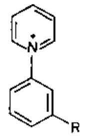
THE ELECTROPHILIC SUBSTITUTION OF HETEROAROMATIC COMPOUNDS. PART 53.[1] THE EXPERIMENTAL ORIENTATION IN THE ELECTROPHILIC SUBSTITUTION OF 1-PHENYLPYRIDINIUM CATIONS, AND A THEORETICAL TREATMENT OF ELECTROPHILIC SUBSTITUTION ORIENTATIONS IN N-PHENYLHETEROCYCLES

Alan R. Katritzky, Hassan M. Faid-Allah, Hudson Luce, and Mati Karelson
Department of Chemistry, University of Florida, Gainesville, Florida 32611,
U.S.A.

George P. Ford
Department of Chemistry, Southern Methodist University, Dallas, Texas 75275,
U.S.A.

Abstract- Nitration, sulfonation and bromination of the title compound occur in the meta position of the 1-phenyl group. This meta substitution, and the para substitution previously observed for other N-phenylheterocycles, cannot be explained by static reactivity indices. However, a MNDO analysis, taking account of the near degeneracy of the two top HOMO's, and using experimentally probable interannular angles, allows rationalization of the orientations observed.

Vorlaender has reported[2] that the 1-phenylpyridinium cation (1) undergoes nitration at the meta position of the phenyl substituent. The reported meta orientation is somewhat surprising, as N-phenyl groups attached to five-membered rings tend to be nitrated in the para position, even when reaction takes place on a cation (cf. pyrazoles 5,[3] 3-pyrazolones,[4] 5-pyrazolones,[5] imidazoles 6[6]). Furthermore, the indolenium cation (7) undergoes nitration exclusively para to the positive pole to yield 8.[7] Moreover, while the nitration of 1-phenyl-4-pyridone (cf. 9) is reported to occur in the para position,[2] 1-phenyl-5-methyl-2-pyridone (cf. 10) is nitrated in the meta position.[8]



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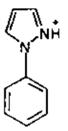
2 R = NO_2 4 R = Br



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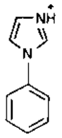

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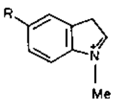
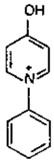


7 R = H
8 R = NO_2



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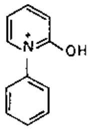

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Table 1. ^{13}C NMR[a] Chemical Shifts of 1-Phenylpyridinium Tetrafluoroborate Derivatives.

	pyridinium ring			phenyl ring					
compd.	C-2	C-3	C-4	C-1	C-2	C-3	C-4	C-5	C-6
1	144.3[b]	128.2	146.3	144.3[b]	124.0	130.1	131.1	130.1	124.0
2	145.2	128.2	147.5	144.4	120.7	148.2	125.9	131.4	131.7
3	145.6	129.6	148.3	144.8	122.7	132.4	126.0	127.5	128.5
4	144.8	128.2	146.6	141.8	124.7	124.1	127.8	130.2	131.3

[a] Solutions in DMSO-d_6 except 3 in DMSO-d_6 + TFA. [b] Peaks overlap.

There appears to be no previous record of other electrophilic substitution reactions of the 1-phenylpyridinium cation (1). Because of these facts we have reinvestigated the nitration and studied some further typical electrophilic substitutions. We find that compound (1) indeed undergoes nitration (fuming HNO_3, d. 1.5, 85 °C), sulfonation (30 % oleum, 118 °C), and bromination (Br_2, 150 °C), to give in each case the corresponding meta substituted derivative (2), (3), and (4) in 60, 46, and 45% isolated yield, respectively. The compounds were isolated as the tetrafluoroborate salts. Examination of the crude reaction products by TLC and by ^{13}C NMR gave no evidence for the formation of any ortho- or para-substituted derivatives. The orientation of the products was proven by ^{13}C NMR (Table 1) which shows clearly the asymmetrical nature of the substitution in the phenyl ring.

