The suppressed reactivity of pyridine towards electrophiles as a result of an interplay between intra- and intermolecular interactions

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Abstract

A new accounting is suggested for the suppressed relative reactivity of all carbon atoms of pyridine as compared to benzene in the bimolecular electrophilic substitution (S_E2) processes in terms of an interplay between intra- and intermolecular interactions. Introduction of a nitrogen atom is shown to be accompanied by emergence of intramolecular interactions between the usual molecular orbitals of benzene that, in turn, give birth to definite mixed terms containing products of intra- and intermolecular interactions in the perturbative expansions for populations transferred between orbitals of the aromatic ring and those of electrophile. For *ortho* and *para* directions of the electrophilic attack, all the principal intramolecular interactions are shown to yield negative contributions to the intermolecular charge transfer in accordance with the dramatically reduced reactivities of these positions in pyridine. By contrast, contributions of different signs are shown to emerge in the relevant expressions referring to the meta attack. In this connection, conditions are revealed and analyzed that ensure the reduced intermolecular charge transfer for the *meta* position as well. Electrophiles of sufficiently high electron-accepting ability are shown to meet these conditions.
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1. Introduction

The last several decades are characterized by an extensive development of computational methods in quantum chemistry, and, consequently, by increasing overall predictability of various phenomena of the molecular world. So far as understanding the molecular structure and properties is concerned, it was emphasized recently to lag behind [1,2]. The suppressed reactivity of pyridine towards electrophiles serves as an excellent example illustrating the above assertion.

The relative reactivity of pyridine is known to be lowered substantially vs. that of benzene in the bimolecular electrophilic substitution processes [3–5]. Moreover, even the most reactive *meta*-positioned carbon atoms of this heterocycle are considerably less reactive as compared to particular atoms of benzene [4]. Although a long time passed since discovering these facts, a straightforward accounting for them keeps to be a real challenge for theoretical organic chemistry.

This especially refers to the suppressed reactivity of *meta*-positioned carbon atoms.

Understanding of molecular properties usually is expected to follow from qualitative models of quantum chemistry, including the simplest versions both of the valence bond method [6] and of the Hückel model [4]. In the framework of the latter, the most popular representation of passing from benzene to pyridine consists of alteration in the Coulomb parameter of the $2p_z$ AO referring to the more electronegative nitrogen atom [4,5,7,8], and relative reactivities usually are correlated to populations of AOs. The latter approach originates from the pioneering model of substitution processes [9–12], wherein the reagent is taken into account implicitly as an additional alteration in the Coulomb parameter of the AO under attack. Increased populations of AOs of *meta*-positioned carbon atoms of pyridine vs. those of benzene follow from the famous rule of alternating polarity [7,8,10,13], and this result is not in line with the relative reactivities. This failure was entirely ascribed to the seemingly oversimplified nature of the Hückel model. In this connection, numerous attempts to 'improve' the charge redistribution in pyridine were undertaken by turning to more sophisticated models and methods (see Refs. [4,8]) and some of them proved to be successful. These achievements, however, gave no real insight into the origin of the suppressed reactivity of this heterocycle.

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Comparison of stabilities of various Wheland intermediates (σ-complexes) also meets analogous difficulties. In particular, application of the simple valence bond method to these complexes shows that the *meta*-positioned nitrogen atoms do not exert any influence upon stability of the relevant resonance structures [4]. As a result, relative reactivities of *meta*-positioned carbon atoms of pyridine are predicted to coincide with those of benzene.

