK_a values, were given in Table 4 and 5. From these data the pK_a value of compound **5** was found to be the highest (i.e. 4.29 by PM5) where as the lowest pK_a value of 3.35 was found for compound **2**. The following sequence of decreasing basicity was obtained;

Molecule	:	5	6	3	4	1	2
Experimental pK_a	:	3,4'-bpy.	4,4'-bpy.	2,4'-bpy.	3,3'-bpy.	2,2'-bpy.	2,3'-bpy

PM5 calculated pK_a : 4.85 > 4.82 > 4.77 > 4.60 > 4.44 > 4.42
 4.29 > 4.24 > 4.08 > 3.72 > 3.48 > 3.35

basicity decrease \longrightarrow
 acidity increase \longrightarrow

A more reliable and closer pK_a values to experimental values however were found by *ab initio* calculations (Table 4 and 5) for compound **3**.

A perfect correlation was observed between theoretically obtained (i.e. PM5 calculated) and experimental acidity constants [46] with a slope and regression of about unity (i.e. $R^2 = 0.99$). This high correlation indicates that the first protonation of compounds **1** and **3** occur over the *cisoid* form (i.e. they are off the line). Whereas the first protonation of compound **4** occur over both *cisoid* and *transoid* form which are exist in equal amounts (Table 6). On the other hand protonation of compounds **2**, **5** and **6** occur over *transoid* form (i.e. they are on the same line)

A graph of experimental pK_a values against the calculated pK_a values using Equation 5 were depicted in Figure 1.