Calculations: Calculations were carried out on compounds 1, 5, and 7-10 using the published MNDO formalism and parameterization[11] with standard program packages.[9,10]. The geometry of compound 5 was completely optimized. In other cases the optimization was limited to the interannular distances and angles with the remaining geometrical variables fixed at the MNDO values for the corresponding mononuclear species.

The coefficients of the highest occupied molecular orbital (HOMO) and the partial atomic charges at the meta and para positions are summarized in Table 2. Both sets of simple reactivity indices suggest[12,13] that electrophilic substitution should occur predominantly at the meta position in all compounds. This, however, is in contradiction with experiment for all but the 1-phenylpyridinium cation (7). Unfortunately, there are at least two difficulties associated with this approach. The MNDO calculations lead to energy minima which, apart from the rigid indolenium ion (7), correspond to interannular angles (alpha) near 90°. It seems highly likely that this is an artifact of the well known tendency of the method to overestimate non-bonded repulsions.[11,14]

Thus, for biphenyl the MNDO minimum energy also corresponds to alpha close to 90°, whereas the experimental value of this angle is 22.5±3.5°.[15] The second problem is associated with the neglect of the deeper lying molecular orbitals implicit in any treatment based only on HOMO properties. It was pointed out some time ago[11] that difficulties arise in the PMO analysis of the nucleophilicity of different sites in substituted benzenes where the highest occupied molecules orbitals are close in energy.

Table 2. Reactivity Indices Obtained from MNDO Calculations

Compd.	Phenyl Ring Position	C^a_{HOMO}	$delta_c^b$	Compd.	Phenyl Ring Position	C^a_{HOMO}	$delta_c^b$
1	m-	0.477	-0.033	8	m-	0.477	-0.044
	p-	0.002	-0.004		p-	-0.003	-0.007
5	m-	-0.559	-0.029	9	m-	0.479	-0.041
	p-	-0.278	-0.003		p-	-0.001	-0.004
7	m-	0.475	-0.041	10	m-	0.480	-0.041
	p-	0	-0.001		p-	0	-0.003

[a] The canonical HOMO coefficient of the p_z^{-A} at the particular site in the substrate of electrophilic addition reaction. [b] The partial charge at the site in the reaction substrate.

This is also the case for compounds 1, and 7-10 where the energies of the two highest lying molecular obitals differ by less than 0.2 eV for all interannular angles. In these situations the following expression for the reactivity index at atom X:

$$f_x = 2\,\frac{c_{HOMO}^{\,2} + c_{HOMO-1}^{\,2}\exp(-D\Delta E)}{1 + \exp(-D\Delta E)}$$

has been proposed,[16] where C_{HOMO} and C_{HOMO-1} are the coefficients of the highest and next highest occupied molecular orbitals at atom X and Delta E is the energy difference between the two orbitals. D is a numerical constant and it was estimated[12,17] that D = 3 for nitration.

Table 3. Relative Energies and Reactivity Indices for Different Conformations of Compound 1.

alpha$^{\circ a}$	E (kcal/mol)	Delta E (kcal/mol)	f_p	f_m	Delta E^{2b} (eV)
0°	229.2	13.0	0.308	0.316	0.0562
30°	222.9	6.3	0.311	0.329	0.0072
45°	219.4	3.2	0.294	0.346	0.0530
49° (opt.)	219.6	3.4	0.285	0.353	0.0843
60°	217.4	1.2	0.270	0.363	0.1196
90°	216.2	0	0.245	0.381	0.1887

[a] The angle between the two ring planes. [b] The energy difference of two HOMO-s.