The more modern way of accounting for different reactivities of alternative routes of reactions in terms of structures of the so-called frontier molecular orbitals (MOs) [14–16] also exhibits a limited success in this field. The suppressed overall reactivity of pyridine may be traced back to the lowered energy of the highest-occupied MO (HOMO) of this heterocycle vs. that of benzene following from both accurate quantum-chemical calculations [17] and photoelectron spectroscopy [16,18]. However, the HOMO of pyridine is predicted by the same methods to correspond to the antisymmetric ($1a_2$) MO containing zero increments of AOs of both heteroatom and *para*-positioned carbon atom along with similar contributions of *ortho*- and *meta*-positioned carbon atoms. Two difficulties arise here. First, no simple accounting may be given for the lowered energy of the actual HOMO of pyridine vs. that of benzene, and, second, constitution of the HOMO is not in line with the fact that exclusively *meta*-derivatives result from the electrophilic substitution of pyridine. Finally, consideration of the next occupied orbital does not yield a way out of this situation. (This orbital is described by the $2b_1$ symmetry and thereby by largest increments of $2p_z$ AOs of *para*-positioned carbon atoms.)

Lack of an explicit consideration of the reagent seems to be among the origins of difficulties under discussion. Moreover, the attempts to relate the relative reactivities of different routes of a certain process exclusively to characteristics of the reactant is likely to give rise to a more profound deficiency of respective approaches, namely to underestimation of the overall importance of intermolecular interaction to chemical reactivity: Certainly, the intramolecular interactions in the reactant are taken into account exactly in these approaches by means of passing to the basis of respective MOs, whilst the interaction between reacting molecules is considered only implicitly as a certain perturbation when looking for an appropriate criterion of reactivity [4,5,7,8].

In this context, the approach suggested recently [19] and based on the power series for the one-electron density matrix (DM) [20] deserves attention. Indeed, orbitals of both the reactant and the reagent are taken into account explicitly in this approach (although simplified models of the reagent involving a single orbital also are possible). Moreover, both intra- and intermolecular interactions are treated on the unified basis, namely by means of the perturbation theory. It is quite likely, therefore, that simplicity may be combined with adequacy of the model just in this case. In this connection, we are about to explore the possibilities of this approach for interpretation of the suppressed reactivity of pyridine in this paper.

Application of the same approach to other reactions (see Ref. [21] and references therein) showed that different relative reactivities referring either to different reactants or reagents or to alternative routes of the same process may be related to dissimilar efficiencies of charge redistributions between pairs of orbitals of the whole reacting system including those of the intermolecular type. Moreover, non-zero intramolecular interactions between orbitals of the reactant (if any) exert an indirect influence upon the intermolecular charge redistribution and vice versa [19]. Invoking of the results of Ref. [22] also is appropriate to the present stage of this discussion. Indeed, passing from benzene to pyridine was shown to be accompanied by emergence of resonance parameters between pairs of MOs of the former and thereby of direct intramolecular interactions inside the aromatic ring. We may then expect that these new intramolecular interactions are able to give rise to an alteration in the extent of charge transfer between the aromatic ring and electrophile and thereby to a related change in the reactivity of the former. Dependence of the actual charge transfer upon the relative position of the reagent with respect to the site of substitution also is among anticipations. Thus, the aim of the present study consists in revealing the immediate effect of substitution of a carbon atom of benzene by a nitrogen atom upon the extent of the charge transfer between the aromatic system and electrophile. To this end, we will derive and analyze the expressions for populations transferred between the relevant orbitals before and after substitution.

The paper is organized as follows. We start with an overview of general expressions for charge redistribution following from the power series for the one-electron density matrix (Section 2). Thereupon, we turn to the model of the reacting pyridine in Section 3 and consider second-order terms of the power series. The most important third-order corrections to charge redistribution describing the effect of substitution upon the intermolecular charge transfer are examined in Section 4.

2. General expressions for charge redistribution

Let the system under interest to be represented by the basis set $\{\varphi\}$ containing initially occupied basis orbitals (IOBOs) $\varphi_{(+)\mathrm{p}}$ and initially vacant orbitals (IVBOs) $\varphi_{(-)\mathrm{l}}$ separated by a substantial energy gap [20,23]. The charge redistribution between these orbitals due to their interaction was shown to be conveniently representable in terms of partial populations $(q_{(-)\mathrm{l},(+)\mathrm{p}})$ transferred between any pair of orbitals of opposite initial occupation, i.e. between an IOBO ($\varphi_{(+)\mathrm{p}}$) and an IVBO ($\varphi_{(-)\mathrm{l}}$) [23]. These populations, in turn, consist of sums of corrections $q_{(-)\mathrm{l},(+)\mathrm{p}}^{(k)}$ of various orders k starting with $k=2$. Furthermore, the corrections $q_{(-)\mathrm{l},(+)\mathrm{p}}^{(k)}$ have been expressed in terms of elements $G_{(k)\mathrm{pl}}$ of certain principal matrices $\mathbf{G}_{(k)}$ discussed below. In particular, the second- and third-order increments of partial transferred populations take the form

