

Electrophilic Benzylation of the Pyridine Ring; a Charge Sensitivity and MNDO Study

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The sensitivity of carbon and nitrogen atoms in two structures of 2-benzylaminopyridine (**I,II**) and its cations (**III,IV**) to an electrophilic agent attack were investigated in order to determine which are responsible for its 5-benzyl and *N*-benzyl derivative formation in the reaction with benzyl cation. For predicting the most sensitive centres, net atomic charges and HOMO electron density plots were calculated by the MNDO-method, as well as the Fukui function (FF) indices and relaxed chemical potentials of atoms-in-molecules (AIM) within a charge sensitivity (CS) scheme. The analysis indicates that only in structures **I** and **II** the sensitivity of the carbon and nitrogen atoms explains the experimental facts. The analysis also shows that 2-benzylaminopyridine cations (**III** and **IV**) did not participate in the 5-benzyl and *N*-benzyl derivatives of 2-benzylaminopyridine formation. Their presence in the reaction mixture influenced the formation and stabilization of the benzyl cation.

INTRODUCTION

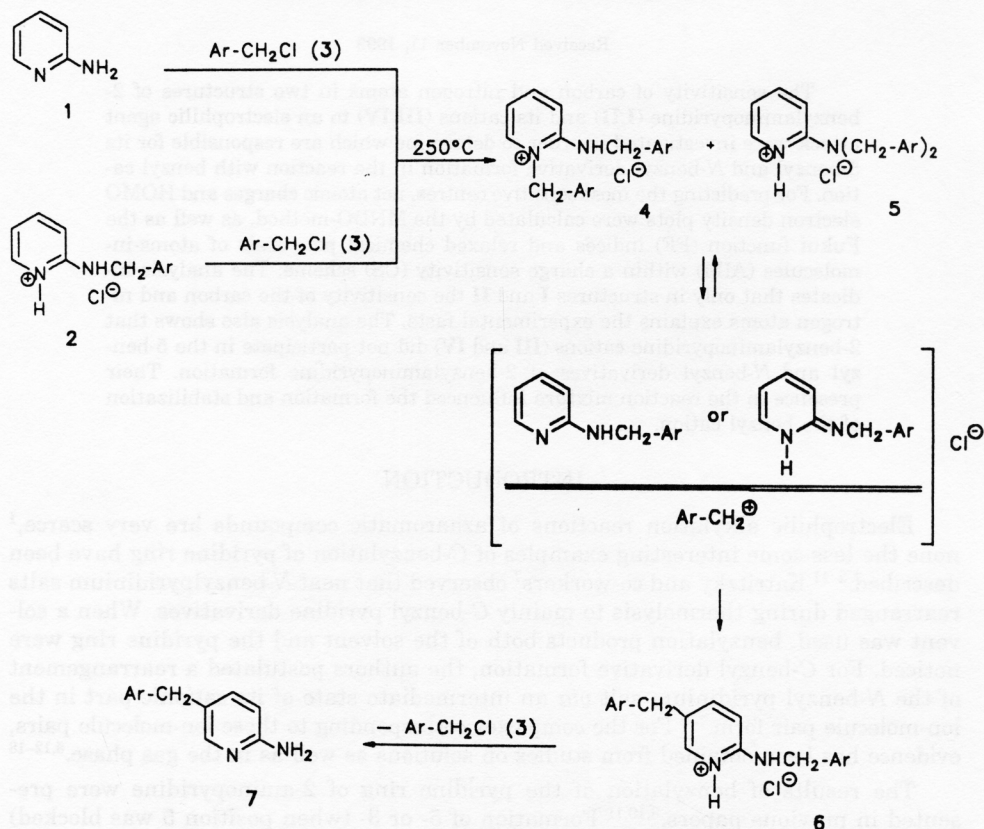
Electrophilic alkylation reactions of azaaromatic compounds are very scarce,¹ none the less some interesting examples of *C*-benzylation of pyridine ring have been described.²⁻¹¹ Katritzky and co-workers⁷ observed that neat *N*-benzylpyridinium salts rearranged during thermolysis to mainly *C*-benzyl pyridine derivatives. When a solvent was used, benzylation products both of the solvent and the pyridine ring were noticed. For *C*-benzyl derivative formation, the authors postulated a rearrangement of the *N*-benzyl pyridinium salt *via* an intermediate state of its cationic part in the ion-molecule pair form.⁷⁻⁹ For the complexes corresponding to these ion-molecule pairs, evidence has been obtained from studies on solutions as well as in the gas phase.^{8,12-18}

