[Chem. Pharm. Bull. 20(12)2686—2693(1972)]

UDC 547.821'551.04 : 542.958.1

Theoretical Considerations on the Nitration of 2-Anilinopyridine

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(Received November 22, 1971)

Simple LCAO-MO calculations were carried out on 2-anilinopyridine and several of the nitro derivatives, and the reaction path of the nitration of the parent anilinopyridine is estimated. The nitration takes place exclusively on the ortho and the para positions of the benzene nucleus when it is carried out in mixed acid, so the reactive species in this condition is estimated to be the monoprotonated species (*i.e.* 2-anilinopyridinium ion). On the other hand, the reactive species for the nitration by acetyl nitrate in inert aprotic solvents must be the 2-anilinopyridine, not the 2-pyridone-anil, tautomer of the neutral molecule. The reaction intermediate to form polynitrated products is also discussed.

Many investigations have been carried out on the syntheses of the fungicidal nitrogen heterocycles,[2] and some nitro substituted anilinoquinolines were shown to have activities on some species of *fungi*. In relation to these studies, the present authors had reported on the Hückel molecular orbital considerations on the nitration products of 2-anilino-4-methylquinoline and related compounds. The products obtained by the nitration of 2-anilinopyridine under various conditions were summarized in Table I.[2d] The products obtained by the nitration of several nitro-substituted 2-anilinopyridines were also included in this Table.

Table I. The Products Obtained by the Nitration of 2-Anilinopyridine and Its Nitro Derivatives

Starting material	Nitrating reagent	Conditions	Product					
			2′-NO_2	4′-NO_2	2′,4′-$(NO_2)_2$	5,4′-$(NO_2)_2$	5,2′,4′-$(NO_2)_3$	3,5,2′,4′-$(NO_2)_4$
2-Anilinopyridine	acetyl nitrate	25°, 5 hr	50	25	—	—	—	—
	acetyl nitrate (excess)	25°, 20 hr	—	—	60	10	30	—
	$H_2SO_4+HNO_3$	60°, 1 hr	20	30	5	—	—	—
	HNO_3	20°, 24 hr	30	50	15	—	—	—
2′-NO_2 Derivative	acetyl nitrate	25°, 10 hr	—	—	30	—	—	—
4′-NO_2 Derivative	acetuy nitrate	25°, 10 hr	—	—	80	—	—	20
2′,4′-$(NO_2)_2$ Derivative	acetyl nitrate	25°, 1 hr	—	—	50[a]	—	—	25
5-NO_2 Derivative	acetyl nitrate	25°, 3 hr	—	—	—	—	35	50
5,4′-$(NO_2)_2$ Derivative	acetyl nitrate	25°, 3 hr	—	—	—	—	60	40

a) recovery of starting materal

The prediction of the orientations of the aromatic electrophilic substitutions by molecular orbital calculations are very fruitful and applied rather extensively in the fields of pyridine

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and quinoline chemistry.[3] In many cases, the orientation of the reactions were reproduced as well by the simple HMO or *omega*-techniques as by more sophisticated MO calculations. Thus the HMO method takes advantage in discussing the reactivities of the complex aromatic or hetero-aromatic compounds in the ground states because of its simplicity in calculations and wider applicability. In this point of view, the present authors have applied this method to the interpretation of the nitration reactions shown in Table I.

Result and Discussion

Coulomb and resonance integrals employed in the calculation are tabulated in Table II.

TABLE II. HMO Parameters employed to the Present Calculations

a) Coulomb Integrals[a]

$\alpha_{\dot{N}}$(pyridine)	$\alpha_0+0.5\beta_0$
$\alpha_{\dot{N}}$(aniline)	$\alpha_0+1.5\beta_0$
α_{N^+}(pyridinium)	$\alpha_0+2.0\beta_0$
α_N(nitro)	$\alpha_0+1.0\beta_0$
α_O(nitro)	$\alpha_0+1.0\beta_0$

b) Resonance Integrals

$\beta_{C\text{-}C}$(ring)	$1.0\beta_0$
$\beta_{C\text{-}N}$(ring)	$1.0\beta_0$
$\beta_{C\text{-}N}$(ring C-anilino N bond)	$0.8\beta_0$
$\beta_{C\text{-}N}$(ring C-nitro N bond)	$1.0\beta_0$
$\beta_{N\text{-}O}$(nitro)	$1.0\beta_0$

a) Auxiliary inductive parameters $1_X=0.1_X$ are employed for all carbon atoms adjacent to the hetero-atoms.