$$q_{(-)\mathrm{l},(+)\mathrm{p}}^{(2)} = 2(G_{(1)\mathrm{pl}})^2, \tag{1}$$

$$q_{(-)\mathrm{l},(+)\mathrm{p}}^{(3)} = 4G_{(1)\mathrm{pl}}G_{(2)\mathrm{pl}}. \tag{2}$$

Let us introduce the following notations for elements of the perturbation operator between basis orbitals $\{\varphi\}$, the latter being indicated inside the bra- and ket-vectors

$$S_{pm} = \langle \varphi_{(+)p} | \hat{V} | \varphi_{(+)m} \rangle, \qquad R_{pl} = \langle \varphi_{(+)p} | \hat{V} | \varphi_{(-)l} \rangle,$$
$$Q_{rs} = \langle \varphi_{(-)r} | \hat{V} | \varphi_{(-)s} \rangle, \tag{3}$$

and note that $S_{pm} = S_{mp}$, $Q_{rs} = Q_{sr}$ but $R_{pl} \neq R_{lp}$. In the framework of the simple Hückel model, the off-diagonal elements defined by Eq. (3) coincide with resonance parameters between respective basis orbitals. Non-zero diagonal elements S_{pp} and Q_{ss} (if any) represent the self-interactions of the corresponding orbitals. Elements $G_{(1)pl}$ and $G_{(2)pl}$ contained within Eqs. (1) and (2) may be then expressed as follows [20]

$$G_{(1)pl} = -\frac{R_{pl}}{E_{(+)p} - E_{(-)l}}, \tag{4}$$

$$G_{(2)pl} = \frac{1}{E_{(+)p} - E_{(-)l}} \left[\sum_m^{\text{IOBOs}} \frac{S_{pm}R_{ml}}{E_{(+)m} - E_{(-)l}} - \sum_s^{\text{IVBOs}} \frac{R_{ps}Q_{sl}}{E_{(+)p} - E_{(-)s}} \right], \tag{5}$$

where the denominators of fractions contain one-electron energies of respective orbitals. The first-order element $G_{(1)pl}$ of Eq. (4) has been interpreted as the direct interaction between orbitals $\varphi_{(+)p}$ and $\varphi_{(-)l}$. Inasmuch as this element is inversely proportional to the relevant energy interval $(E_{(+)p} - E_{(-)l})$, the direct interactions usually are insignificant for orbitals described by distant energy levels. Similarly, the second-order increment $G_{(2)pl}$ of Eq. (5) describes the indirect interaction of the same orbitals by means of mediators. It is seen that both IOBOs ($\varphi_{(+)m}$) and IVBOs ($\varphi_{(-)s}$) are able to play this role. To be an efficient mediator, however, the orbital under consideration should overlap with both $\varphi_{(+)p}$ and $\varphi_{(-)l}$. Given that a certain self-interaction takes a non-zero value (e.g. $S_{pp} \neq 0$), a self-mediating effect of the respective orbital is expected. Finally, the above interpretation of elements $G_{(1)pl}$ and $G_{(2)pl}$ allows the corrections $q_{(-)l,(+)p}^{(2)}$ and $q_{(-)l,(+)p}^{(3)}$ of Eqs. (1) and (2) to be considered as describing the direct and indirect charge transfer, respectively, between the IOBO $\varphi_{(+)p}$ and the IVBO $\varphi_{(-)l}$.