The results of benzylation of the pyridine ring of 2-aminopyridine were presented in previous papers.^{6,10,11} Formation of 5- or 3- (when position 5 was blocked) benzyl derivatives were assigned in the reaction of 2-aminopyridines or 2-benzylami-

nopyridines with benzyl chlorides at 250 °C. For example (see Scheme I), the reaction of 2-aminopyridine (1) or 2-benzylaminopyridine (2) hydrochloride with benzyl chloride (3) gives *C*-benzylation products 6 and 7, *i.e.*, 2-benzylamino-5-benzylpyridine and 2-amino-5-benzylpyridine, respectively. In the reaction mixture, as the intermediate substance, 1-benzyl-2-benzylaminopyridinium and 2-(*N,N*-dibenzylamino)pyridinium chlorides (4 and 5) were detected.¹⁰

Formation of 7 takes place as the result of thermolysis of the aminomethylene bond in 6 hydrochloride. For 6 hydrochloride formation, rearrangement of 4 and 5 was postulated to be occurring according to an electrophilic mechanism.¹¹ Literature data and the performed calculations indicate that both cations of 4 and 5 appear in the form of an ion-molecule pair, where benzyl cation coexists with 2-benzylaminopyridine in an amino or imino structure.¹¹ Analysis of the products of the reaction involving labeled benzyl chloride leads to the conclusion that the ion-molecule pair also rearranged into *N*-benzyl derivatives (4 and 5) in the reversible reaction.

Due to the fact that, during the reaction run, 2-benzylaminopyridine is present in the reaction mixture in a significant quantity, and that the reaction is carried out in the presence of hydrogen chloride, the two possible transformations of the ion-molecule pair occur. The first transformation occurs with participation of free 2-benzy-



laminopyridine, formed upon dissociation of the ion-molecule pair, whilst the second transformation takes place with participation of 2-benzylaminopyridine hydrochloride, as solvent.

In order to determine which of the 2-benzylaminopyridine structures are responsible for the observed 5-benzyl and *N*-benzyl derivatives formation in the reaction with benzyl cation, the net atomic charges, HOMO electron densities and sensitivity parameters in *atoms-in-molecules* (AIM) resolution were calculated for free 2-benzylaminopyridine in amino (**I**) and imino (**II**) forms as well as for its cation **III** and **IV** (see Figure 1).

Despite the fact that, in a low acidity medium, the cationic part of 2-benzylaminopyridine hydrochloride may have only structure **III**,¹⁹⁻²¹ reactivities of both, (**III** and **IV**), were studied.

METHOD

Standard MNDO calculations were performed to obtain net atomic charges and HOMO electron density plots.²² In order to obtain additional information on the behavior of atoms in systems **I-IV**, the *Charge Sensitivity* (CS) calculations were done.

The usefulness of *Charge Sensitivity Analysis* (CSA) for predicting site and path selectivities in chemical processes was shown.^{23,24} The basic concepts of CSA, such as hardness (softness), Fukui function (FF) and electronegativity (minus chemical potential) have a special significance for quantifying intuitive chemical concepts and rationalizing reactivity and stability trends.^{32,35} The CSA allows one to discuss the reactivity of *atoms-in-molecules* (AIM) in terms of the molecular charge distribution.