In order to evaluate appropriate values for these integrals and to check the reliability of the obtained reactivity indices, the calculations were carried out by employing systematically varied parameters for the hetero-atoms. The results were shown in Fig. 1 and 2. As the coulomb and resonance integrals for pyridine and quinoline nitrogen atoms and for the corresponding onium cations were well established,[2c,3,4] the coulomb intgrals for the anilino nitrogen atom alone of the anilinopyridine tautomer (I) is varied in a wide range as shown in Fig. 1. As expected, larger $\alpha_{\dot{N}}$ values lower the reactivities of the molecule towards electrophiles. In other words, the larger $\alpha_{\dot{N}}$ value corresponds to the poorer electron donating power of the nitrogen atom. Fig. 2 (A) shows how the reactivity indices change as the resonance integrals including the anilino nitrogen atom is altered. These two figures reveal that the indices are nearly the same for the case $h_{\dot{N}}=1.5$ and

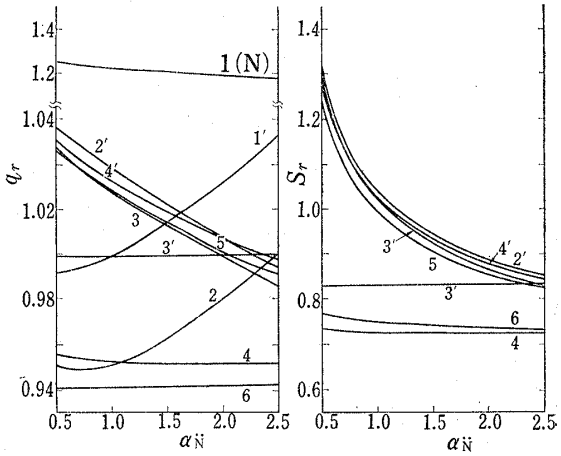


Fig. 1. Electron Density q_r *vs.* α_N and Superdelocalizability Sr *vs.* α_N Plots.

3) R.D. Brown and R.D. Harcourt, *J. Chem. Soc.*, **1959**, 3451; *b*) D.A. Brown and M.J.S. Dewar, *ibid.*, **1953**, 2406; *c*) T. Kubota, *Nippon Kagaku Zasshi*, **80**, 578 (1959); *d*) M. Dasgupta and S. Basu, *Compt. Rend.*, **1960**, 186; *e*) J. Bertran, O. Chalvet, R. Daudel, T.F. Mckillop, and G.H. Schmid, *Tetrahedron*, **26**, 339, 349, 365 (1970).

4) J.I.F. Alonso, *Compt. Rend.*, **233**, 403 (1951); see also ref. 3*a*.

