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Theoretical Study of the Features of the Nuclear-Chemical Synthesis of Phenyl-Substituted Picoline Derivatives

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Abstract—Sections of potential energy surfaces (PES) of phenyl cation addition to picolines were constructed using the DFT/B3LYP and MRCI methods. In the framework of the SA-MCSCF method energies of excited states of the products and intermediates in the reaction of phenyl cation with 4-picoline were determined. The equilibrium geometry and the dissociation energy of intermolecular complexes of benzene and picolines were calculated by the DFT/B3LYP method. The experimentally observed decrease in the yield in the reaction of phenyl cation addition to the 4-picoline as compared with 2- and 3-picolines was substantiated.

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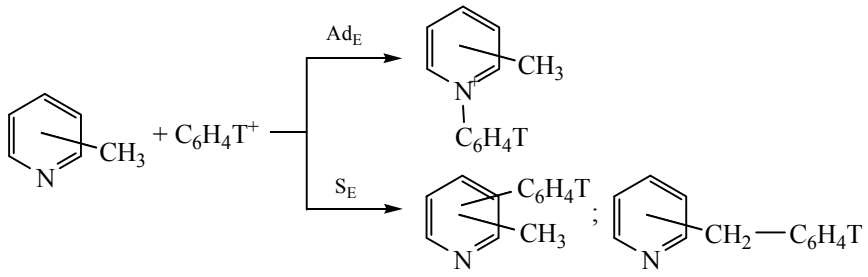
Picolines, heterocyclic compounds containing a methyl group and a nitrogen atom in the six-membered ring, are used in the compositions of the anesthetics and pharmaceutical preparations for the treatment of cardiovascular and neurological diseases, and are used in medicine as antiviral drugs [1–9]. It is established that the reactions of picolines with electrophiles proceed in three ways [10–13]. In particular, the reaction of the free phenyl cation with picoline proceeds along three competing routes: electrophilic addition, electrophilic substitution at the aromatic ring, and electrophilic substitution of the hydrogen in the methyl group.



The recent experiments on the nuclear-chemical synthesis of tritium-labeled phenyl derivatives of picolines showed that depending on the location of the methyl group in the heterocyclic ring of picoline the yields of the products of the addition reaction and the products of two kinds of substitution reactions vary. In the reaction with 4-picoline of the phenyl cation obtained at the β-decay of the benzene double-labeled with tritium the yield of the products of electrophilic substitution reaches 72±1%, therewith the yield of adduct of *N*-phenyl-4-picoline attains 25±1%, whereas in the reactions of phenyl cation with 2- and 3-picoline the yield of addition products is 35±5% and 36±2%, and of the substitution products, 61±3 and 63±3%, respectively [14, 15]. Complete explanation of these experimental results failed. Quantum-chemical studies of such reactions have not been performed.

The aim of this work was a theoretical study of the characteristics of nuclear-chemical synthesis of the picoline derivatives and finding the causes of an experimentally observed low yield of *N*-phenyl-4-picoline.

Calculation methods. We selected the 6-31G(1p,1d) basis and the B3LYP functional in the method of DFT [16, 17] as adequately describing geometry, electron spectrum and vibrational frequencies of pyridine molecule after preliminary calculations performed