3. The model of the reacting pyridine. The direct intermolecular charge transfer

Let us start with the simple Hückel model for benzene in the basis of six $2p_z$ AOs of carbon atoms $\{\chi\}$. The AOs will be enumerated in the usual cyclic way so that χ_1 will correspond later to the site of perturbation (Fig. 1). Let the energy
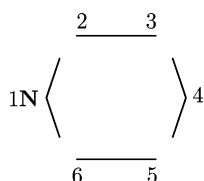

Fig. 1. Numbering of $2p_z$ AOs of pyridine.

reference point and the energy unit to be defined by equalities $\alpha = 0$ and $\beta = 1$, where α and β stand for the standard Coulomb and resonance parameters, respectively.

To comply with the requirements of the power series of Ref. [20], let us turn to the basis of canonical MOs of benzene. The relevant transformation matrix takes the form [22]

$$\mathbf{C} = \begin{vmatrix} a & b & 0 & 0 & b & a \\ a & c & d & -d & -c & -a \\ a & -c & d & d & -c & a \\ a & -b & 0 & 0 & b & -a \\ a & -c & -d & -d & -c & a \\ a & c & -d & d & -c & -a \end{vmatrix}, \tag{6}$$

where $a = 0.408$, $c = 0.289$, $b = 2c = 0.577$, $d = 0.500$. The MOs defined by separate columns of the matrix $\mathbf{C}$ will play the role of the principal basis functions of our study $\{\varphi\}$ (Section 2) along with orbitals of the reagent specified below. Let these orbitals to be correspondingly denoted by $\varphi_{(+)1}^s$, $\varphi_{(+)2}^s$, $\varphi_{(+)3}^a$, $\varphi_{(-)4}^a$, $\varphi_{(-)5}^s$ and $\varphi_{(-)6}^s$, where the superscripts s and a indicate the symmetric and antisymmetric nature of the MO, respectively, relatively to the plane embracing the first and the fourth carbon atoms (Fig. 1). One-electron energies of these MOs correspondingly equal to 2, 1, 1, -1, -1, -2 in our negative energy units.

Let us assume now that the benzene molecule is under attack of electrophile (E). The latter will be modelled by a single initially vacant orbital $\varphi_{(-)E}$ represented by the one-electron energy $-\varepsilon_{(-)E}$, where the minus sign in front of $\varepsilon_{(-)E}$ is introduced for convenience. Moreover, the energy level of electrophile will be additionally assumed to be situated above the energy reference point so that $\varepsilon_{(-)E} > 0$ (Fig. 2). To model different directions of the attack of electrophile upon the ring, the orbital $\varphi_{(-)E}$ will be situated above a particular AO χ_i, where $i = 2$, 3 and 4 correspond to *ortho*, *meta* and *para* positions, respectively. The intermolecular resonance parameter between the AO under attack and the orbital $\varphi_{(-)E}$ will be denoted by σ, i.e. $\langle \chi_i | \hat{V} | \varphi_{(-)E} \rangle = \sigma$. To make a
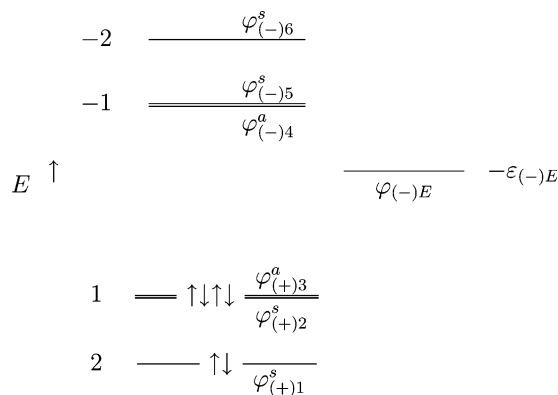

Fig. 2. Relative positions of one-electron energies corresponding to basis orbitals of the reacting pyridine. The MOs of benzene are shown in the left part of the diagram, whereas the electron-accepting orbital of electrophile is displayed in the right part.

comparison of various directions of the attack easier, this resonance parameter will be assumed to take the same value whatever the actual direction of the attack.

