

EFFECT OF THE BASICITY OF THE AZA GROUP
ON THE DIRECTION OF NUCLEOPHILIC SUBSTITUTION
REACTIONS IN IMIDAZO[4,5-*f*]QUINOLINES

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The quinoline ring in imidazo[4,5-*f*]quinolines is more reactive than the imidazole ring with respect to nucleophiles (phenyllithium and sodium amide). An assumption, which is confirmed by molecular orbital calculations and the pK_a values, is expressed that the direction of the corresponding reactions is primarily determined by the relative basicity of the aza groups (the nucleophile attacks the C atom next to the more basic nitrogen atom) and not by the magnitude of the positive charge or the energy of anionic localization on the C_2 and C_7 atoms in the neutral molecule.

An examination of nucleophilic substitution reactions in the nitrogen heterocycle series demonstrates that in some cases the ease of their occurrence is determined not only by the magnitude of the effective positive charge on the carbon atom at which substitution takes place but also by the basicity of the pyridine nitrogen atom. Examples of this are Chichibabin amination [1], hydroxylation with alkalis [2], alkylation by organometallic compounds [3], halogen substitution by arylthio groups [4], etc. The common origin of all of these reactions is coordination of the pyridine nitrogen atom with the cationic part of the reagent or solvent (H^+ , Me^+); the electrophilicity of the C_α atom increases sharply in the cation formed in the process, as a result of which, the second step of the reaction — the direct addition of a nucleophile (anionic part of the reagent) — is facilitated. It is possible that both steps of the process are to a certain extent synchronous, but it appears that the coordination step plays the preeminent role.

This can be most clearly seen in the behavior of the rather basic aza aromatic systems that contain several nonequivalent aza groups. If the considerations expressed above are correct, the action of a nucleophile can be directed to the carbon atom next to the most basic N atom of the molecule. Within this plan, we have investigated imidazo[4,5-*f*]quinoline (Ia), in which there are two potentially active (with respect to nucleophiles) centers — the 2 and 7 positions.

Hückel MO calculations show that the 2 position in the neutral Ia molecule should be considerably more active, since it is characterized by the minimum energy of anionic localization and the highest positive charge (Table 1). However, the pyridine nitrogen atom next to it is less basic than the N atom of the quinoline ring, since quaternization [5] proceeds with the formation of the 6-cation (quinolinium). The

TABLE 1. π -Electron Charges (q) and Anionic Localization Energies (a^-) on the C Atoms of 3H-Imidazo[4,5-*f*]quinoline (Ia) and Its Protonated Forms

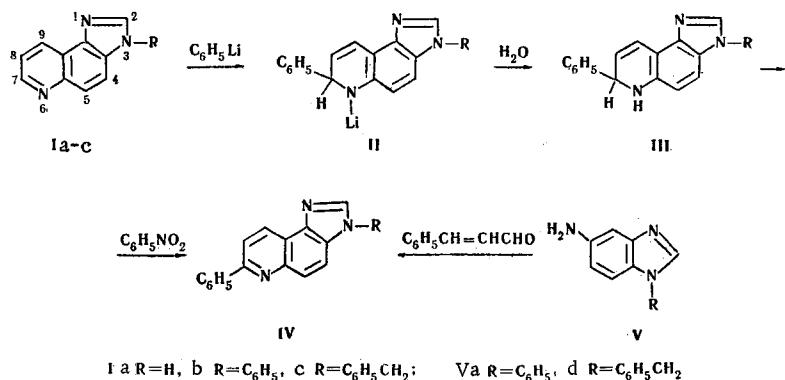
Type of particle	q			a^-	
	C_2	C_7	C_8	C_2	C_7
Neutral molecule	+0,158	+0,092	+0,059	1,928	2,278
1-Cation	+0,422	+0,096	+0,065	1,467	2,262
6-Cation	+0,172	+0,283	+0,193	1,886	1,740

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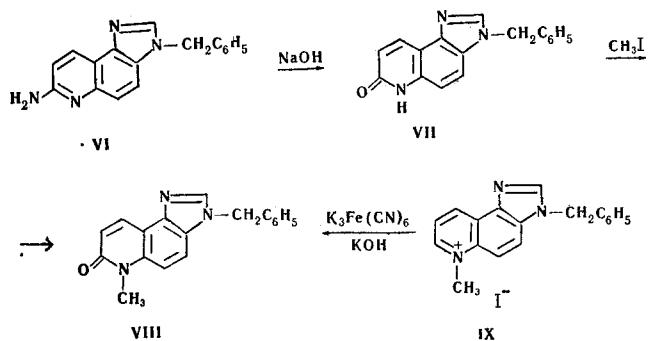
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small change in the pK_a on passing from 3-methylimidazo[4,5-*f*]quinoline (pK_a 4.55 ± 0.06) to the 2,3-dimethyl derivative (pK_a 4.84 ± 0.06) indicates that protonation of I also proceeds at the quinoline nitrogen atom.* The ΔpK_a value for these compounds would be considerably higher for protonation of the imidazole ring [6].