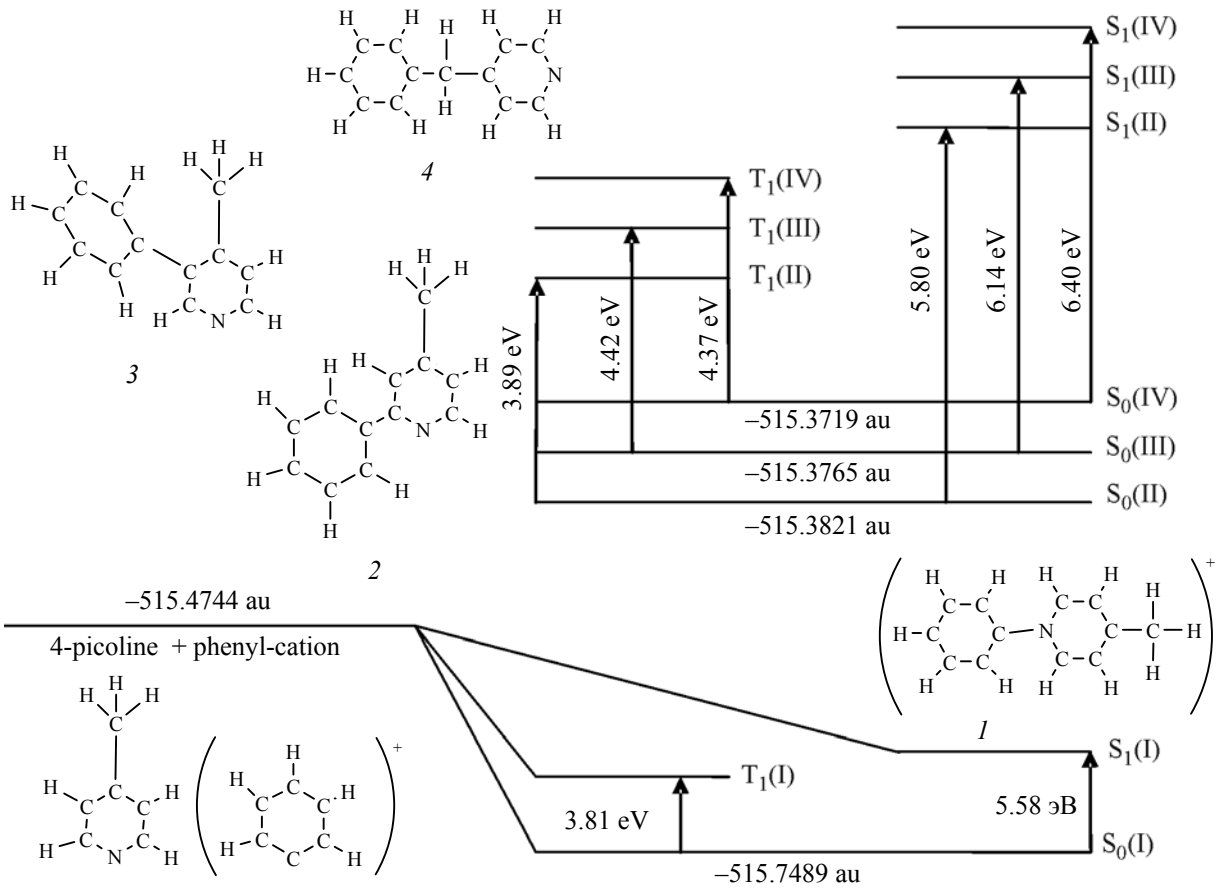


Fig. 1. The energy levels of products of electrophilic reaction between 4-picoline and phenyl cation. (*1*) *N*-phenyl-4-picoline; (*2*) 2-phenyl-4-picoline; (*3*) 3-phenyl-4-picoline; and (*4*) 4-benzylpyridine [SA-MCSCF/6-31G(1p, 1d) (8 , 8)].

using the bases 6-31G, TZV, 6-31G(1p,1d) and the functionals BLYP, B3LYP, PW91.

Calculations of the ground and excited states of the starting materials and the products of phenyl cation reaction with 4-picoline were carried out by the SA-MCSCF method with averaging over the first four states in the active space of eight electrons in eight MOs (8, 8).

Simulation of the PES of *N*-phenyl-2-, 3-, and 4-picolines in the ground and excited states was carried out by the methods DFT/UB3LYP/6-31G(1p,1d) and MRCI with accounting for 4-fold excitations in the active space (28, 18) . All calculations were performed with the PC GAMESS software [18], partly based on the source code of GAMESS (US) [19].

The location of the energy levels of the initial reactants and the products of phenyl cation reaction with 4-picoline shows that the most probable direction of the reaction is the addition with the formation of *N*-phenyl-4-picoline (Fig. 1), which does not explain the increase in the yield of the products of substitution in this reaction.

We believed that by calculating the PES profiles for the addition and substitution reactions we would estimate the activation barriers and from their values evaluate the relative yield of the products of different reactions.

Calculating by the DFT/UB3LYP/6-31G(1p, 1d) and MRCI methods the profiles of the PES of the electrophilic addition reactions of phenyl cation to the 2-, 3-, and 4-picoline in the ground singlet state we took as the reaction coordinate the distance (N–C) between the picoline nitrogen atom and the carbon atom corresponding to the electrophilic center of phenyl cation. It turned out that all these reactions must proceed barrier-free (Fig. 2).