Table 4 - Relative Energies and Reactivity Indices F_x for Different Conformations of Compound 10.

alpha[a] (deg)	E (kcal/mol)	Delta E (kcal/mol)	fp	fm	Delta E[b] (eV)
0°	200.9	34.4	0.326	0.306	0.0640
20°	190.7	24.2	0.329	0.311	0.0463
45°	173.6	7.1	0.291	0.335	0.0530
60°	169.0	2.5	0.272	0.357	0.1104
89.8°	166.5	0	0.251	0.379	0.1765
90.2°	166.5	0	0.251	0.379	0.1765
120°	169.0	2.5	0.272	0.366	0.1104
135°	173.6	7.1	0.291	0.352	0.0530
160°	190.7	24.2	0.329	0.329	0.0463
180°	200.9	34.4	0.326	0.320	0.0640

[a-b] cf. the corresponding footnotes at Table 3.

Calculated values of f_m and f_p for various interannular angles in compounds 1, 5, 6, 9, and 10 are shown in Tables 3-7. We have also included the relative energies for each value of alpha. However, it should be pointed out that since the geometries were not completely optimized, these data exaggerate the energetic difference between the planar (alpha 0°) and perpendicular (alpha 90°) forms. Since the incorrect treatment of the interannular angle is associated with deficiencies in the MNDO formalism for the internuclear repulsion function,[14] reactivity indices based on the electronic wavefunction should be reliable. Thus, at angles near 20-25° the reactivity of compounds 5, 6, 9, and 10 is in each case predicted to be higher at the para

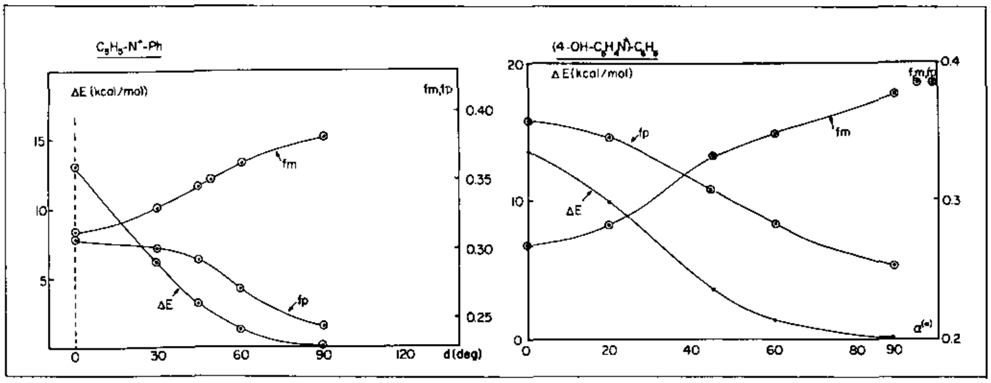

Figure 1. The relative energies and reactivity indices f_p and f_m for the compounds (1) and (9) as the function of interannular angle, alpha.

position. For compound 1, the meta position should be more reactive for all angles (cf Fig. 1). These conclusions now correspond with the experimental observations. For compound 7, in which the rings are constrained to be coplanar, the para position is also predicted to be more reactive (f_p=0.358, f_m=0.302) in agreement with experiment but not with predictions based solely on the HOMO coefficients.

Table 5 - MNDO Relative Energies and Reactivity Indices f_x for Different Conformations of the Compound 5

alpha[a] (deg)	E (kcal/mol)	Delta E (kcal/mol)	f_p	f_m	Delta E[b] (eV)
0°	248.0	7.4	0.358	0.271	0.1530
20°	244.4	3.8	0.353	0.300	0.1389
45°	243.9	3.3	0.315	0.323	0.0288
60°	242.1	1.5	0.316	0.395	0.0719
85°	240.6	0	0.271	0.384	0.2214
95°	240.6	0	0.271	0.386	0.2214
120°	242.1	1.5	0.316	0.397	0.0719
135°	243.9	3.3	0.315	0.318	0.0288
160°	244.4	3.8	0.353	0.285	0.1389
180°	248.0	7.4	0.358	0.283	0.1530

[a-b] cf. the corresponding footnotes at Table 3.