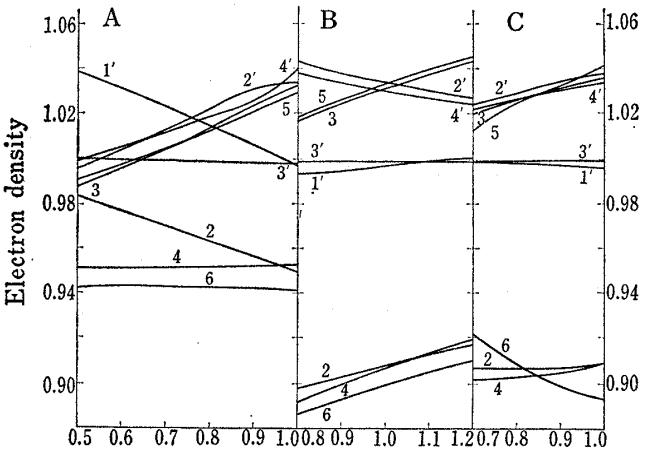


Fig. 2 (a). Flectron Density *vs.* Resonance Integral Plots

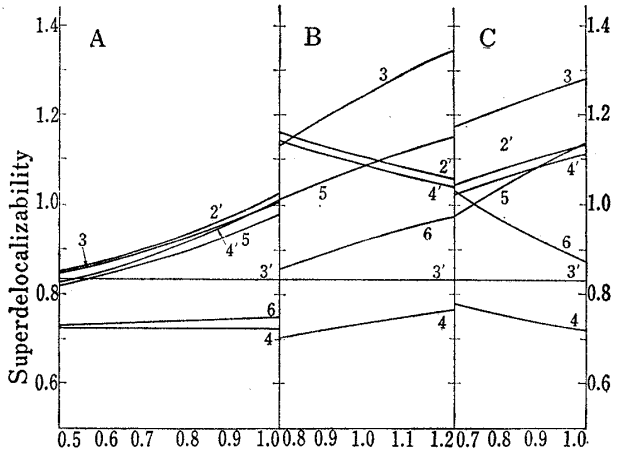


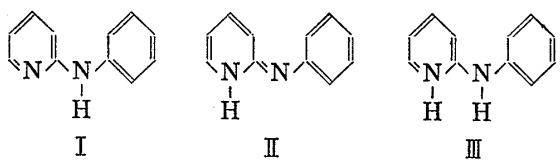
Fig. 2 (b). Superdelocalizability *vs.* Resonance Integral plots

The β_{CN} (involving anilino nitrogen atom) in anilinopyridine (I) tautomer was varied in Fig. A, and the β_{C-N} (of the heterocyclic part) and the $\beta_{C=N}$ (of the anil C=N bond) in pyridoneanil (II) tautomer were varied in Fig. B and C, respectively.

k_{CN}=0.5 and the case $h_{\ddot{N}}$=2.5 and k_{CN}=0.8. Thus, the integrals $\alpha_{\ddot{N}}$ and β_{CN} can be evaluated rather arbitrarily because of the compensative nature of these two integrals. The $\alpha_{\ddot{N}}$ value is assigned to be $\alpha+1.5\,\beta$ which is the standard value for the di-positive core of the nitrogen atom. This value is rather larger when compared with other aromatic amines. However, this is compensated by a little larger β_{CN} values for the C-N bonds sterically forced to take non-planar conformation. Fortunately, the reactivity indices are not sensitive to the variations of these integrals, and thus the reactivity indices are reliable for the anilinopyridine tautomers.

In the choice of the HMO parameters, the pyridoneanil tautomer (II) differs from the former tautomer in the following points: i) the larger α_N ($h_{\ddot{N}}$=1.5) for the ring nitrogen atom and the smaller α_N ($h_{\ddot{N}}$=0.5) for the anil nitrogen atom, ii) the larger β_{CN} for the anil C–N bond (k_{CN}=1.1), and iii) a little smaller β_{CN} for the ring C-N bonds (k_{CN}=0.9). The coulomb integrals were rather well established standard values, and, just the same as the case previously shown for the anilinopyridine tautomer, their variation would cause no considerable change in the relative reactivities. The larger resonance integrals of the ring C-N bonds activate the 5-position and deactivate the 6-position of the pyridine nucleus remarkably, while the larger $\beta_{C=N}$ value deactivates the phenyl ring and activates the pyridine ring by the stronger electron donating resonance. The most remarkable characteristics of the pyridoneanil tautomer might be the double bond character of the anil C=N bond, which activates the hetero-cyclic nucleus. In comparison with the experimental results on nitration, the contribution of the pyridone-anil tautomer is, therefore, rather doubtful.

In conclusion, the parameters previously proposed for the calculations on the similar molecules[4,5] are also suitable for the present investigations and, thus, the parameters given in Table II were employed. The care was taken so as to select a set of parameters in which the coulomb integrals were transferable from molecule to molecule.