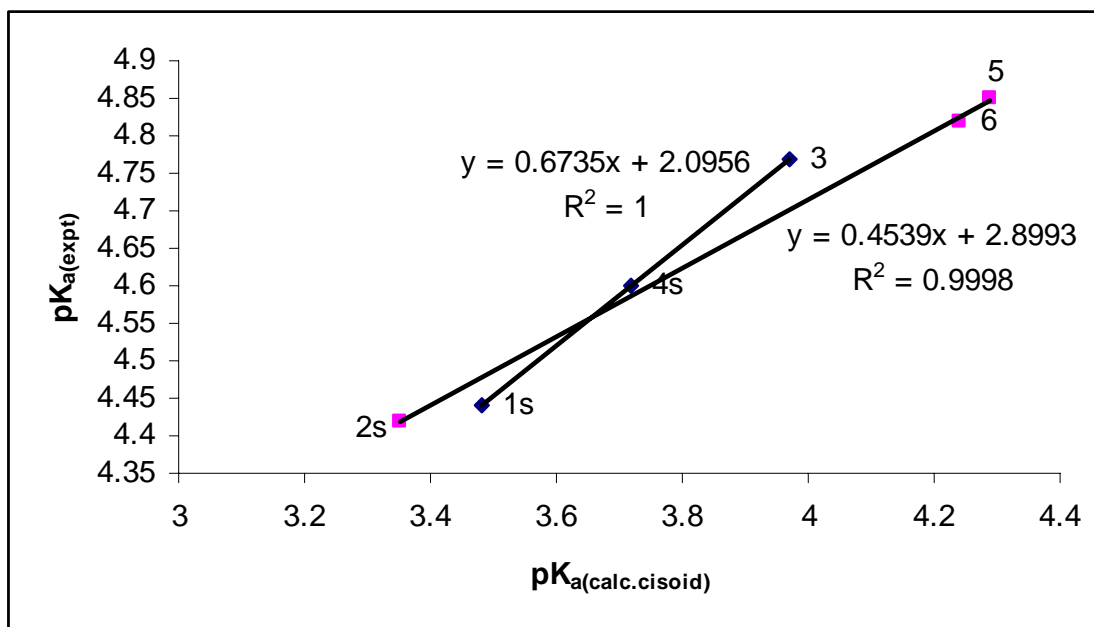
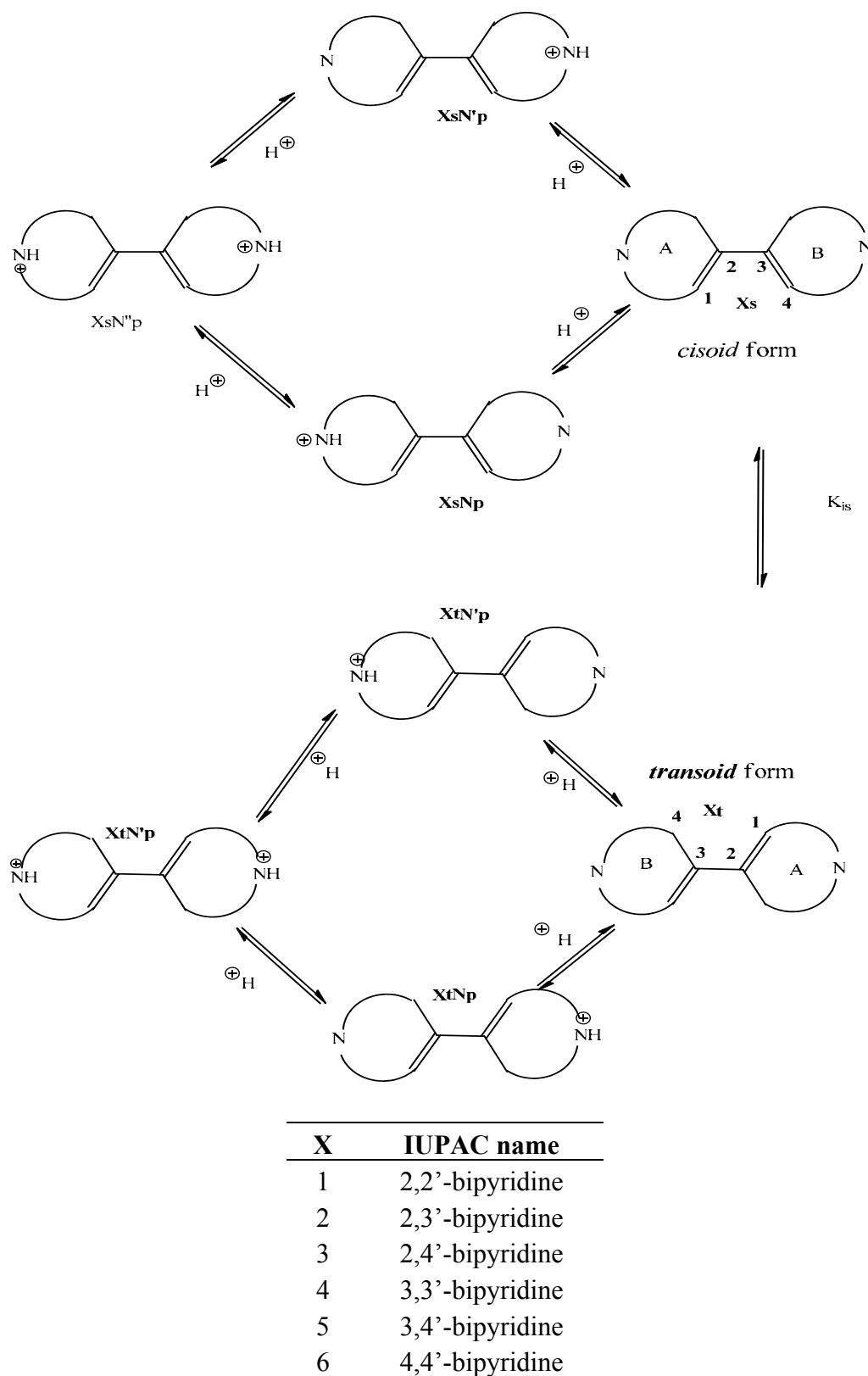


Figure 1. The plot of the aqueous phase PM5, calculated acidity constants, $pK_{a(\text{calc.cisoid})}$, and experimental acidity constants, $pK_{a(\text{expt.})}$, for bipyridine derivatives.



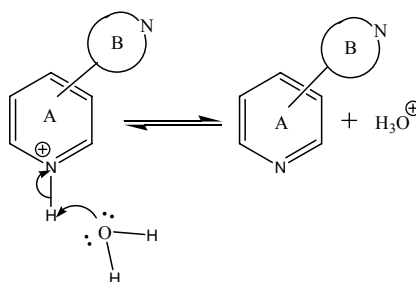
Scheme 2. Possible stereoisomerism and protonation pattern for studied molecules.