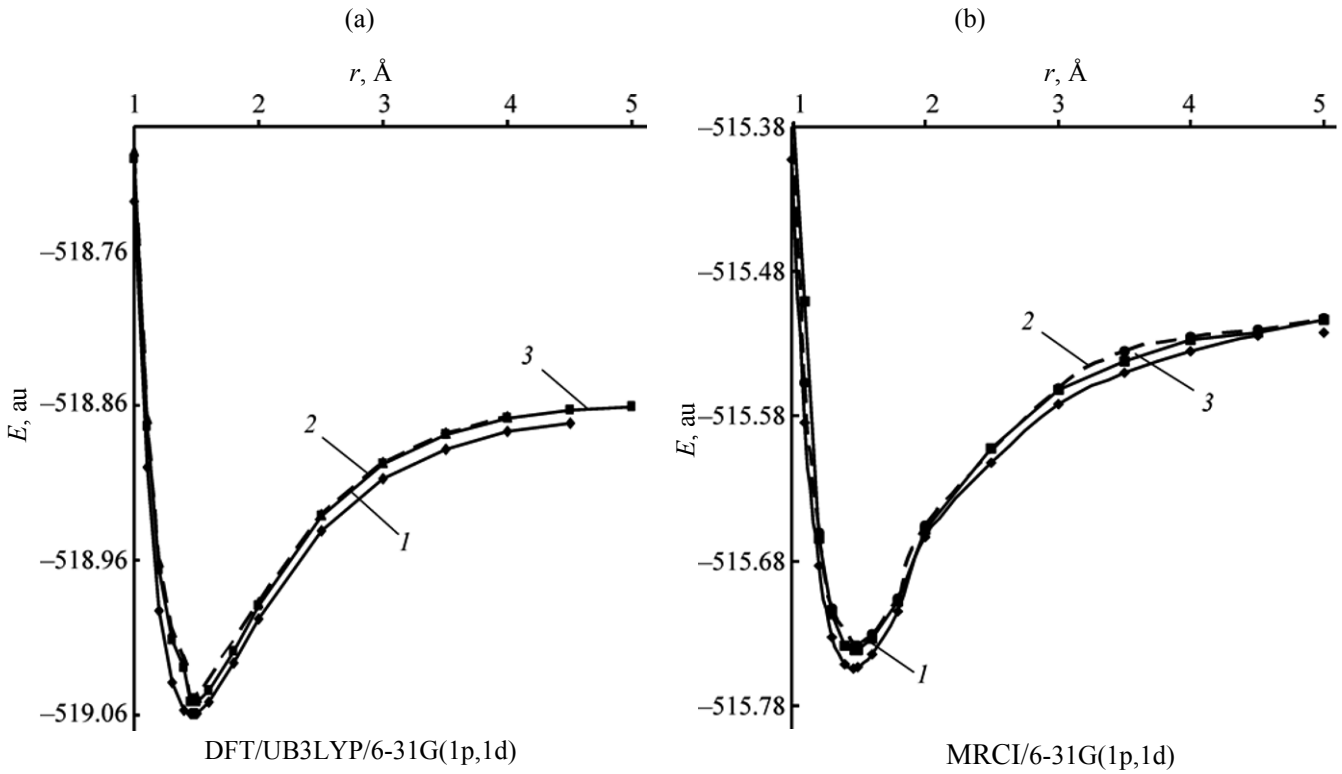


Fig. 2. Section of the potential energy surface of phenyl cation addition to (*1*) *N*-phenyl-2-picoline, (*2*) *N*-phenyl-3-picoline, and (*3*)*N*-phenyl-4-picoline.

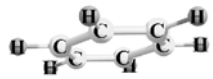
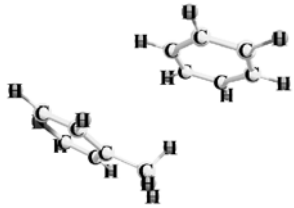
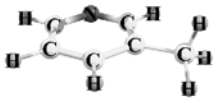
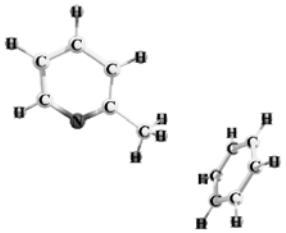
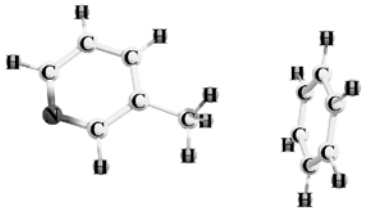
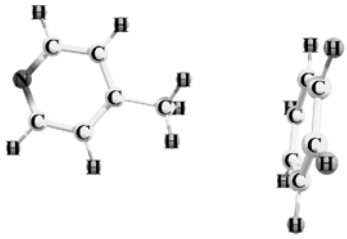
Dissociation energy of *N*-phenyl-2-, 3-, 4-picolines and the equilibrium bond length of C–N along the reaction coordinate calculated by DFT are 5.07 eV, 4.91 eV, 5.16 eV, 1.4646 Å, 1.4719 Å, and 1.4696 Å, respectively; by MRCI method 6.32 eV, 6.16 eV, 6.21 eV; 1.4646 Å, 1.4719 Å, and 1.4696 Å respectively.