The reactivity indices for the electrophilic substitutions of the parent 2-anilinopyridine and several of its nitro-substituted derivatives were presented in Table III.

5) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley Sons & Inc., New York, 1961, pp. 117—135.

TABLE III. Reactivity Indices of the Nitro-Substituted 2-Anilinopyridines

a) Electron Densities

Position	H	3-NO_2	4-NO_2	5-NO_2	6-NO_2	2′-NO_2	3′-NO_2	4′-NO_2	5,4′-$(NO_2)_2$	2′,4′-$(NO_2)_2$
Anilinopyridine (I)										
1N	1.210	1.210	1.178	1.207	1.189	1.208	1.210	1.208	1.205	1.206
2	0.963	0.916	0.965	0.926	0.956	0.963	0.963	0.963	0.926	0.964
3	1.014	1.008	0.969	1.014	0.970	1.011	1.014	1.012	1.012	1.010
4	0.952	0.909	0.957	0.914	0.955	0.952	0.952	0.952	0.913	0.952
5	1.013	1.013	0.973	1.007	0.959	1.011	1.013	1.011	1.006	1.009
6	0.942	0.901	0.945	0.890	0.952	0.942	0.942	0.942	0.891	0.942
NH	1.831	1.812	1.831	1.816	1.830	1.813	1.831	1.816	1.802	1.800
1′	1.014	1.015	1.014	1.015	1.014	0.967	1.015	0.970	0.970	0.929
2′	1.022	1.020	1.022	1.020	1.022	1.014	0.978	1.021	1.019	1.013
3′	0.999	0.999	0.999	0.999	0.999	0.956	0.996	0.955	0.955	0.904
4′	1.019	1.017	1.019	1.017	1.019	1.018	1.973	1.012	1.011	1.011
5′						0.956	1.000			0.918
6′						1.021	0.977			1.022
Pyridone-anil (II)										
1N	1.714	1.702	1.724	1.691	1.744	1.705	1.714	1.705	1.645	1.697
2	0.912	0.899	0.916	0.907	0.909	0.954	0.912	0.905	0.927	0.901
3	1.031	1.027	0.933	1.031	0.942	1.026	1.031	1.026	0.999	1.022
4	0.911	0.830	0.931	0.907	0.929	0.904	0.911	0.904	0.868	0.899
5	1.029	1.029	1.026	1.021	0.915	1.025	1.029	1.025	1.001	1.021
6	0.916	0.838	0.935	0.806	0.959	0.909	0.916	0.909	0.793	0.903
NH	1.414	1.379	1.361	1.383	1.359	1.397	1.415	1.399	1.456	1.384
1′	1.000	1.001	1.000	1.000	1.000	0.957	1.000	0.959	0.956	0.924
2′	1.026	1.021	1.018	1.021	1.017	1.019	0.980	1.017	1.030	1.017
3′	0.999	0.999	0.999	0.999	0.999	0.958	0.996	0.957	0.957	0.904
4′	1.023	1.018	1.015	1.019	1.015	1.022	0.977	1.024	1.021	1.015
5′						0.959	1.000			0.925
6′						1.025	0.982			1.024
Anilinopyridinium ion (III)										
1N	1.624	1.623	1.618	1.619	1.636	1.623	1.624	1.623	1.619	1.621
2	0.866	0.821	0.865	0.846	0.842	0.867	0.866	0.866	0.846	0.876
3	0.983	0.984	0.939	0.987	0.945	0.980	0.983	0.980	0.985	0.979
4	0.843	0.802	0.864	0.819	0.848	0.842	0.843	0.842	0.817	0.841
5	0.979	0.983	0.954	0.980	0.910	0.978	0.979	0.978	0.979	0.977
6	0.851	0.816	0.856	0.784	0.888	0.850	0.851	0.850	0.783	0.849
NH	1.790	1.771	1.784	1.779	1.777	1.776	1.790	1.778	1.769	1.766
1′	1.016	1.017	1.016	1.016	1.016	0.970	1.017	0.972	0.972	0.931
2′	1.017	1.015	1.016	1.015	1.015	1.010	0.972	1.016	1.015	1.009
3′	0.999	0.999	0.999	0.999	0.999	0.956	0.996	0.955	0.955	0.904
4′	1.015	1.013	1.013	1.013	1.013	1.014	0.969	1.008	1.007	1.008
5′						0.956	1.000			0.917
6′						1.018	0.972			1.017