After passing to the basis $\{\varphi\}$, intermolecular resonance parameters arise between the orbital $\varphi_{(-)E}$ and MOs of benzene. These equal to

$$R_{pE}^{(i)} = \sigma C_{ip}; \qquad Q_{rE}^{(i)} = \sigma C_{ir}, \tag{7}$$

where p and r refer to orbitals $\varphi_{(+)p}$ and $\varphi_{(-)r}$. Coefficients C_{ip} and C_{ir} coincide with elements of the matrix $\mathbf{C}$ of Eq. (6) contained within the pth and rth column, respectively, and corresponding to the AO χ_i. Non-zero values of resonance parameters shown in Eq. (7) evidently imply emergence of the relevant direct intermolecular interactions (see Eq. (4)). The latter, in turn, give rise to direct charge redistribution between MOs of benzene and the orbital of the reagent described by the second-order partial transferred populations $q_{(-)E,(+)1}^{(2)}$, $q_{(-)E,(+)2}^{(2)}$ and $q_{(-)E,(+)3}^{(2)}$. Uniform total populations acquired by the electrophile for various directions of the attack upon benzene easily follow from the relevant expressions for the above-enumerated partial increments after invoking the relation $c^2 + d^2 = b^2$ for elements of the matrix $\mathbf{C}$. (The relation results from the unitarity condition for this matrix.)

Let us turn finally to the pyridine molecule under attack of the same reagent (E). In the basis of $2p_z$ AOs $\{\chi\}$, replacing of the carbon atom C_1 by a nitrogen atom (N) is described by an alteration in the relevant Coulomb parameter as usually. As a result, the respective perturbation matrix contains a single non-zero element $\langle\chi_i|\hat{V}|\chi_i\rangle = \alpha$. It should be emphasized here that the above-specified basis set $\{\varphi\}$ will be retained in the case of pyridine as well. The transformed perturbation matrix then contains several non-zero elements determined by coefficients of the first row of the matrix $\mathbf{C}$. In particular, elements referring to the HOMO and the LUMO of benzene are

$$S_{22} = R_{25} = Q_{55} = \alpha b^2, \qquad S_{33} = R_{34} = Q_{44} = 0. \tag{8}$$

The second relation indicates that the antisymmetric subspace of MOs $(\varphi_{(+)3}^a, \varphi_{(-)4}^a)$ is not embraced by the perturbation. This result implies emergence of direct intramolecular interactions, as well as of intramolecular self-interactions in the heterocycle.

It is evident that the direct intermolecular interactions represented by parameters of Eq. (7) are not influenced by the intramolecular perturbation due to substitution. The same refers also to the above-discussed second-order intermolecular partial populations transferred between pairs of orbitals directly. At the same time, the intramolecular perturbation examplified by Eq. (8) gives rise to a certain direct intramolecular charge redistribution [22] that is not influenced by the approaching electrophile. Hence, intra- and inter-molecular charge redistributions are mutually independent (additive) effects within the second-order terms inclusive. Thus, the third-order (indirect) charge redistributions should be examined when looking for the effect of the intramolecular perturbation due to substitution upon the extent of the

intermolecular charge transfer. We turn to this analysis in Section 4.

4. Analysis of expression for the indirect intermolecular charge transfer

The scheme of energy levels shown in Fig. 2 indicates that the lowest occupied MO of benzene $\varphi_{(+)1}^s$ takes a rather remote position vs. the electron-accepting orbital of the reagent. Consequently, the correction $q_{(-)E,(+)1}^{(3)}$ hardly plays a decisive role in the intermolecular charge redistribution. Again, from Eq. (8), it follows that the charge transfer from the antisymmetric MO $\varphi_{(+)3}^a$ to electrophile is not influenced by the perturbation of the Coulomb parameter of the AO χ_1 and thereby $q_{(-)E,(+)3}^{(3)}$ vanishes. Consequently, the partial population $q_{(-)E,(+)2}^{(3)}$ transferred between orbitals $\varphi_{(+)2}^s$ and $\varphi_{(-)E}$ indirectly becomes of primary interest.