In contrast to the 1-cation (imidazolium), the C_7 atom in the imidazo[4,5-*f*]quinolinium cation already had the highest positive charge and the lowest anion localization energy (Table 1). Consequently, if coordination of the aza group with the cationic part of the nucleophile is the deciding factor, the reaction ought to proceed at the quinoline ring. We confirmed this experimentally in the case of the reactions of Ib and Ic with phenyllithium in ether. Dihydro derivatives III are formed initially and are then aromatized by refluxing in nitrobenzene to 3-R-7-phenylimidazoquinolines (IV). Their structures were confirmed by alternative Doebner-Miller synthesis from 1-phenyl- and 1-benzyl-5-aminobenzimidazoles (V).



The amination of 3-benzylimidazo[4,5-*f*]quinoline (Ic) by sodium amide in dimethylaniline also proceeds at the 7 position. Although amine VI could not be isolated in analytically pure form, its formation was proved indirectly as a result of the following transformations:



The crude, red-brown, crystalline product that was isolated from the amination was heated in alcoholic alkali. The VII that was formed in the process was methylated, without isolation, by methyl iodide to give 3-benzyl-6-methylimidazo[4,5-*f*]-2-quinolone (VIII). The latter was also obtained independently from quaternary salt IX by oxidation with potassium ferrocyanide. The two substances were identical. The yield of VIII (and consequently of VI) was, however, low (about 20%), which we explain by the difficulty in aromatization of the product of the addition of sodium amide to Ic. Evidence in favor of this is the deep coloration of the reaction products (adducts of the II type are usually so colored [7]), and their instability, which consists in their ready polymerization and oxidation. Similar phenomena were previously noted during the amination of the quinoline (but not the imidazole) ring [8]. The amination of Ic at the imidazole ring apparently does not occur, since we could not isolate the corresponding amine, despite the fact that we did obtain it previously via another route [9].

It is curious that 5,6-benzoquinoline – the electronic analog of I – is readily aminated under the same conditions to give a high yield of the 2-amino derivative. The higher basicity (pK_a 5.15) [10] of 5,6-

* The pK_a for protonation at the imidazole ring of the 3,6-dimethylimidazo[4,5-*f*]quinolinium cation is 1.86 ± 0.07 .

benzoquinoline as compared with quinoline (pK_a 4.94) [10] and imidazo[4,5-*f*]quinolines apparently favors its amination.*

EXPERIMENTAL

3,7-Diphenylimidazo[4,5-*f*]quinoline (IVb). A. A solution of 4 ml [6 g (38.2 mmole)] of dry bromobenzene in 5 ml of ether was added dropwise to a mixture of 0.42 g (60.5 mg-atom) of lithium and 6 ml of absolute ether. The reaction was carried out under nitrogen with mechanical stirring. When dissolution of the lithium was almost complete, the mixture was gently refluxed for another 30 min. A solution of 1.85 g (7.6 mmole) of 3-phenylimidazo[4,5-*f*]quinoline [5] in 150 ml of absolute benzene was added dropwise to the resulting solution, and the reaction mixture was stirred under nitrogen for 2 h. It was then cooled with ice. 3 ml of water was added dropwise, and the aqueous layer was separated from the benzene layer. The benzene extract was vacuum-evaporated, and the residual oil was refluxed for 5 min with 5 ml of nitrobenzene. The IVb was extracted with 60 ml of 5-7% H_2SO_4 . The acid extract was washed with ether, and a small excess of concentrated ammonium hydroxide was added. The oil (2.3 g) that separated gradually solidified. To purify it, it was dissolved in benzene and passed through a small column packed with aluminum oxide. Evaporation of the benzene gave slightly yellowish plates with mp 198-199° that were soluble in chloroform, ether, alcohol, and acetone. Found %: C 82.1; H 4.9. $C_{22}H_{15}N_3$. Calculated %: C 82.2; H 4.7.

B. A mixture of 3.3 g (15.8 mmole) of Va [11], 14.5 ml [27.1 g (276 mmole)] of orthophosphoric acid, and 3 ml of water was heated to 110°, and, in the course of an hour, 2.64 ml [2.9 g (22 mmole)] of cinnamaldehyde was added dropwise through a dropping funnel with stirring. Simultaneously, 0.6 ml [0.72 g (5.85 mmole)] was added in small portions. The mixture was heated for another 3 h, cooled, 20-30 ml of water was added, and the nitrobenzene was removed by steam distillation. The residual solution was filtered and made alkaline with ammonium hydroxide, and the resulting oil was extracted with chloroform. The extract was purified by chromatography with a column packed with Al_2O_3 with monitoring of the separation in UV light. (The product obtained by method A was used as the reference spot.) The yield of product with mp 198-199° was 0.3 g (6%). The substance was identical to the product of the direct phenylation of Ib and did not depress its melting point.