Table 6 - Relative Energies and Reactivity Indices f_x for Different Conformations of Compound 6

alpha[a] (N-C bl. A°)	E (kcal/mol)	Delta E (kcal/mol)	f_p	f_m	Delta E[b] (eV)
0°	219.5	6.3	0.349	0.310	0.1027
20°	218.1	4.9	0.340	0.318	0.0685
45°	215.0	1.8	0.306	0.342	0.0295
60°	213.9	0.7	0.280	0.360	0.0968
85°	213.2	0	0.251	0.375	0.1726
95°	213.2	0	0.251	0.378	0.1726
120°	213.9	0.7	0.280	0.355	0.0968
135°	215.0	1.8	0.306	0.335	0.0295
160°	218.1	4.9	0.340	0.307	0.0685
180°	219.5	6.3	0.349	0.295	0.1027

[a-b] cf. the corresponding footnotes at Table 3.

Table 7 - Relative Energies and Reactivity Indices f_x for Different Conformations of Compound 9.

alpha[a] (N-C bl. A^o)	E (kcal/mol)	Delta E (kcal/mol)	f_p	f_m	Delta E[b] (eV)
0^o	188.5	13.7	0.358	0.269	0.1964
20^o	184.7	9.9	0.347	0.281	0.1563
45^o	178.2	3.4	0.310	0.333	0.0250
60^o	176.1	1.3	0.282	0.348	0.0696
89^o (opt.)	174.8	0	0.253	0.377	0.1717

[a-b] cf. the corresponding footnotes at Table 3.

An alternative, but far more computationally intensive approach to the same problem involves calculation of the relative energies of the Wheland intermediates directly. This avoids the uncertainties inherent in the use of reaction indices, but is still subject to the problems associated with the correct treatment *of the interannular angles. These calculations* were carried out for the protonation of compounds 1, 7, and 9 (Table 8). Again the perpendicular conformations (alpha = 90^0) of protonated 1 and 9 were calculated to be energy minima. Here the calculations were limited to the planar and perpendicular conformations. However, all geometries were completely optimized subject only to the inherent symmetry constraints. For the planar compound, 7, the most reactive site was again predicted to be para to the nitrogen pole (lowest DELTA H_f). In the perpendicular conformations, the preferred sites of attack of 1 and 9 were the meta, and in the planar conformations, the para positions. However, for 1 the latter difference was rather small.

Table 8. MNDO Heats of Formation (Delta H_f) for Protonated 1, 5, and 9.

Compd.	Protonation site	Delta H_f alpha = 90^0	 alpha = 0^0
1	2	487.2	495.4
	3	484.3	496.5
	4	487.4	495.0
7	2		495.0
	4		480.1
	5		478.2
	6		478.5
	7		479.6
9	3	429.5	441.6
	4	432.0	437.6

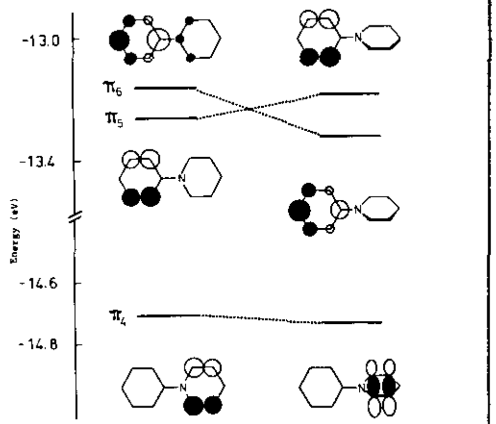

Figure 2. Correlation of the three highest lying pi orbitals in the planar and perpendicular structures of the 1-phenylpyridinium ion (1).