Substituent constants

One of the commonly used method to search for the effect of substituent on an equilibrium processes has been the usage of the Hammett Equation (Equation 7).⁴⁵

$$\text{pK}_a(\text{unsubstituted molecule}) - \text{pK}_a(\text{substituted molecule}) = \rho\sigma \quad (7)$$

The σ (i.e. substituent constant) values for 2-, 3- and 4- pyridinyl group can be calculated by using Equation 7. The ρ (i.e. equilibrium constant) value for the pyridine protonation was given as 5.77.⁴⁶ Hence the ionization equilibrium in water for protonated pyridinium molecules can be written as in Scheme 3. The experimental pK_a value for unsubstituted pyridine was taken as 5.17.⁴⁶



B = 2-(2'-pyridyl, 3'-pyridyl, 4'-pyridyl); 3-(3'-pyridyl, 4'-pyridyl); 4-(4'-pyridyl)

Scheme 3. Deprotonation pattern for pyridinium ionization in water.

The substituent constants using the experimental and theoretical pK_a values were calculated and obtained results were depicted in Table 7. When we take σ values of which calculated using the experimental pK_a values into account we observed that all σ values have positive sign indicating the electron-withdrawing effect of the substituted pyridyl ring (B).

We also can predict that this electron-withdrawing effect is not big and it is close to the σ_p value of 0.06 for fluorine atom.⁴⁷ It seems that the obtained calculation results are quite satisfactory and PM5 calculated σ values for all studied molecules were close enough to experimental values to be considered successful.

Relative Stabilities

Equation 8 was used to calculate the relative stabilities (RS) using the heat of formation value of the studied molecules.

$$\text{RS} = \Delta H_f(\text{transoid form}) - \Delta H_f(\text{cisoid form}) \quad (8)$$

The aqueous phase PM5 calculated relative stabilities were given in Table 6. The RS values

indicate that the *transoid form* is predominant over the *cisoid form* for molecule **1** and **2**. RS values for **3**, **5** and **6** indicate equal amount of *cisoid* and *transoid* forms, as expected, because of the symmetry. On the other hand the PM5 calculated RS values are indicative of equal amount of *cisoid* and *transoid forms* for compound **4**. Whereas the *ab initio* calculated RS values suggest the predominance of *cisoid* forms.

Table 6. The aqueous phase PM5, HF and B3LYP calculated isomeric equilibrium constants (K_{is}) stability constants (RS) and mole fraction (N) values of studied molecules

Process Isomerism	$\delta\Delta G$ (kcal/mol)) ^a	K_{is} ^b	N_s ^c	N_t ^c	K_{is} ^d	N_s ^e	N_t ^e	RS ^f	Suggested Confirmation
PM5									
1s-1t	-0.05	1.09	0.48	0.52	22.38	0.04 0.96		0.10	<i>Transoid</i> ^{b,c, d,e,f}
2s-2t	0.16	0.76	0.57	0.43	1.38	0.42 0.58		0.18	<i>Transoid</i> ^{d,e,f} <i>Cisoid</i> _{b,c}
4s-4t	0.00	1.00	0.50	0.50	0.95	0.51 0.49		0.01	<i>Equal amount</i> ^{b,c,d,e,f}
HF/6-31G(d)									
1s-1t	-2.58	78.10	0.01	0.99	2951	0.01 0.99		-6.57	<i>Transoid</i> ^{b,c, d,e} <i>Cisoid</i> ^f
2s-2t	0.09	0.85	0.54	0.46	2.34	0.30 0.70		-0.63	<i>Transoid</i> ^{d,e} <i>Cisoid</i> _{b,c, f}
4s-4t	-0.14	1.26	0.45	0.55	0.001	0.99 0.01		-0.14	<i>Transoid</i> ^{b,c, Cisoid} _{d,e, f}
B3LYP/ 6-31G(d)									
1s-1t	2.27	0.02	0.98	0.02	134.8	0.01 0.99		-6.96	<i>Transoid</i> ^{b,c, d,e} <i>Cisoid</i> ^f
2s-2t	-0.75	3.59	0.22	0.78	8.12	0.32 0.68		-0.70	<i>Transoid</i> ^{b,c, d,e} <i>Cisoid</i> ^f
4s-4t	-0.45	2.13	0.32	0.68	0.001	0.99 0.01		-0.14	<i>Transoid</i> ^{b,c, Cisoid} _{d,e, f}

^a $\delta\Delta G = \Delta G(\text{product}) - \Delta G(\text{reactant})$.

^b $K_{is} = e^{-(\delta\Delta G / RT)}$.