b) Superdelocalizabilities

Position	H	3-NO_2	4-NO_2	5-NO_2	6-NO_2	2′-NO_2	3′-NO_2	4′-NO_2	5,4′-$(NO_2)_2$	2′,4′-$(NO_2)_2$
Anilinopyridine (I)										
3	0.923	(0.818)	0.893	0.910	0.856	0.915	0.923	0.915	0.903	0.909
4	0.723	0.698	(0.663)	0.700	0.724	0.723	0.723	0.723	0.699	0.273
5	0.903	0.890	0.876	(0.804)	0.844	0.896	0.903	0.896	(0.798)	0.891
6	0.739	0.677	0.739	0.684	(0.679)	0.738	0.739	0.738	0.684	0.732
2′	0.941	0.934	0.941	0.934	0.940	(0.831)	0.913	0.925	0.919	(0.819)
3′	0.831	0.831	0.831	0.831	0.831	0.806	(0.749)	0.791	0.792	0.755
4′	0.932	0.924	0.932	0.925	0.931	0.916	0.888	(0.825)	(0.819)	(0.812)
5′						0.766	0.826			0.737
6′						0.940	0.872			0.923

Pyridone-anil (II)										
3	1.255	(1.049)	1.049	1.193	0.990	1.213	1.256	1.214	1.029	1.180
4	0.769	0.617	(0.720)	0.809	0.789	0.742	0.769	0.741	0.722	0.720
5	1.058	0.998	1.102	(0.916)	0.812	1.029	1.058	1.029	(0.833)	1.006
6	1.003	0.772	1.025	0.764	(0.926)	0.964	1.003	0.963	0.697	0.933
2′	1.049	1.009	1.017	1.020	1.006	(0.910)	1.027	1.016	1.052	(0.887)
3′	0.830	0.830	0.830	0.830	0.830	0.816	(0.747)	0.792	0.791	0.754
4′	1.032	0.993	0.999	1.003	0.989	0.999	0.983	(0.899)	(0.928)	(0.875)
5′						0.766	0.824			0.749
6′						1.040	0.975			1.009
Anilinopyridinium (III)										
3	0.846	(0.761)	0.814	0.842	0.789	0.839	0.846	0.834	0.836	0.833
4	0.566	0.538	(0.531)	0.564	0.573	0.564	0.566	0.564	0.561	0.563
5	0.793	0.789	0.790	(0.720)	0.719	0.789	0.793	0.789	(0.716)	0.875
6	0.670	0.616	0.677	0.597	(0.633)	0.666	0.670	0.665	0.594	0.661
2′	0.924	0.917	0.921	0.919	0.919	(0.818)	0.894	0.910	0.906	(0.808)
3′	0.831	0.831	0.831	0.831	0.831	0.804	(0.748)	0.792	0.792	0.775
4′	0.914	0.907	0.912	0.910	0.909	0.900	0.872	(0.812)	(0.808)	(0.801)
5′						0.767	0.826			0.737
6′						0.922	0.856			0.908

