# THEORETICAL INTERPRETATION OF THE REACTIVITY OF THE IMIDAZOLE RING IN TRANSFORMATIONS AT THE MESO CARBON ATOM

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Quantum-mechanical calculations by the Pariser–Parr–Pople (PPP) SCF MO and Hückel MO methods explain the previously observed dependence of the reactivities of imidazole derivatives in reactions at the meso carbon atom on the nature of the aromatic nuclei and substituents bonded to the imidazole ring in the 4 and 5 positions.

A difference in the behavior of the imidazole ring toward nucleophilic and electrophilic agents in benz(naphth)imidazole and uncondensed imidazole systems [1-5] was observed during a study of the reactivity of the imidazole ring.

In contrast to imidazole, benzimidazole does not couple with diazonium salts [6]. Halogenation, hydroxymethylation, and a number of other electrophilic substitution reactions [1-3, 7] proceed differently in imidazole (at the carbon atoms) and benzimidazole (at the nitrogen atom of the NH group). The labilities of the hydrogen atoms in imidazole and in condensed imidazole systems [1-3, 8, 9] differ substantially. Nucleophilic exchange of atoms and groups in the 2 position of the imidazole ring, which is extremely characteristic for benz(naphth)imidazole derivatives [3, 10-15], proceeds with much more difficulty in the case of 2-substituted imidazole itself and its C- and N-alkyl derivatives [1-3, 16]. Replacement of halogen by an amino group in 2-bromo derivatives of 4,5-diphenylimidazole [17, 18] also occurs under relatively severe conditions.

The most detailed data on the problem under consideration were obtained as a result of a comparative study of direct amination reactions (the Chichibabin reaction) [3, 19, 20], opening of the cycloammonium salts of the imidazolium ion with alkaline agents [3, 21, 22], and azo coupling [3, 19, 20] of imidazole-containing systems. An analysis of the facts obtained in [3, 19-22] together with previously known facts [23-29] demonstrated that the Chichibabin reaction proceeds only in the case of N-alkyl-substituted imidazole systems that are condensed with aromatic rings at the 4 and 5 positions [3, 19, 20]. However, uncondensed imidazoles and their derivatives that contain a ring with disrupted aromaticity in the 4 and 5 positions (phenanthro [9, 10-d]imidazole and tetrahydrobenzimidazole) do not undergo this conversion [3, 19, 20]. On the other hand, azo coupling is peculiar only to imidazole itself and those of its derivatives in which the imidazole ring is annelated with a ring of the nonaromatic type [3, 19]. These observations made it possible to conclude that an aromatic ring annelated in the 4 and 5 positions acts as an electron-acceptor system and creates on the meso carbon atom of the imidazole ring the definite critical positive charge that is necessary for the successful occurrence of nucleophilic substitution reactions [3, 19, 20].

The aim of the present study was an explanation of the observed experimental dependence of the reactivities of imidazole derivatives on the structure by means of quantum-mechanical calculations. The calculations were made by means of Hückel MO methods with Streitwieser parameters [30] and the Pariser–Parr–Pople (PPP) SCF MO method with the parametrization described in [31, 32].

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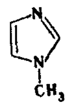
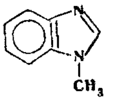
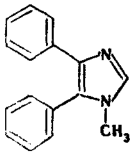
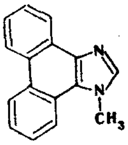
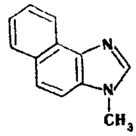
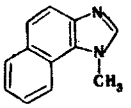
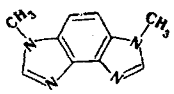
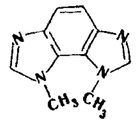
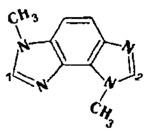
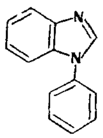
TABLE 1. Correlation of Nucleophilic Substitution

| No. | Compound | $\Delta q_2$ | $L^-(\beta_0)$ | SN | Amination capacity | |
|---|---|---|---|---|---|---|
| | | | | | result | literature |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 1 |  | +0,094<br>(0,0980)* | 3,2900 | 1,0716 | — | 19 |
| 2 |  | −0,006<br>(+0,070) | 3,8100 | 0,9064 | — | 19 |
| 3 |  | +0,107<br>(+0,101) | 2,1820 | 1,1254 | — | 19 |
| 4 |  | +0,137<br>(0,0969) | 1,9760 | 1,1942 | — | 19 |
| 5 |  | +0,152<br>(+0,104) | 1,9402 | 1,2508 | + | 20 |
| 6 |  | +0,151<br>(+0,105) | 1,9648 | 1,2134 | + | 20 |
| 7 |  | +0,152 | 1,9491 | 1,2185 | + | Not studied |
| 8 |  | +0,153 | 1,9490 | 1,2170 | — | 37 |
| 9 |  | $C_2$+0,150<br>$C_7$+0,152 | 1,9511<br>1,9503 | 1,2024<br>1,2194 | +<br>+ | Not studied<br>Not studied |
| 10 |  | +0,161 | 1,9146 | 1,276 | + | 38 |