^c $N_s = 1/(1+K_{is})$ $N_t = K_{is}/(1+K_{is})$ (K_{is} values were calculated by using $\delta\Delta G$ values).

^d $K_{is} = K_a(\text{transoid})/K_a(\text{cisoid})$.

^e $N_s = 1/(1+K_{is})$ $N_t = K_{is} / (1+K_{is})$ (K_{is} values were calculated by utilizing the pK_a values).

^f $RS = \Delta H_f(\text{transoid}) - \Delta H_f(\text{cisoid})$ The negative sign indicates the favorability of *cisoid* form.

Table 7. Aqueous phase PM5, HF and B3LYP calculated substituent constants, σ values, for investigated compounds

Molecule	Substituent	Form	$\sigma_{(\text{calc.})}^a$	$\sigma_{(\text{calc.})}^b$	$\sigma_{(\text{calc.})}^c$	$\sigma_{(\text{expt.})}^d$
1	2'-pyridine	Cisoid	0.29	0.68	1.49	0.13
		Transoid	0.53	0.08	0.09	
2	3'-pyridine	Cisoid	0.32	0.12	0.32	0.13
		Transoid	0.34	0.21	0.89	
3	4'-pyridine		0.21	-0.17	-0.25	0.07
4	3'-pyridine	Cisoid	0.25	-0.34	-1.07	0.10
		Transoid	0.25	-0.41	-0.60	
5	4'-pyridine		0.15	0.03	0.10	0.06
6	4'-pyridine		0.16	0.06	-0.79	0.06

^a Calculated using PM5 semiempiric pK_a values. The plus sign indicates the electron-withdrawing effect.

^b Calculated using HF/ 6-31 G (d) calculated pK_a values.

^c Calculated using B3LYP/ 6-31 G (d) calculated pK_a values.

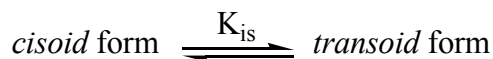
^d Calculated using experimental pK_a values using the Hammett equation $\text{pK}_a(\text{unsubst. pyridine}) - \text{pK}_a(\text{subst. pyridine}) = \rho\sigma$; ρ (for pyridine protonation) = 5.77⁴⁶

Isomeric Equilibrium Constants

The isomeric equilibrium constants, K_{is} values, of the studied molecules were calculated by two methods as described below;

i- Using the equation $K_{\text{is}} = e^{(\delta\Delta G_f / RT)}$

Where K_{is} is the isomeric equilibrium constant between the *cisoid* and *transoid* forms. $\delta\Delta G_f$ is the difference in Gibbs free energies of the isomers, $\delta\Delta G_f = \Delta G_f(\text{transoid form}) - \Delta G_f(\text{cisoid form})$. The R value is 1.987×10^{-3} kcal/mol and T is 298 K. The following equilibrium represents the isomeric equilibrium between isomers *cisoid* form and *transoid* form. The K_{is} values obtained by this way suggest the predominance of *transoid* form over the *cisoid* forms for compounds **1** and **4**. The predominance of *cisoid* form over the *transoid* form for compound **2**. Whereas for compounds **3**, **5** and **6** they suggest the presence of the equal amount of *cisoid* and *transoid* forms.



ii- Using the equations 6 and 7

$$pK_a(\text{transoid}) - pK_a(\text{cisoid}) = pK_{is} \quad (9)$$

$$K_{is} = K_a(\text{transoid}) / K_a(\text{cisoid}) \quad (10)$$

The obtained K_{is} values by using Equations 9-10 were depicted in Table 6. The K_{is} values obtained using Equations 9-10, like the other K_{is} values mentioned above have suggested the predominance of the *transoid* form over the *cisoid* form for compound **1**. Similarly for compound **2** the predominance of *transoid* form over the *cisoid* form for compound **2** was confirmed. For compound **4** supporting to above conclusion it indicates the predominance of the *cisoid* form over the *transoid* form. Whereas for compounds **3**, **5**, **6** it suggest the presence of the equal amount of *cisoid* and *transoid* forms. *Ab initio* calculated K_{is} values are however suggest the predominance of *transoid* forms with a values of 1.26 and 2.13 respectively (Table 6).