c) Frontier Electron Densities

Position	H	3-NO_2	4-NO_2	5-NO_2	6-NO_2	2′-NO_2	3′-NO_2	4′-NO_2	5,4′-$(NO_2)_2$	2′,4′-$(NO_2)_2$
Anilinopyridine (I)										
3	0.189	(0.152)	0.192	0.179	0.162	0.188	0.191	0.195	0.184	0.194
4	0.001	0.006	(0.008)	0.002	0.001	0.001	0.001	0.001	0.001	0.001
5	0.207	0.196	0.204	(0.171)	0.181	0.208	0.209	0.216	0.179	0.217
6	0.074	0.049	0.074	0.050	(0.063)	0.076	0.075	0.080	0.057	0.083
2′	0.159	0.159	0.160	0.160	0.162	(0.122)	0.179	0.148	0.149	0.113
3′	0.029	0.031	0.028	0.031	0.030	0.050	(0.022)	0.015	0.017	0.030
4′	0.262	0.268	0.262	0.271	0.269	0.250	0.246	(0.218)	0.226	0.209
5′						0.013	0.033			0.005
6′						0.179	0.141			0.167
Pyridone-anil (II)										
3	0.291	(0.247)	0.225	0.283	0.207	0.290	0.293	0.296	0.196	0.294
4	0.086	0.036	(0.083)	0.115	0.101	0.079	0.086	0.079	0.080	0.073
5	0.180	0.171	0.211	(0.151)	0.101	0.178	0.181	0.182	(0.105)	0.180
6	0.211	0.138	0.227	0.136	(0.206)	0.207	0.212	0.211	0.095	0.208
2′	0.124	0.123	0.116	0.122	0.119	(0.097)	0.135	0.116	0.144	(0.091)
3′	0.006	0.007	0.006	0.007	0.007	0.021	(0.004)	0.001	0.002	0.006
4′	0.146	0.151	0.138	0.148	0.145	0.138	0.136	(0.119)	(0.148)	(0.113)
5′						0.001	0.006			0.002
6′						0.135	0.114			0.126
Anilinopyridinium (III)										
3	0.209	(0.179)	0.199	0.202	0.178	0.208	0.211	0.215	0.207	0.213
4	0.019	0.010	(0.018)	0.026	0.022	0.018	0.019	0.018	0.024	0.017
5	0.130	0.122	0.137	(0.111)	0.099	0.129	0.131	0.134	(0.115)	0.134
6	0.155	0.126	0.158	0.125	(0.142)	0.154	0.156	0.160	0.131	0.160
2′	0.169	0.167	0.168	0.169	0.169	(0.130)	0.191	0.158	0.157	(0.121)
3′	0.038	0.041	0.038	0.040	0.040	0.062	(0.030)	0.022	0.024	0.041
4′	0.303	0.308	0.169	0.308	0.309	0.292	0.285	(0.257)	(0.261)	(0.248)
5′						0.020	0.044			0.010
6′						0.192	0.148			0.180

In order to discriminate the true reactive species, the calculations were carried out on the anilinopyridine (I) and the pyridone-anil (II) tautomers of the neutral species, as well as a monoprotonated species (III). From the survey on the results in Table III, the anilinopyridine forms generally have larger frontier electron density values at the 4′-position of the benzene ring and the 5-position of the pyridine ring. The highest *pi*-electron density

and superdelocalizability values are assigned to the 2′- and the 4′-positions of the benzene nuclei. The introduction of a nitro group will tend to decrease the frontier electron densities of the atoms in the ring bonded to the nitro group. The pyridone-anil forms (II) are predicted to have higher reactivity in the hetero-aromatic part of the molecules, which behaves as a diene rather than as an aromatic nucleus. The absolute values of its superdelocalizabilities are larger than other tautomers, and the tautomer (II) is expected to be a highly reactive species. Hetero-aromatic nucleus of the pyridinium ion (III) is estimated to be considerably deactivated towards the attack of electrophiles judging from its lower electron densities and superdelocalizabilities. Thus, electrophiles may attack to the 2′, 4′, and/or 6′-positions of the benzene nucleus.

Then, the behavior of 2-anilinopyridine towards several nitrating reagents under various reaction conditions must be interpreted. 2-Anilinopyridine may be protonated in strongly acidic media, and the protonation is estimated to take place on the nitrogen atom in the pyridine nucleus. The site of the protonation is estimated from the fact that the basicity of diphenylamine (K_b=*ca.* 10^{-14} at 25°) is by far lower than that of pyridine ($K_b=2.3\times10^{-9}$ at 25°).[6] The monoprotonated species must be stable under the conditions for the nitration in nitric or sulfuric acid medium. The second protonation will never occur to a considerable extent under the reaction conditions, since the monoprotonated species is supposed to be a weaker base than diphenylamine. The diprotonated species, if in existence, is considered to be reactive at the *meta*-positions of the benzene nucleus. However, no 3′-nitrated products were obtained in the course of the present investigation and the participation of the dication is denied experimentally. In short, the nitration in strongly acidic media may be properly reproduced by employing the reactivity indices of the monoprotonated species (III).