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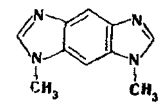
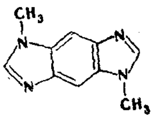
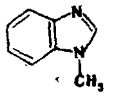
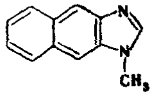
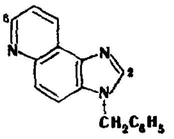
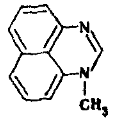
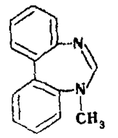
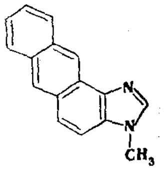
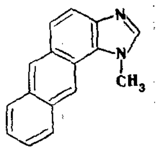
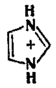
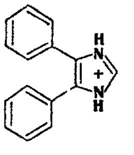
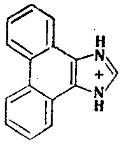
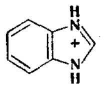
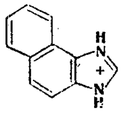
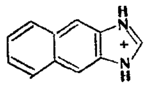
*The $\Delta q_2$ values calculated by the Pariser–Parr–Pople method are presented in parentheses.

TABLE 1 (continued)

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| 11 |  | +0,166 | 1,9342 | 1,2611 | + | Not studied |
| 12 |  | +0,167 | 1,9335 | 1,2782 | + | Not studied |
| 13 |  | +0,170<br>(0,125) | 1,9308 | 1,2626 | + | 38 |
| 14 |  | +0,186<br>(+0,112) | 1,8378 | 1,3654 | + | 39 |
| 15 |  | $C_2$+0,158 | 1,9274 | 1,2722 | — | 40 |
|  |  | $C_6$+0,092 | 2,2770 | 1,0688 | + | 40 |
| 16 |  | +0,256<br>(0,169) | 1,761 | 1,5250 | + | 41 |
| 17 |  | +0,264<br>(0,221) | 1,705 | 1,6686 | + | Not studied |
| 18 |  | +0,174<br>(+0,100) | — | — | + | Not studied |
| 19 |  | +0,170<br>(+0,103) | — | — | + | Not studied |

It was shown that although the numerical values of the charges in the meso position of the imidazole ring calculated by means of the indicated methods differ from one another, their relative order as a function of the molecular structure is retained (Table 1). Calculation of the distribution of the $\sigma$ charges by the Del Re method [33] also demonstrated that, within the limits of the amidine grouping of the imidazole ring, it is almost independent of the structure of the rest of the molecule. This serves as an additional basis for the correlation of the reactivity on the basis of data on the $\pi$-electron distribution. The calculated charges in the meso positions of the imidazole ring ($\Delta q_2$), the anionic localization energies ($\alpha^-$), and the superdelocalizabilities ($S^N$) are presented in Table 1.

TABLE 2. Positive Charges on the Meso Carbon Atom of Imidazolium Cations

| Cation | $\Delta q_2$ |  | Ring opening | Literature |
|---|---|---|---|---|
|  | Hückel MO | PPP |  |  |
|  | +0,289 | +0,268 | — | 3, 42 |
|  | +0,313 | +0,226 | — | 3, 21, 42 |
|  | +0,247 | +0,237 | — | 3, 42 |
|  | +0,380 | +0,302 | + | 28, 29 |
|  | +0,355 | +0,293 | + | 22, 42 |
|  | +0,399 | +0,237 | + | Not studied |

## Direct Amination

The data presented in Table 1 demonstrate that all of the nucleophilic reaction indexes display a clear proportional dependence: the anion localization energy decreases monotonically and the superdelocalizability increases as the positive charge on the meso carbon atom ($\Delta q_2$) increases.

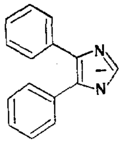
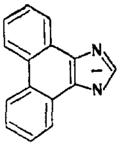
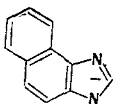
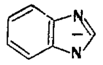
Thus the noncrossing rule is satisfied on examination of nucleophilic substitution at the meso carbon atom of the imidazole ring; this means a uniform effect of the structure of the reacting molecule on its capacity for amination for the different normally conceivable variants of the structure of the transition state. A comparison of the $\Delta q_2$ values (Table 1) clearly attests to a shift of the electron density from the meso position of the imidazole ring when the aromatic ring is annelated to it. Calculation of the electron structure of benzimidazole by the SCF MO LCAO method within the CNDO/2 (complete neglect of differential overlap) approximation with inclusion of all of the valence electrons demonstrated that the positive charge (+0.1677) on the meso carbon atom is achieved almost exclusively through polarization of the $\sigma$ framework [34]. However, in the case of imidazole, the overall charge on the meso carbon atom is +0.031 (calculation within the CNDO/2 approximation) [35] and is made up of the positive $\sigma$ charge (+0.145) and negative $\pi$ charge (−0.114). It hence becomes understandable why in contrast to N-substituted benzimidazole, N-alkyl derivatives of imidazole do not react with sodium amide [5]. The critical values of $\Delta q_2$, $\alpha^-$ ($\beta_0$), and $S^N$ are apparently found between IV and V, VI (Table 1).