Mole Fractions

The mol fractions of the *cisoid* and *transoid* isomers were calculated by using the following equations and the obtained results were depicted in Table 6.

$$N(\text{cisoid form}) = 1 / (1 + K_{is})$$

$$N(\text{transoid form}) = K_{is} / (1 + K_{is})$$

Mole fraction values indicate that the predominance of *transoid* form over the *cisoid* form for **1**. For **2** however two different mole fraction calculation methods indicates two different conclusions; the first one, N^c values, indicates the predominance of *cisoid* form (with the exception of the B3LYP method). Whereas the second one, N^e values, indicates the predominance of *transoid* form. This discrepancy presumably source out from the difference between two methods of calculations. In the first one, K_{is}^b values, the solvation effect is being neglected in the second one, K_{is}^d values, the solvation effect has been taken into account. This point had reflected also in the geometry of the neutral and protonated species in calculations of acidity constants, pK_a values which were used in calculations of N^c values. The change in the dihedral angle of N1-C2-C3-C4 (i.e. changes from -53.74 to -0.06 for *cisoid* protonation and from -0.04 to -0.02 for *transoid* form) for *cisoid* protonation may explain why compound **2** prefers to exist in the *transoid* form (Table 8). For compound **4** the calculated mole fraction values leads to two different conclusions; N^c values, indicates the predominance of *transoid* form. Whereas the other conclusions, N^e values, indicates the predominance of *cisoid* form. For **3**, **5**, **6** however they suggest the existence of equal amount of two isomers (Table 6).

Table 8. Aqueous phase PM5, HF and B3LYP calculated dihedral angles for studied neutral and protonated molecules

Molecule		Neutral		First Protonation
Dihedral Angles		cisoid		
PM5		Xs	XsNp	XsN'p
N1-C2-C3-N4	1	-0.05	179.80	179.65
N1-C2-C3-C4	2	-0.017	-53.74	-0.056
N1-C2-C3-C4	3	-5.215	-0.10	-0.03
C1-C2-C3-C4	4	0.027	0.18	0.00
C1-C2-C3-C4	5	-0.009	0.03	0.02
C1-C2-C3-C4	6	-0.013	0.037	0.07
		transoid		
		Xt	XtNp	XtN'p
N1-C2-C3-N4	1	-0.047	-0.09	-0.08
N1-C2-C3-C4	2	0.009	-0.04	-0.02
C1-C2-C3-C4	4	0.016	0.02	0.02
HF		cisoid		
		Xs	XsNp	XsN'p
N1-C2-C3-N4	1	-43.50	-0.008	-0.055
N1-C2-C3-C4	2	-27.96	-14.34	-41.03
N1-C2-C3-C4	3	-15.14	-44.20	-13.10
C1-C2-C3-C4	4	-40.21	-40.98	-42.51
C1-C2-C3-C4	5	-43.23	-48.09	-33.80
C1-C2-C3-C4	6	-43.57	-40.21	-40.20
		transoid		
		Xt	XtNp	XtN'p
N1-C2-C3-N4	1	-0.029	34.34	-25.73
N1-C2-C3-C4	2	-25.63	-23.83	-41.32
C1-C2-C3-C4	4	-36.60	-42.35	-42.27
B3LYP		cisoid		
		Xs	XsNp	XsN'p
N1-C2-C3-N4	1	-35.09	-0.055	-0.027
N1-C2-C3-C4	2	-20.84	-0.015	-35.18
N1-C2-C3-C4	3	-15.14	-35.68	-0.01
C1-C2-C3-C4	4	-35.60	-34.19	-35.04

Table 8. Continued

Molecule		Neutral		First Protonation
Dihedral Angles		<i>cisoid</i>		
B3LYP		Xs	XsNp	XsN'p
C1-C2-C3-C4	5	-43.23	-48.09	-33.80
C1-C2-C3-C4	6	-36.19	-31.65	-31.63
		<i>transoid</i>		
		Xt	XtNp	XtN'p
N1-C2-C3-N4	1	-0.025	13.46	-13.40
N1-C2-C3-C4	2	-17.90	-8.19	-34.88
C1-C2-C3-C4	4	-26.11	-34.20	-34.35

Nucleophilicity Criteria

The hard/soft base principle has been applied to kinetic phenomena for a long time. In this connection, organic chemistry has provided most of the examples, because the organic reactions are often slow enough for their rates to be easily measured. In organic chemistry, we are generally interested in the reactions of electrophiles and nucleophiles. These reactions are a particular kind of the general acid-with-base type of reaction, and so the principle of hard and soft acids and bases applies equally to the reactions of electrophiles and nucleophiles. So the acidity and basicity can be related to the theoretical interpretation of hard-soft acids and bases.