As the theory of CSA has been described elsewhere,³² only some basic definitions will be summarized here. Useful reactivity information may be extracted from the AIM rigid chemical potential and hardness tensor. The former quantity is defined

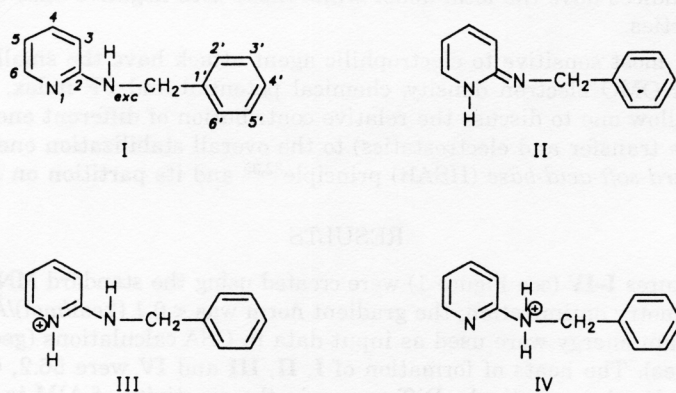


Figure 1. Structural formulas and the labeling of atoms in the investigated compounds: a) 2-benzylaminopyridine (**I**), b) 2-benzylimino-1,2-dihydropyridine (**II**), c) 2-benzylaminopyridinium cation (**III**), d) *N*-(benzyl)-*N*-(2-pyridyl)-ammonium cation (**IV**).

by the first partial derivative of the system electronic energy, E , with respect to the population of AIM, $\mathbf{N} = \{N_1, N_2, \dots, N_m\}$,

$$\underline{\mu} = \{\mu_1, \mu_2, \dots, \mu_m\} = \partial E(\mathbf{N})/\partial \mathbf{N},$$

while the latter as the respective second partial derivative,

$$\underline{\eta} = \partial^2 E(\mathbf{N})/\partial \mathbf{N}^2 = \partial \underline{\mu}(\mathbf{N})/\partial \mathbf{N},$$

where m denotes the number of atoms in the system. Both quantities are interpolated into actual valence states, characterized by the AIM charges and correspond to a system (M) composed of mutually closed atoms. It means that there is no flow of electrons between atoms

$$\mathbf{M} = (i | j | \dots).$$

By removing the barriers on charge flow, one can obtain a whole hierarchy of relaxed quantities. Such relaxed parameters contain information about the »real« chemical processes and better described site and path phenomena.³⁴

An important part in discussing charge rearrangement during a chemical process is played by the FF indices. The FF index describes a change in electron population of the i -th AIM per global perturbation in the number of electrons, dN ,

$$f_i = \partial N_i / \partial N.$$

One should observe that the sign of the index is responsible for the local donor/acceptor behavior. Thus, when a molecule, as a whole, acts as a base, atoms with positive FF indices have the local donor while these with negative ones the local acceptor properties.

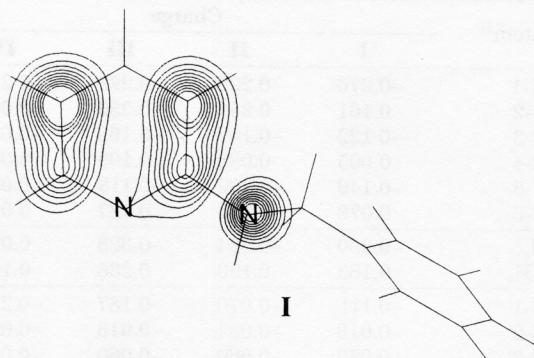
The AIM most sensitive to electrophilic agent attack have the smallest charge, the highest HOMO electron density, chemical potential and FF index. Significant hardnesses allow one to discuss the relative contribution of different energy components (charge transfer and electrostatics) to the overall stabilization energy according to the *hard-soft-acid-base* (HSAB) principle^{32,35} and its partition on AIM.

RESULTS

All structures **I-IV** (see Figure 1) were created using the standard MNDO-method with full geometry optimization; the gradient norm was < 0.1 (kcal/mol)/Å. Conformers of minimum energy were used as input data in CSA calculations (geometry and atomic charges). The heats of formation of **I**, **II**, **III** and **IV** were 56.2, 67.8, 206.9, and 217.7 kcal/mol, respectively. Differences in the reactivity of AIM in all investigated structures **I-IV** are reflected in the net atomic charges (Table I) and HOMO electron density plots (Figures 2 and 3).