To derive the relevant formula, the expressions for $G_{(1)2E}$ and $G_{(2)2E}$ following from Eqs. (4) and (5), respectively, should be substituted into Eq. (2). For reasons mentioned above, we will confine ourselves to contributions embracing orbitals $\varphi_{(+)2}^s$ and $\varphi_{(-)5}^s$ in the expression for $G_{(2)2E}$. We then obtain

$$q_{(-)E,(+)2}^{(3)} = -\frac{4S_{22}(R_{2E})^2}{(1 + \varepsilon_{(-)E})^3} + \frac{2R_{25}Q_{5E}R_{2E}}{(1 + \varepsilon_{(-)E})^2}. \tag{9}$$

This formula contains both intra- and intermolecular parameters in the form of products. Inasmuch as the correction $q_{(-)E,(+)2}^{(3)}$ vanishes after returning to benzene, it represents alteration in the intermolecular charge transfer due to substitution.

The first fraction of Eq. (9) may be traced back to the self-mediating effect of the orbital $\varphi_{(+)2}^s$. The positive value of the self-interaction S_{22} seen from Eq. (8) ensures the negative sign of this fraction whatever the direction of the attack. Hence, the self-mediating effect of the electron-donating orbital $\varphi_{(+)2}^s$ always contributes to the suppressed charge transfer between the aromatic ring and electrophile after introducing the nitrogen atom. Inasmuch as the same matrix element (S_{22}) gives rise to an increase of absolute value of the one-electron energy of the orbital $\varphi_{(+)2}^s$ and thereby to lowering of the respective energy level under influence of the perturbation α (the negative sign of our energy unit should be taken into consideration here), the above-obtained reduction of the intermolecular charge transfer may be considered as being related to the increasing energy interval between the electron-donating orbital ($\varphi_{(+)2}^s$) and the electron-accepting one ($\varphi_{(-)E}$) after passing from benzene to pyridine. Finally, the relative absolute values of the first fraction of Eq. (9) for various positions of the reagent are in line with the shape of the electron-donating orbital, namely, the largest value is obtained for the para-position of the reagent.

The second fraction of Eq. (9) represents the mediating contribution of the nearest vacant orbital $\varphi_{(-)5}^s$ in the indirect charge transfer between orbitals $\varphi_{(+)2}^s$ and $\varphi_{(-)E}$. The direct intramolecular interaction R_{25} offers a possibility of such a contribution. The actual effect of the latter, however, is

determined by the product of intermolecular resonance parameters $Q_{5E}R_{2E}$. This factor depends on the product of coefficients $(C_{i2}C_{i5})$ at the AO under attack (χ_i) in the orbitals of the reactant $\varphi_{(+)2}^{s}$ and $\varphi_{(-)5}^{s}$ as Eq. (7) indicates. Multiplying the respective coefficients of the matrix **C** of Eq. (6) yields the result $-c^2$, c^2 and $-b^2$ for the AOs χ_2, χ_3 and χ_4, respectively. Thus, the contribution of the second fraction of Eq. (9) proves to be of alternating sign in contrast to that of the first fraction. Moreover, the positive value of the intramolecular resonance parameter R_{25} seen from Eq. (8) ensures the negative sign of the second fraction for *ortho-* and *para-*positions of the reagent and a positive one for the *meta-*position.

The above-established negative signs of both fractions of Eq. (9) for *ortho-* and *para-*attacks imply negative total values of respective third-order partial transferred populations $q_{(-)E,(+)2}^{(3),ortho}$ and $q_{(-)E,(+)2}^{(3),para}$. Hence, the reduced extents of the intermolecular charge transfer vs. that for benzene unambiguously follow for the above-indicated directions of the electrophilic attack upon pyridine. Moreover, the most pronounced suppression results for the *para-*positioned reagent.