The solvated proton is a *hard electrophile* and little affected by frontier orbital interactions. For this reason, the pK_a of the conjugated acid of a nucleophile is a good measure of the rate at which that *nucleophile* will attack to another *hard electrophiles*.⁴⁸

Taking all those above mentioned points into account we have attempted to search a possible correlations between the experimental and computed *acidity* constants, pK_a values, and computed *nucleophilicity* of the studied molecules. The unusual behaviour of any molecule which will cause a deviation from correlation line then would let us to think the external effects such as solvation on this molecule in such a way to alter the *nucleophilicity-electrophilicity* or/and *acidity-basicity* character of the molecule at a great extend.

The *nucleophilicity*, $n = E_{HOMO} - E_{LUMO}$,⁴⁹ of studied molecules were calculated and the aqueous phase calculated n values of the studied neutral molecules were depicted in Table 9.

The best fit of *nucleophilicity* to pK_a values comes from PM5 calculated nucleophilicities and PM5 calculated pK_a values (Figure 2).

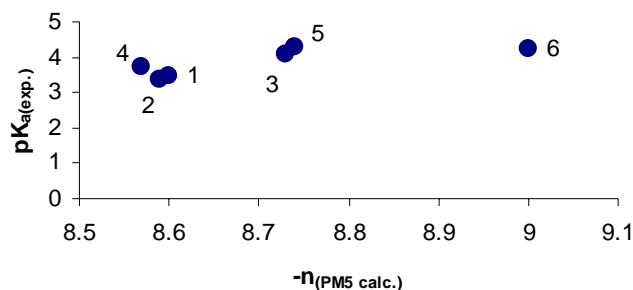


Figure 2. The plot of PM5 aqueous phase calculated *nucleophilicities*, $-n$ values, and experimental acidity constants, $pK_{\text{a(expt.)}}$, for studied bipyridine derivatives.

Table 9. Aqueous phase PM5, HF and B3LYP calculated *nucleophilicity* values for neutral molecules

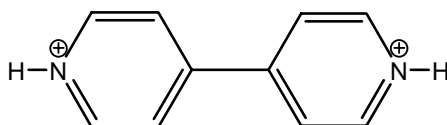
Molecule	E_{HOMO}	E_{LUMO}	n^{a}
PM5			
1s	-9.443	-0.823	-8.620
1t	-9.405	-0.800	-8.605
2s	-9.355	-0.760	-8.595
2t	-9.363	-0.756	-8.607
3	-9.628	-0.890	-8.738
4s	-9.293	-0.721	-8.572
4t	-9.291	-0.721	-8.570
5	-9.591	-0.851	-8.740
6	-9.985	-0.979	-9.006
HF			
1s	-0.32	0.09	-0.41
1t	-0.31	0.08	-0.39
2s	-0.31	0.08	-0.39
2t	-0.31	0.08	-0.39
3	-0.32	0.07	-0.39
4s	-0.30	0.08	-0.38
4t	-0.30	0.09	-0.39
5	-0.33	0.08	-0.41
6	-0.34	0.08	-0.42
B3LYP			
1s	-0.24	-0.04	-0.20

Table 9. Continued

Molecule	EHOMO	ELUMO	na
1t	-0.23	-0.05	-0.18
2s	-0.23	-0.05	-0.18
2t	-0.23	-0.05	-0.18
3	-0.24	-0.05	-0.19
4s	-0.23	-0.04	-0.19
4t	-0.23	-0.04	-0.19
5	-0.25	-0.04	-0.21
6	-0.26	-0.05	-0.21

$$^a n = E_{\text{HOMO}} - E_{\text{LUMO}}$$

The lower solvation effect on compounds **1**, **2** and **4** comparing to compounds **3** and **5** is reflected by decrease in *nucleophilicities*. It seems that the most solvated molecule among the others is compound **6** which possess two nitrogen atoms which are positioned very suitably for solvation after protonation and form *paraquat like* stable dication which plays a very important role in electron transport phenomena.⁵⁰



It seems that the nucleophilicity is more substituent dependant than that of ionization constant, K_a value, for these derivatives. This means that the position of substituent is also an important factor and effects the electronic changes on the protonation center.

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