On the contrary, the 2-anilinopyridines are supposed to exist as a neutral species, either I or II, in non-polar solvents and even in acetic acid. An evidence as to the existence of the neutral species is supplied by the ultraviolet spectral measurement, which will be reported elsewhere. It is difficult to distinguish whether the anilinopyridine tautomer (I) or the pyridone-anil tautomer (II) is the reactive species. The *pi*-electron energies obtained by the HMO calculations are listed in Table IV. The tautomer I is assumed to be the more pre-

Table IV.[a] *pi*-Electronic Energies of the Two Tautomeric Forms and the Protonated Species

Tautomer	H	3-NO_2	4-NO_2	5-NO_2	6-NO_2	2′-NO_2	3′-NO_2	4′-NO_2	5,4′-$(NO_2)_2$	2′,4′-$(NO_2)_2$
I	20.417	27.684	27.647	27.679	27.650	27.688	27.666	27.683	34.944	34.950
II	20.067	27.378	27.476	27.344	27.356	27.351	27.315	27.344	34.341	34.623
III	22.844	30.097	30.050	30.086	30.079	30.112	30.093	30.108	37.348	37.372
ΔE (I–II)	0.350	0.306	0.171	0.335	0.294	0.337	0.351	0.339	0.603	0.327
ΔE (III–I)	2.427	2.413	2.403	2.407	2.429	2.424	2.427	2.425	2.404	2.422

a) In this table, the energy value $(E-n\alpha)/\beta$ is given, where n is the number of p-orbitals involved. ΔE (I–II) and ΔE (III–I) refer to the relative stability of the pyridone-anil tautomer and the relative feasibility of the ionization of the anilinopyridine, respectively.

dominant of the two for the parent 2-anilinopyridine and all nitro-substituted derivatives. However, the energy differences between the two tautomers tend to decrease by the introduction of a nitro group to the pyridine nucleus. This tendency is in accordance with the results by Dewar and co-workers[3b] on their SCF-MO calculations. The investigations of the present authors on the infrared N-H stretching absorptions and the ultraviolet spectra of these compounds have shown that the tautomer I is by far predominant even with 5-nitro-2-

6) *a*) J.D. Roberts and M.C. Caserio, "Basic Principles of Organic Chemistry," Benjamin Inc., New York, 1965, p. 880; *b*) H.C. Brown, H.D. McDaniel, and O. Häfliger, "Determination of the Organic Structures by Physical Methods," Academic Press Inc., New York, 1955, p. 597.

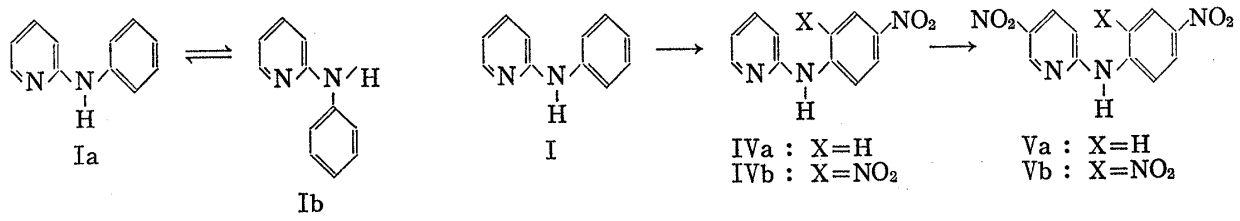
anilinopyridine.[7] However, the reactivity of the compound cannot directly be related with that of the most stable tautomer. A very little amount of the pyridone-anil tautomer II can contribute to the determination of the orientation of the reaction because of its higher reactivity arising from the lower aromatic character of the pyridone structure. Thus, its reactivity can control the course of the whole reaction, even when it is less favorable in equilibrium. In practice, the nitration mainly proceeds to form only 2′- and 4′-mononitro products, and the participation of the pyridone-anil tautomer is not probable under the reaction conditions employed in this investigation.