All nitrogen atoms, except N_{exc} in **IV**, have higher negative charges than the carbon atoms in **I-IV** (see Table I). The highest negative charges are for the N_{exc} in **I-III** and N-1 in **IV**. Among carbon atoms, the highest negatively charged ones are

a)



b)

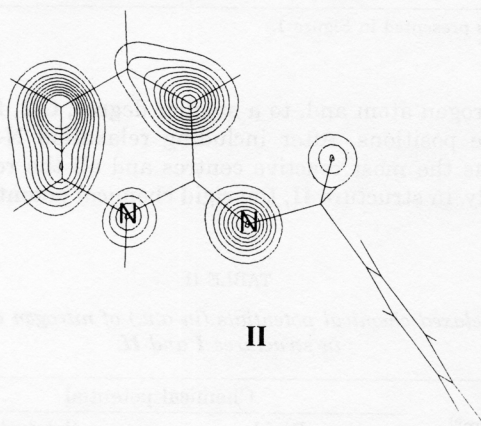


Figure 2. HOMO electron density plots for surface 1 Å above the pyridyl ring plane; a) 2-benzylaminopyridine (**I**), b) 2-benzylimino-1,2-dihydropyridine (**II**). The first contour at 0.0005, interval between contour levels 0.0005.

the C-5 atoms in **I** and **II**, C-3 atom in **III**; in the case of **IV**, charges of C-3 and C-5 atoms are almost the same.

The main value of electron density on HOMO orbitals in structure **I** is that of the N_{exc} atom and, to a smaller degree, of the C-3 and C-5 ones (Figure 2a). In the case of **II**, the electron density on HOMO orbitals decreases in the sequence $C-5 \approx N_{exc} > C-3 > N-1$ (Figure 2b). In structures **III** (Figure 3a) and **IV** (Figure 3b), HOMO orbitals are mainly occupied by the phenyl ring electrons.

Table II lists rigid and totally relaxed chemical potential parameters of the atoms in structures **I** and **II**. The rigid chemical potentials in structure **I** favor es-

TABLE I

Net atomic charges (in a.u.), on nitrogen and carbon atoms in structures I-IV.

Atom ^{a)}	Charge			
	I	II	III	IV
N-1	-0.276	-0.290	-0.229	-0.218
C-2	0.161	0.256	0.385	-0.009
C-3	-0.122	-0.157	-0.168	-0.052
C-4	0.005	0.038	0.109	0.009
C-5	-0.149	-0.202	-0.118	-0.056
C-6	0.078	0.133	0.127	0.096
N _{exc}	-0.290	-0.394	-0.328	0.029
CH ₂	0.183	0.190	0.235	0.166
C-1'	-0.111	-0.070	-0.187	-0.228
C-2'	-0.018	-0.034	-0.013	-0.008
C-3'	-0.070	-0.069	-0.060	-0.058
C-4'	-0.044	-0.056	-0.013	0.011
C-5'	-0.068	-0.069	-0.060	-0.058
C-6'	-0.035	-0.035	-0.005	-0.001

^{a)} as presented in Figure 1.

pecially the N-1 nitrogen atom and, to a smaller degree, C-2, N_{exc} and C-6 atoms as the highest reactive positions. After including relaxation N-1, N_{exc}, C-5 and C-3 atoms of **I** appear as the most reactive centres and all the remaining ones as less reactive. Analogously, in structure **II**, the rigid chemical potential distinguishes N_{exc},

TABLE II

Rigid (μ) and relaxed chemical potentials (in a.u.) of nitrogen and carbon atoms in structures I and II.