3-Benzyl-7-phenylimidazo[4,5-*f*]quinoline (IVc). A. This compound was similarly obtained by the direct phenylation of Ic [9] with phenyllithium, with the difference that the nitrobenzene was removed from the 7-phenyl derivative by steam distillation. The yield was 30%. Molecular distillation at 165° (1.5 mm) gave slightly yellowish prisms with mp 165-167° that were soluble in benzene, acetone, alcohol, and chloroform. Found %: C 82.1; H 5.3. $C_{23}H_{17}N_3$. Calculated %: C 82.4; H 5.1.

B. A 0.56-g sample of Vb [12] was dissolved in 15 ml of absolute ethanol, 0.7 ml of cinnamaldehyde was added, and the mixture was heated for 30 min on a water bath in a flask equipped with a reflux condenser fitted with a calcium chloride tube. After cooling, four to five drops of orthophosphoric acid were added to the mixture, and heating was continued for another 20 h. The reaction mixture was evaporated, and the residual oil was repeatedly triturated with ether until it had completely solidified. The residue was dissolved in chloroform, and the impurities were removed from it by chromatography with a column packed with Al_2O_3 to give 0.3 g of a product with mp 166-167° after molecular distillation. The product did not depress the melting point of the sample obtained by method A.

Reaction of 3-Benzylimidazo[4,5-*f*]quinoline [9] with Sodium Amide. A mixture of 2.8 g (11.5 mmole) of Ic and 1.1 g (28.2 mmole) of finely ground sodium amide was stirred in 50 ml of dimethylaniline at 160° for 4 h under nitrogen. Copious gas evolution (apparently hydrogen) was observed. The mixture was cooled, 1-1.5 ml of water was added, and the initially red (but gradually becoming brown) precipitate of VI was filtered. It was dried in a vacuum desiccator to give 1.3 g of product. The compound could not be purified, and it was therefore subjected to the following transformations.

A. A 0.5-g sample of the precipitate was dissolved in 15 ml of alcohol, 0.5 ml of 40% NaOH was added, and the mixture was refluxed gently for 1.5 h. The alcohol was evaporated, and the residue was washed with water, filtered, and dissolved in 20 ml of alcohol. After adding three to four drops of 40% NaOH and 0.5 ml of methyl iodide to the solution, the mixture was evaporated to dryness, and the residue was heated

* The reference [9] to the high (85%) yield of 2-aminoquinoline in the amination of quinoline in dimethylaniline is erroneous.

and extracted with benzene. The benzene extract was passed through a small column packed with Al_2O_3 . The light-yellow substance (0.1 g) with strong blue luminescence (the separation was monitored with UV light) was collected. Molecular distillation at 190° (2 mm) gave slightly yellowish prisms of VIII with mp 182° that were soluble in alcohol.

B. A solution of 3.3 g (10 mmole) of $\text{K}_3\text{Fe}(\text{CN})_6$ in 15 ml of water and 15–20 ml of benzene were added in turn to a mixture of 1.8 g (4.5 mmole) of IX [5] and 40 ml of water. After the mixture was made alkaline with a KOH solution (1 g in 10 ml of water), it was heated with mechanical stirring on a water bath for approximately 5 h and extracted several times with hot benzene. Evaporation of the benzene extracts gave 0.8 g (62%) of VIII with mp 182° (from alcohol). A sample of this product did not depress the melting point of the compound obtained by the methylation of VII. The compounds also were identical with respect to their chromatographic and spectral characteristics. Found %: C 74.7; H 5.4; N 14.2. $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}$. Calculated %: C 74.7; H 5.2; N 14.5.

2-Amino-5,6-benzoquinoline. A mixture of 3.6 g (20 mmole) of 5,6-benzoquinoline, 3.2 g (80 mmole) of finely ground sodium amide, and 30 ml of dimethylaniline was stirred at $140\text{--}150^\circ$ for 1 h until hydrogen evolution had ceased. The mixture was cooled, and 10 ml of water was added. The next day the copious gray precipitate was filtered, washed with water, benzene, and petroleum ether to give a quantitative yield of crude product. Recrystallization from water gave 3.0 g (77%) of almost colorless crystals with mp $234\text{--}235^\circ$, in agreement with the data in [13].

The ionization constants were determined by potentiometric titration [14] of aqueous solutions (0.01 M in the substance determined). The cuvette was thermostated at 25° , and stirring was accomplished with a stream of nitrogen. The titrant was 0.1 N hydrochloric acid.

The Hückel MO calculations were carried out by the method in [15]. The solution of the secular determinants was obtained with a "Razdan" computer. The authors thank E. N. Malysheva for her assistance in performing the calculations.

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