The nitronium ion, which is assumed to be the reactive species in the nitration, is a resonance hybrid and its lowest unoccupied orbital lies at a lower energy than its component atoms. Thus, the nitronium ion is rather a softer acid and the reaction tends to be frontier-controlled. Frontier electron densities, rather than electron densities, might be suitable to predict the orientation of the frontier-controlled reaction. It is widely recognized that the frontier electron densities can foresee properly the site of the substitution reaction in the substrate molecule, but the predicted reactivities becomes less quantitative when the molecule has an occupied orbital whose energy is very close to that of the highest occupied orbital.[8] The orientation of the nitration is interpreted by assuming either neutral anilinopyridine tautomer (I) or monocation (III) as the reactive species, and is consistent with the experimental consequence that the anilinopyridine tautomer (I) is the reactive species in inert solvents while the monocation (III) is the one in sulfuric or nitric acid. The nitration in acidic media produces 2′-nitro, 4′-nitro, and 2′,4′-dinitro derivatives and further nitration on the pyridine ring never occurs. This is in accordance with the conclusion from the molecular orbital calculations. On the other hand, nitration with an excess of acetyl nitrate in methylene chloride medium gives 5,4′-dinitro and 5,2′,4′-trinitro derivatives other than the products nitrated in the benzene ring (2′-nitro, 4′-nitro, and 2′,4′-dinitro derivatives). With the neutral anilinopyridine tautomer of 4′-nitro- and 2′,4′-dinitro-2-anilinopyridines, the carbon atom at the 5-position in the pyridine ring is predicted to be the most reactive site to electrophiles in each molecule, and a rather large frontier electron density and superdelocalizability value suggests the possibility of the substitution by another nitro group to this position. Thus, the formation of the 5-nitro-substituted products during the nitration with acetyl nitrate proceeds through the nitration of the neutral anilinopyridine tautomers of the lower nitrated products IVa and IVb. This reaction path is supported by the independent nitration of 4′-nitro and 2′,4′-dinitro-2-anilinopyridines (IVa and IVb), forming the 5-nitrated products as shown in Table I.

As described before, the gross feature of the nitration reaction is reproduced by the Hückel molecular orbital calculations. The 3-nitro derivatives never isolated from the nitration products of the parent 2-anilinopyridine, even though rather high reactivity is expected from the reactivity indices, and the nitration to the 3-position is observed only when the 5,2′ and 4′-positions have been occupied already by nitro groups. This may be explained in terms of the effect of steric hindrance, however, there remain some problems to be settled. From the infrared spectra of 2-anilinopyridine in the N-H stretching region, the most stable comformation is estimated to be Ia, and this may be a favorable fact for the effect of the steric hindrance, since the attack of the electrophile to the 3-position is partly blocked by the anilino group in this conformation.

7) T. Mizuno, M. Hirota, Y. Hamada, and Y. Ito, *Tetrahedron*, **27**, 6011 (1971). Concerning the infrared and violet spectroscopic investigation, see also M.G.W. Bell, M. Day, and T. Peters, *J. Chem. Soc.*, **1967**, 132. ultra

8) Lower frontier electron density in 2′-position is reasonable if the second highestoccup ied orbital is taken into consideration. The following figures show the highest and the second highest MO's of 2-anilinopyridine. A high electron density in 2′-position of the second highest MO and their close energy values imply the underestimation of the reactivity at the 2′-position when employed its forntier electron density.



Acknowledgement The authors are grateful to Prof. H. Kakiuchi for his encouragement and valuable advice throughout this work. The present investigation was partly supported by a Scientific Research Grant from the Ministry of Education for which the authors are also grateful.