We failed to calculate the energy and structure of the transition states of electrophilic substitution reactions by phenyl cation of the hydrogen atom in the aromatic ring and the methyl group of picoline because the optimization procedure, regardless of the initial location of the fragments of the intermolecular complex, resulted only in a single pattern with the coordination of the positive center of phenyl cation to the negatively charged picoline nitrogen atom.

Quantum-chemical calculation of the PES profiles at the forced convergence of phenyl cation with picoline along the given coordinate for the substitution reaction led to an increase in the total electron energy of the supersystem. Hence, while the substitution reactions require at least a small activation barrier, these reactions are less likely than non-barrier coupling reaction and it is impossible to explain the high yield of products of substitution reactions by the phenyl cation of the hydrogen atoms in the ring and methyl group of 4-picoline. Thus, this way of study proved to be a dead end road.

We succeeded to understand the experimental results proceeding from the following assumptions. Firstly, all these addition and substitution reactions with phenyl cation can be regarded as very fast reactions, where the duration of the bimolecular chemical act is much less than the duration of intermolecular reorganization of phenyl cation relative to the 2-, 3- or 4-picoline. This point can be substantiated based on the fact that most of the ionic and radical reactions are limited by diffusion [20]. As a consequence, the reaction of phenyl cation with picoline, in our opinion, can be attributed to fast reactions. Secondly, since the decay of tritium is a slow process (half-life is 12.32 years), in the reaction solution before the chemical interaction event intermolecular complexes can form with the predominance of coordination of doubly tritiated benzene (source of phenyl cation) to the methyl group of picoline. This can be justified by non-empirical calculations, which show that indeed

Table 1. Intermolecular complexes of benzene with picoline [DFT/UB3LYP/6-31G(1p,1d)]

Type of coordination	Intermolecular complex		
	[2-picoline–benzene]	[3-picoline–benzene]	[4-picoline–benzene]
Parallel			
			
Terminal			

stable intermolecular complexes are formed only at such coordination. In this case there are two possible conformations (Table 1). Thirdly, with two preceding assumptions, the phenyl cation formed after the collapse of one of the tritium atoms reacts instantly with the picoline and yields products of the reaction with the structure depending on the initial coordination of the twice labeled benzene to the picoline molecule and the location of tritium in the formed phenyl cation.

Indeed, in the 4-picoline the methyl group is the farthest from the nitrogen atom, and it is expectable that the phenyl cation formed after the decay of tritium, being coordinated to the methyl group from the end, will immediately react with the nearest atom, namely, will enter in the reaction of electrophilic substitution of the hydrogen atom of the methyl group to form 4-benzylpyridine. In the case of benzene coordination relative to methyl group parallel to the picoline ring, the probability of substitution in the 4-picoline ring increases. However, the yield of the product of substitution in the methyl group must be the greatest, because 4-picoline forms the most stable complex at the coordination of benzene to the end of the methyl group (Table 2).

Table 2. Dissociation energies of intermolecular complexes of benzene with picoline [DFT/UB3LYP/6-31G(1p, 1d)]

Intermolecular complex	Dissociation energy D_e, eV	
	parallel	terminal
[2-Picoline–benzene]	0.030	0.019
[3-Picoline–benzene]	0.033	0.025
[4-Picoline–benzene]	0.016	0.030

In the 2- and 3-picoline molecules the methyl group is located closer to the nitrogen atom, and the probability of addition reaction increases as the phenyl cation generated from double-labeled benzene interacts easier with the nitrogen atom. That is why the 2- and 3-picoline addition reaction proceed with a much higher yield.

Thus, we may conclude as follows. The addition reaction of phenyl cation to picoline proceeds barrier-free. According to the SA-MCSCF calculations, the most probable direction of the reaction of phenyl cation with 4-picoline is addition. Low yield of the phenyl cation addition to the 4-picoline is due to the existence of intermolecular complexes with the coordination of benzene to the picoline methyl group. The highest stability of the intermolecular complex of benzene and 4-picoline with the end coordination allows the prediction of the predominantly large yield of substitution of the hydrogen atom in the methyl group.

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