For the *meta* attack, the sign of the relevant third-order increment $q_{(-)E,(+)2}^{(3),meta}$ evidently depends on relative absolute values of the two fractions of Eq. (9): a negative correction is obtained if the absolute value of the first fraction exceeds that of the second fraction. This implies that the reduced intermolecular charge transfer between the two participants of the reaction corresponds to the case of predominance of the self-mediating effect of the orbital $\varphi_{(+)2}^{s}$ over the mediating effect of the vacant orbital $\varphi_{(-)5}^{s}$ in the indirect intermolecular charge transfer. Using Eqs. (6)–(8), the relevant third-order correction of Eq. (9) may be expressed as follows

$$q_{(-)E,(+)2}^{(3),meta} = \frac{2b^2c^2\alpha\sigma^2}{(1+\varepsilon_{(-)E})^2}\left[1-\frac{2}{1+\varepsilon_{(-)E}}\right]. \quad (10)$$

The sign of the right-hand side of Eq. (10) actually is determined by the relative position of the one-electron energy $\varepsilon_{(-)E}$ of the electron-accepting orbital of the reagent $\varphi_{(-)E}$ relatively to energies of the remaining orbitals. Moreover, a negative correction and thereby the suppressing effect of the intramolecular perturbation α upon the charge transfer is ensured under condition that $\varepsilon_{(-)E}$ does not exceed 1 for the given reagent. It is evident that electrophiles of sufficiently high electron-accepting ability (i.e. those represented by small positive parameters $\varepsilon_{(-)E}$) meet this condition. Moreover, the relative reactivity of the *meta-*position of pyridine is predicted to be suppressed more substantially if the electron-accepting ability of electrophile grows (i.e. $\varepsilon_{(-)E}$ turns to zero). It is also seen that the *meta-*positioned carbon atoms remain to be the most reactive ones in the pyridine cycle in any case.

Two remarks deserve to be made before finishing this section. The first one concerns comparison of the above-suggested criterion of relative reactivity to populations of AOs of an isolated pyridine. The population alteration of the ith AO of pyridine vs. that of benzene is approximately representable as follows [22]

$$\Delta P_{ii} \approx -2C_{i2}C_{i5}G_{(1)25} = C_{i2}C_{i5}R_{25}. \quad (11)$$

This expression contains the product of coefficients of orbitals $\varphi_{(+)2}^{s}$ and $\varphi_{(-)5}^{s}(C_{i2}C_{i5})$ along with the intramolecular resonance parameter (R_{25}) as it was the case with the second fraction of Eq. (9). In this context, alternation in occupation numbers of AOs of pyridine over the cycle (Section 1) causes no surprise. We may also conclude that populations of AOs of an isolated pyridine fail to predict the suppressed reactivity of the *meta-*position vs. that of benzene because these are exclusively determined by alternating terms originating from the direct interaction R_{25}.

The second remark is about feasibility of extending the above-outlined analysis to other heteroaromatic compounds. To this end, no more is required as to use the MOs and one-electron energies of the respective parent hydrocarbon in the expressions of Eqs. (1)–(5). After such an extending and testing, the approach could probably acquire a certain predicting ability too.

5. Conclusions

1. Interpretation of chemical reactivity of pyridine suggested in this paper is based on consideration of the mixed terms of the perturbative expansion for charge redistribution, containing Coulomb and resonance parameters of intra- and intermolecular type in the form of products. The results demonstrate possibility of a successful accounting for the observed suppressed relative reactivities of all positions of pyridine vs. that of a particular position of benzene. Hence, an interplay between intra- and intermolecular interactions may be concluded to be responsible for this outstanding phenomenon of organic chemistry. In this context, the limited success of traditional approaches in dealing with the same problem may be traced back to an excessive concentration upon the role of intramolecular interaction in the formation of relative reactivities under interest.