Atom ^{a)}	Chemical potential			
	Rigid		Relaxed	
	I	II	I	II
N-1	-0.180	-0.219	-0.221	-0.224
C-2	-0.191	-0.194	-0.257	-0.272
C-3	-0.209	-0.210	-0.229	-0.219
C-4	-0.217	-0.223	-0.247	-0.251
C-5	-0.209	-0.216	-0.228	-0.219
C-6	-0.206	-0.232	-0.244	-0.247
N _{exc}	-0.203	-0.157	-0.222	-0.190
CH ₂	-0.228	-0.205	-0.233	-0.235
C-1'	-0.210	-0.196	-0.241	-0.242
C-2'	-0.218	-0.204	-0.238	-0.230
C-3'	-0.218	-0.207	-0.234	-0.228
C-4'	-0.218	-0.208	-0.238	-0.231
C-5'	-0.217	-0.207	-0.234	-0.229
C-6'	-0.216	-0.204	-0.236	-0.230

^{a)} as presented in Figure 1

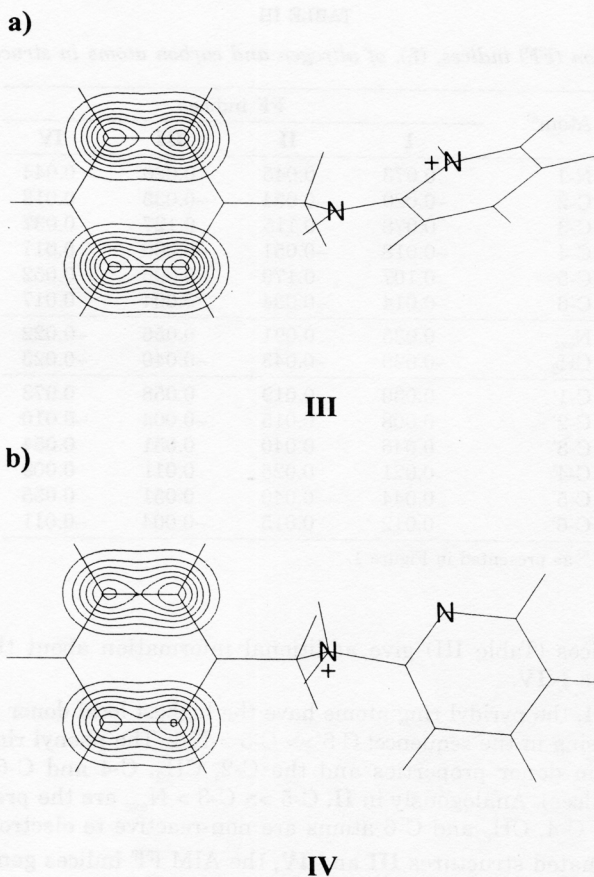


Figure 3. HOMO electron density plots for surface 1 Å above the phenyl ring plane; a) 2-benzylaminopyridinium cation (**III**), b) *N*-(benzyl)-*N*-(2-pyridyl)-ammonium cation. (**IV**). The first contour at 0.0005, interval between contour levels 0.001.

C-2, C-1 and C-3 while relaxed parameters N_{exc} , C-3, C-5 and N-1 as the preferred reaction sites. General comparison of these data points to the great importance of relaxation corrections for distinguishing electron-donating centres in molecules. For both forms of 2-benzylaminopyridine, **I** and **II**, the same groups of more- and less-reactive centres were obtained.

Differences in the relaxed chemical potentials between AIM disappear in the cationic forms **III** and **IV**. In the case of **III**, nearly for all atoms, the values oscillate between -0.366 for N_{exc} and -0.389 for N-1. The smallest values, -0.400 and -0.391 , are possessed by C-2 and C-4, respectively. In structure **IV**, the reactivity of atoms is almost the same, except for the protonated nitrogen atom which has the smallest relaxed chemical potential (-0.430). For the remaining atoms of **IV**, the values oscillate between -0.368 for C-1' to -0.385 for C-6'.

TABLE III

Fukui function (FF) indices, (f_i), of nitrogen and carbon atoms in structures **I-IV**.