Given the clear importance of the interannular angle, and the role of both highest lying orbitals, it is of interest to examine further. The forms of the three highest lying pi orbitals in the planar and perpendicular conformations of 1 are shown in Fig. 2. In the former the HOMO (Pi 6) is symmetric with its largest coefficient at the para-position of the phenyl ring, while the (HOMO - 1) (Pi 5) is antisymmetric with a zero coefficient at the para-position. As the interannular ring angle increases, two effects are evident. Firstly, the antibonding interaction between the two rings in Pi 6 is eliminated, resulting in a more tightly bound orbital in the perpendicular conformation. Secondly, charge delocalization between the rings is reduced as the interannular angle increases. Thus, the energies of orbitals concentrated on the phenyl ring in the planar form are raised (Pi 5), while those concentrated on the charged ring are lowered (Pi 4). The overall result is therefore an inversion of the two highest pi orbitals and a corresponding reduction in the favorability of para- relative to meta-attack. The greater preference for para-attack predicted in the planar geometry of 9 relative to the present case follows from the preferential raising of the energy of the symmetric (Pi 6), relative to the antisymmetric (Pi 5), orbital by the OH group in the 4-position of the heteroaromatic ring.

EXPERIMENTAL

^{1}H NMR spectra were recorded with a Varian EM 360L spectrometer or on a Nicolet NT-300 Spectrometer, operating at a field of 7 Tesla using Me_4Si as a standard. ^{13}C NMR spectra were recorded with a JEOL JNM - FX 100 Fourier transform NMR spectrometer. Melting points were recorded on a Kofler hot-stage apparatus and are uncorrected. 1-Phenylpyridinium tetrafluoroborate was prepared using a literature method, mp 178 °C; [lit. mp 178 °C].[18]

1-(3-Nitrophenyl)pyridinium Tetrafluoroborate (2).- 1-Phenylpyridinium tetrafluoroborate (0.5 g, 2 mmol) was refluxed with fuming nitric acid (2 ml, d. 1.5) for 8 h. The reaction mixture was then cooled and treated with ether to give white crystals, (0.36 g, 61%) which are filtered and recrystallized from methanol as prisms, mp 170 °C; ^{1}H nmr [$(CD_3)_2SO$] delta: 8.03 (1H, t, J = 4 Hz, 5-CH), 8.34 (3 H, m, beta-CH + 6-CH), 8.57 (1H, d, J = 4 Hz, 4-CH), 8.86 (2H, m, gamma-CH + 2-CH), 9.39 (2H, d, J = 3 Hz, alpha-CH). Anal. Calcd. for $C_{11}H_9BF_4N_2O_2$: C 45.84, H 3.14, N 9.71. Found: C 45.88, H 3.03, N 9.78.

1-(3-Sulphoniophenyl)pyridinium Tetrafluoroborate (3).- 1-Phenylpyridinium tetrafluoroborate (0.5 g, 2 mmol) was heated with 30% oleum (3 ml) at 118 °C for 16 h. The reaction mixture was then cooled and treated with ether, the sticky material which separated out was treated with methanol to give white plates of (3) (0.31 g, 46%), mp 350 °C; ^{1}H nmr [$(CD_3)_2SO$] delta: 8.08-8.68 (5 H, m, Ar + gamma-CH), 8.95 (2 H, t, J = 4 Hz, beta-CH), 9.5 (2 H, d, J = 3 Hz, alpha-CH). (Satisfactory analysis was not obtained due to loss of compound during analysis.)

1-(3-Bromophenyl)pyridinium Tetrafluoroborate (4). - 1-Phenylpyridinium tetrafluoroborate (0.5 g, 2 mmol) was heated with bromine (0.35 g, 2.2 mmol) in a sealed tube at 150 °C for 24 h. The reaction mixture was then treated with chloroform to give white solid bromo derivative (4) (0.30 g, 44.7 %) which crystallized from methanol as needles, mp 108°C; ^{1}H nmr [$(CD_3)_2SO$] delta: 7.7-8.15 (4 H, m, Ar), 8.30 (3 H, t, *J* = 4 Hz, gamma-CH), 8.68 (3H, t, *J* = 4 Hz, beta-CH), 9.20 (2 H, d, *J* = 3 Hz, alpha-CH); *Anal.* Calcd. for $C_{11}H_9BBrF_4N$: C 41.04, H 2.82; N 4.35. Found: C 40.70, H 2.70, N 4.20.

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