2. The simplest interpretation of the suppressed reactivity of pyridine vs. that of benzene consists in relating this phenomenon to the less efficient charge transfer from the aromatic system to electrophile after introducing a nitrogen atom. Such a reduction in charge redistribution, in turn, may be traced back to the lower energy of the electron-donating orbital of pyridine relatively to that of benzene. As opposed to expectation, this principal orbital corresponds to the MO of benzene of the $2b_1$ symmetry and does not coincide with the actual HOMO of pyridine. In terms of an interplay between intra- and intermolecular interactions, the above-mentioned suppressed intermolecular charge transfer may be considered to be determined mainly by the product of certain intermolecular interactions and of the self-interaction of the electron-donating orbital of the heterocycle. The self-interaction originates from the local alteration in the

Coulomb parameter at the site of substitution after transforming the relevant perturbation matrix into the basis of MOs of benzene.

3. Replenishment of the above-outlined simple accounting for the suppressed reactivity of pyridine and thereby a more profound understanding of its origin also are possible on the basis of the results obtained. The point is that the above-mentioned self-interaction-containing increments to the intermolecular charge redistribution actually are accompanied by terms involving the direct intramolecular interaction between the HOMO and the LUMO of the reactant originating from the same alteration in the Coulomb parameter. Moreover, competition is observed between these increments for the *meta*-position of the reagent with respect to the nitrogen atom. As a result, the suppressed intermolecular charge transfer between pyridine and the *meta*-positioned electrophile is ensured under certain conditions only. Fortunately, these conditions prove to be met for electrophiles of sufficiently high electron-accepting ability.

References

[1] R. Hoffmann, J. Mol. Struct. (Theochem) 424 (1998) 1.

[2] J.-P. Malrieu, J. Mol. Struct. (Theochem) 424 (1998) 83.

[3] C.K. Ingold, Structure and Mechanism in Organic Chemistry, Cornell University Press, Ithaca, 1953.

[4] M.J.S. Dewar, R.C. Dougherty, The PMO Theory of Organic Chemistry, Plenum Press, New York, 1975.

[5] V.I. Minkin, B.J. Simkin, R.M. Mineev, Teorija Strojenija Molekul, Visshaja Shkola, Moscow, 1979 (in Russian).

[6] M. Edenborough, Organic Reaction Mechanisms. A Step by Step Approach, Taylor & Francies, London, 1999.

[7] R. Zahradnik, R. Polak, Elements of Quantum Chemistry, Plenum Press, New York, 1980.

[8] M.V. Basilevskii, The MO Method and Reactivity of Organic Molecules, Khimia, Moscow, 1969 (in Russian).

[9] C.A. Coulson, H.C. Longuet-Higgins, Proc. R. Soc. (Lond.) A191 (1947) 39.

[10] C.A. Coulson, H.C. Longuet-Higgins, Proc. R. Soc. (Lond.) A192 (1947) 16.

[11] C.A. Coulson, H.C. Longuet-Higgins, Proc. R. Soc. (Lond.) A193 (1948) 447 (see also page 456).

[12] C.A. Coulson, H.C. Longuet-Higgins, Proc. R. Soc. (Lond.) A195 (1948) 188.

[13] I. Gutman, Z. Naturforsch. 36A (1981) 1112.

[14] I. Fleming, Frontier Orbitals and Organic Chemical Reactions, Wiley, Chichester, UK, 1976.

[15] J.M. Tedder, A. Nechvatal, Pictorial Orbital Theory, Pitman, London, 1985.

[16] V.F. Traven, Electronic Structure and Properties of Organic Compounds, Khimia, Moscow, 1989 (in Russian).

[17] C. Batich, E. Heilbronner, J. Am. Chem. Soc. 95 (1973) 928.

[18] T. Munakata, K. Kuchitsu, Y. Harada, J. Electron Spectrosc. Relat. Phenom. 20 (1980) 235.

[19] V. Gineityte, Int. J. Quantum Chem. 94 (2003) 302.

[20] V. Gineityte, J. Mol. Struct. (Theochem) 343 (1995) 183.

[21] V. Gineityte, J. Mol. Struct. (Theochem) 726 (2005) 205.

[22] V. Gineityte, J. Mol. Struct. (Theochem) 507 (2000) 253.

[23] V. Gineityte, J. Mol. Struct. (Theochem) 585 (2002) 15.