Atom ^{a)}	FF indices			
	I	II	III	IV
N-1	0.073	0.045	0.020	0.044
C-2	-0.029	-0.054	-0.035	0.013
C-3	0.078	0.115	0.127	0.037
C-4	-0.018	-0.051	-0.030	0.017
C-5	0.107	0.170	0.096	0.052
C-6	-0.014	-0.034	0.004	0.017
N _{exc}	0.035	0.091	0.056	-0.022
CH ₂	-0.029	-0.043	-0.040	-0.023
C-1'	0.030	0.019	0.058	0.073
C-2'	0.008	0.015	-0.004	-0.010
C-3'	0.046	0.040	0.051	0.054
C-4'	0.021	0.025	0.011	0.009
C-5'	0.044	0.040	0.051	0.055
C-6'	0.012	0.015	-0.004	-0.011

^{a)} as presented in Figure 1.

The FF indices (Table III) give additional information about the reactivity of atoms in systems **I-IV**.

In structure **I**, the pyridyl ring atoms have the highest local donor properties, with reactivity decreasing in the sequence: C-5 >> C-3 > N-1. The phenyl ring carbon atoms have the medium donor properties and the C-2, CH₂, C-4 and C-6 local acceptor (negative FF indices). Analogously in **II**, C-5 >> C-3 > N_{exc} are the preferred reaction sites, while C-2, C-4, CH₂ and C-6 atoms are non-reactive to electrophilic attack.

In the protonated structures **III** and **IV**, the AIM FF indices generally decrease in comparison to the corresponding atoms in **I** and **II**. The most reactive centres are C-3 > C-5 > N_{exc} atoms in **III** and C-5 > N-1 > C-3 in **IV**.

DISCUSSION

Comparison of negative charge values, HOMO electron density plots, relaxed chemical potentials and FF indices of carbon atoms in **I** and **II** indicates that the C-5 pyridyl carbon atoms in both structures are the preferred reaction sites of electrophilic attack. In structure **III**, the C-3 pyridyl carbon atom appears as the most reactive one, and in the last structure **IV**, reactivities of C-3 and C-5 are close to each other.

It is therefore apparent that, if structures **III** and **IV** were taking part in the electrophilic *C*-benzylation processes, compounds substituted at position 3 should be formed in a noticeable amount. Such compounds, however, were not found in the reactions of 2-aminopyridines (with unblocked positions 3 and 5) with benzyl chlorides.^{6,10,11} This points to the conclusion that structures **III** and **IV**, and in this way 2-benzylaminopyridine hydrochloride, do not participate in the 5-benzyl derivatives formation. In other words, the electrophilic *C*-benzylation of the 2-benzylaminopyridine ring should take place with the free bases **I** or **II**.

Experimentally, the influence of the 2-benzylaminopyridine hydrochloride on increasing reaction yields is related to its influence on stabilization of the benzyl cation because the highly polar reaction medium favors cation formation and stabilization. Dipole moments, calculated by the MNDO-method, for **III** and **IV** are 7.90 D and 3.77 D, while for **I** and **II** 1.41 and 2.42 D, respectively.

Elimination of the influence of structures **III** and **IV** on the 5-benzyl derivatives formation indicates that cationic forms of 2-aminopyridine do not participate in the transformation of the ion-molecule pair. For this reason, consideration of the transformations of the ion-molecule pair into *N*-benzyl derivatives formation (salts **4** and **5**) is reduced to discussion of the reactivity of nitrogen atoms (N-1 and N_{exc}) in the free bases of 2-benzylaminopyridine, *i.e.* **I** and **II**.

It should be noted here that, in the spirit of the HSAB principle, the FF indices are responsible for soft-soft interactions and the charges for hard-hard interactions.

The calculated relaxed diagonal hardnesses for N-1, N_{exc}, C-3 and C-5 atoms in structure **I** are: 0.245, 0.217, 0.184 and 0.177, and in **II**: 0.201, 0.208, 0.174 and 0.167, respectively. These data indicate that with decreasing hardness of the electrophilic agents, the affinity of the atoms to this attack increases in the sequence; N-1, N_{exc}, C-3 to C-5 atoms in **I** and N-1 \approx N_{exc}, C-3 to C-5 atoms in **II**.

