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LONE PAIR INTERACTION IN THE CHICHIBABIN REACTION

H. Lloyd Jones[1] and David L. Beveridge

Department of Chemistry
University of Cincinnati
Cincinnati 21, Ohio

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The amination of pyridine, widely known as the Chichibabin reaction[2], is generally considered as a nucleophilic substitution reaction. Substitution occurs exclusively at a position adjacent to the nitrogen atom in the molecule.

Several authors have discussed possible mechanisms for this reaction in terms of a sigma complex intermediate[3]. However, molecular orbital calculations of electron densities and localization energies (Fig. 1) indicate the 4-position is a more favorable nucleophilic reaction site.

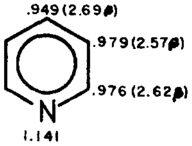
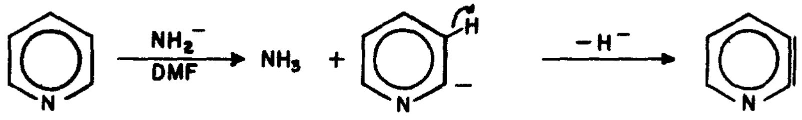
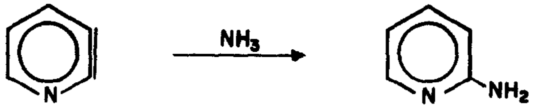


FIG. 1
Electron Densities in Pyridine
Parentheses contain localization energies after
A. Barnes, J. Am. Chem. Soc., 81, 1935 (1959).

To account for the observed phenomena such arguments as possible violation of the non-crossing rule[4], variations on the sigma complex intermediate[5], and steric factors involving the formation of a stabilizing intramolecular hydrogen bond have been invoked.

Recently, the formation of an aryne intermediate, 2,3,-dehydropyridine, has been proposed in the amination of pyridine[6].





Molecular orbital calculations[+] on the electronic structure of this intermediate have led us to a possible explanation of the exclusive formation of 2-aminopyridine.

The structure of an aryne intermediate is that of an aromatic species in which two hydrogen atoms have been removed from adjacent positions. There results a bonding interaction between the available sp^2 hybrid orbitals, orthogonal to the pi-electron system of the molecule, which has been estimated to be about one-fourth as strong as a pure pi-bond[7]. The species is thus very reactive and has been shown to be highly susceptible to attack by nucleophiles[8].

A unique situation occurs in the formation of 2,3-dehydropyridine. Here the sp^2 carbon orbitals are coplanar with the sp^2 hybrid orbital containing the nitrogen lone pair, and a delocalized molecular orbital system may be formed by allowing the three sp^2 orbitals to interact. This leads to a stabilized reaction intermediate in which the lowest

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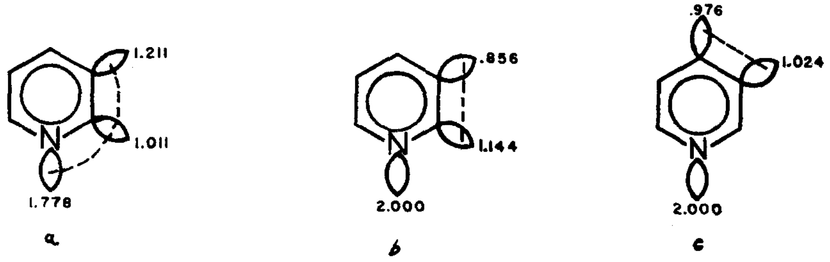
[+] The method of calculation and parametrization is discussed in Appendix I.

electron density of the aryne-sp^2 system occurs at the position adjacent to the nitrogen atom (Fig. 2). Thus, the possibility of a nucleophile reacting at this position is considerably enhanced.