In fact, while N-substituted naphtho[1,2-d]imidazole is aminated with sodium amide [5, 20], analogous derivatives of phenanthro[9,10-d]imidazole do not undergo this transformation [3, 5, 19].

Other examples that fundamentally confirm the correctness of the indicated approach to the Chichibabin reaction in a series of imidazole-containing and related systems can be found in [5].

In addition, as demonstrated by the research of A. F. Pozharskii and one of the authors of the present paper, other factors that affect the occurrence of the Chichibabin reaction besides the positive charge are the basicity of the heteroring [5] and the influence of specific effects [36, 37].

TABLE 3. Negative Charges on the $C_2$ Atom of Imidazole Anions Hückel MO)

| Anion | $\Delta q_2$ | Azo coupling | |
|---|---|---|---|
| | | Result | Literature |
|  | −0,458[44] | + | 1–4, 16, 19, 43 |
|  | −0,4300 | + | 19, 43 |
|  | −0,4182 | + | 3, 19 |
|  | 0,4059 | — | 3, 20 |
|  | 0,3910 | — | 3, 6, 20 |

Calculation of the electronic structure indexes of angular anthrimidazole (XVIII, XIX) shows that the accumulation of rings in aromatic systems annelated in the 4 and 5 positions of the imidazole ring will lead to a decrease in $\Delta q_2$. In this connection, the problem of the amination of linear and angular anthrimidazoles, acenaphtheno[4,5-d]imidazole, chryseno[5,6-d]imidazole, and other polyaromatic imidazole-containing compounds is of considerable interest.

## Opening of Cycloammonium Salts of the Imidazole Series

The conversion of 1,3-disubstituted imidazolium salts to "pseudo bases," which is a consequence of nucleophilic attack of the carbon atom in the 2 position of the imidazole ring by a hydroxyl ion [3, 16], enables one to be persuaded that the effect of an annelated aromatic ring is exerted on the reactivity of the meso carbon atom not only in the free base (amination) but also in the imidazolium cations.

It was found that 1-(2,4-dinitrophenyl)-3-alkyl derivatives of benz- [28, 29] and naphth-1,2-d-imidazolium salts [3, 21, 22, 42] are irreversibly converted to 2-amino-2',4'-dinitrodiarylamine derivatives even by the action of such weak basic agents as aniline and pyridine. At the same time, the analogous 4,5-diphenylimidazolium and 4,5,6,7-tetrahydrobenzimidazolium salts undergo this conversion under much more severe conditions – by heating with aqueous sodium carbonate or ammonia solutions [21, 22]. These results are in complete agreement with the $+\Delta q_2$ values in the cations of imidazole-containing systems presented in Table 2.

## Azo Coupling

It has been experimentally established that azo coupling, which proceeds at the meso carbon atom of the imidazole anion [1–4, 16], is characteristic only for uncondensed imidazole systems [3, 16, 20, 21, 43].

A comparison of the negative charges on the meso carbon atom of the anions of various imidazole-containing systems (Table 3) explains this regularity: the negative charge ($-\Delta q_2$) for anions of imidazoles with aromatic rings annelated at the 4 and 5 positions is lower than for uncondensed imidazoles. As in the case of amination, the critical $-\Delta q_2$ value is situated between that of phenanthro [9,10-d]imidazole and that of naphtho[1,2-d]imidazole.

The unique case of intramolecular azo coupling of the nonanionic form of the imidazole ring, which is observed in the case of diazotized N-(o-aminophenyl)imidazoles [45, 47], may be explained not only by the tendency for the formation of a new aromatic system – imidazobenzotriazine [47] – but also by the considerable negative $\pi$ charge on the meso carbon atom of imidazole [35]. If one takes into account that the meso carbon atom of benzimidazole bears a positive $\pi$ charge [34], it becomes understandable why intramolecular azo coupling does not proceed in the case of diazotized N-(o-aminophenyl)benzimidazole [46, 47]. In agreement with the concepts evolved above, intramolecular azo coupling is also characteristic for tetrahydrobenzimidazole [46].

Thus the difference in the behavior of the meso carbon atom of imidazole systems toward electrophilic and nucleophilic reagents is associated with the electron-acceptor action of the aromatic rings annelated at the 4 and 5 positions of the imidazole ring. This action is sufficiently distinctly fixed by the reactivity indexes and the experimental data in the neutral bases (amination), imidazolium cations (opening of cycloammonium salts), and anions of imidazole-containing systems (azo coupling).

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