Chemical intuition indicates that the benzylic cation hardness has a medium value with the position between the hard proton and the soft iodide cation. For such a cation, the chemical reactivity of AIM's is limited to a few reactivity criteria, which correspond to different components (e.g., electrostatic, charge transfer, polarizational, geometry relaxation and Pauling) of the total interaction energy. Of course, it is not entirely clear which of them is dominant. Crossing of the high values of negative charges of the nitrogen atoms with the high values of FF indices of the C-5 carbon atoms in **I** and **II** makes it difficult to anticipate the priority of *N*-benzyl or *C*-benzyl derivatives formation in the reaction of benzyl cation with 2-benzylaminopyridine (**I** or **II**).

Nevertheless, comparisons of the FF indices, HOMO electron density plots, relaxed chemical potentials as well as the negative charges of the carbon atoms in **I** and **II**, show that, in the 5-benzyl derivative of 2-benzylaminopyridine (**6**) formation, the most effective C-5 carbon atom appears in structure **II**.

Analogously, the relaxed chemical potentials, FF indices and the negative charge values calculated for nitrogen atoms in **I** and **II**, indicate that N_{exc} in **II** appears as the most effective in the *N*-benzyl derivatives formation. The performed analysis of the reactivity of nitrogen atoms in **I** and **II** leads to the conclusion that ingredients of the ion-molecule pair, composed of 2-benzylaminopyridine and benzyl cation, should preferentially form 2-(*N,N*-dibenzylamino)pyridinium cation in the reversible reaction. This is in full agreement with the experimental results, where concentration of compound **5** in the reaction mixture is much higher than that of **4**.¹¹

CONCLUDING REMARKS

The performed analyses indicate that the formation of *C*-benzyl and *N*-benzyl derivatives of 2-benzylaminopyridine, as stated in the reactions of 2-amino- and 2-benzylaminopyridines with benzyl chlorides, is a result of the reaction of free-bases of 2-benzylaminopyridine (**I** or **II**) with the benzyl cation. This may support the hypothesis that the reaction takes place *via* a ion-molecule pair composed of 2-benzylaminopyridine (**I** and **II**) and the benzyl cation.

A general comparison of the calculated reactivity indices of pyridyl carbon (3 and 5) and nitrogen atoms in **I** and **II** indicated that carbon atoms appear as softer electron-donating centres than the nitrogen atoms. This is in agreement with the results obtained in a CSA analysis of 2-aminopyridine and its derivatives on an electrophilic agent attack, where it was found that the pyridyl carbon atoms (3 and 5) in the amino and imino forms of 2-aminopyridine are less hard than N_{exc} and N_{an} , so the electrophilic attack on carbon atoms is mainly charge transfer controlled, while on nitrogen atoms it is mainly electrostatically controlled.^{34,36}

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SAŽETAK

**Elektrofilno benziliranje piridinskog prstena:
studija metodama osjetljivosti naboja i MNDO***Piotr Kowalski i Jacek Korchowicz*

Istražene su osjetljivosti ugljikovih i dušikovih atoma u dvjema strukturama 2-benzilaminopiridina (**I**, **II**) i njihovih kationa (**III**, **IV**) prema napadu elektrofilnog agensa, s ciljem da se odrede atomi odgovorni za nastajanje 5-benzil- i *N*-benzil-derivata u reakciji s benzilnim kationom. Za proračun najosjetljivijih centara izračunani su metodom MNDO atomski naboji i elektronske gustoće HOMO, kao i Fukuijevi indeksi i relaksirani kemijski potencijali atoma-u-molekulama unutar koncepta osjetljivosti naboja. Analiza pokazuje da osjetljivost ugljikovih i dušikovih atoma objašnjava eksperimentalne činjenice samo u strukturama **I** i **II**, te da u nastajanju 5-benzil- i *N*-benzil-derivata 2-benzilaminopiridina ne sudjeluju 2-benzilaminopiridin-kationi (**III** i **IV**). Njihova prisutnost u reakcijskoj smjesi utječe na nastajanje i stabilizaciju benzil-kationa.