a) 2,3-dehydropyridine with lone pair interaction

$E_{sp^2} = 4.4\beta$

b) 2,3-dehydropyridine without lone pair interaction

$E_{sp^2} = 4.0\beta$

c) 3,4-dehydropyridine

$E_{sp^2} = 3.7\beta$

FIG. 2

Electron Densities in Variations on Aryne Intermediates

Examination of the proposed reaction mechanism and products indicates further evidence for significant lone pair interaction in the aryne intermediate. Without lone pair interaction, the amination of the aryne intermediate should give 3-aminopyridine as well as 2-aminopyridine, analogous to the corresponding dehydrobenzene.[9] Also, in the formation of the aryne intermediate the more acidic proton in the 4-position should be more readily removed than the proton in the 2-position, hence the formation of some 3,4-dehydropyridine would be indicated. If this were the case one would expect as products 4-aminopyridine and 3-aminopyridine as well as 2- aminopyridine. The yeild of 2-aminopyridine obtained in the Chichibabin reaction is 75-85 per cent[10] and the presence of 3-aminopyridine or 4-aminopyridine has never been reported. A comparison of the relative energies of 3,4-dehydropyridine and 2,3-dehydropyridine with and without lone pair interaction indicates the increased stabilization of 2,3-dehydropyridine with lone pair interaction (Fig. 2). It is also of interest to note that the aryne 2,6-dehydropyridine would be an even more stable intermediate than 2,3-dehydropyridine, but it is not likely to form in the amination of pyridine since the 3-position is more favorable for the hydride ion elimination. However, this intermediate is feasible in the amination of a 3,5-disubstituted pyridine.

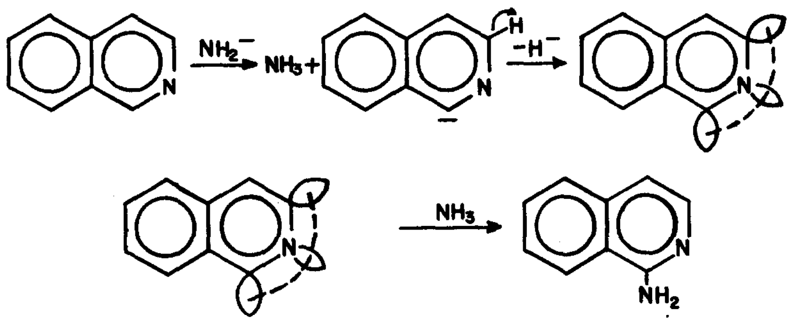
An analogous reaction scheme appears likely in the case of quinoline. The electron density pattern (Fig. 3) is parallel to that of pyridine, indicating that a nucleophile should favor the 4-position.

Quinoline Isoquinoline

FIG. 3
Electron Densities in Quinoline and Isoquinoline

Substitution occurs predominately at the 2-position, but in this case the presence of small amounts of 4-aminoquinoline have been reported.[11] The formation of the 4-amino product is more likely in this case than in pyridine since the localization energy at an analogous position in a series of aromatic compounds generally decreases as the number of benzenoid rings involved increases.[12]

The exclusive formation of 1-aminoisoquinoline is observed in the amination of isoquinoline. This is the product expected from both sigma complex and aryne intermediate arguments. The aryne intermediate most likely to form is 1,3-dehydroisoquinoline, by the following mechanism:



The charge densities of isoquinoline (Fig. 3) indicate the proton in the 1-position is the most acidic and therefore most likely to be eliminated. The 3-position, having the highest electron density, is then favorable to hydride ion elimination which results in the formation of 1,3-aryne intermediate. The reaction proceeds with the formation of 1-aminoisoquinoline.

Thus, a reaction mechanism for the amination of pyridine, quinoline, and isoquinoline involving an aryne intermediate gives a reasonable account of experimental observations on these systems. This type of intermediate seems also quite likely in other nucleophilic reactions characteristic of the aza-aromatic compounds.

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APPENDIX I: CALCULATIONS

All molecular orbital calculations were performed in the Hückel LCAO-MO approximation with electronegativity considerations. Following the usual procedure, diagonal elements of the secular determinant were expressed as

$$\alpha_X = \alpha_C + h_X\beta_{C=C} \qquad (1)$$

where α represents the coulomb integral and β the resonance integral and h_X the electronegativity parameter. Off diagonal elements were expressed as

$$\beta_{C=X} = k_{C=X}\beta_{C=C} \qquad (2)$$

where k is a proportionality constant.

For the pi-electron systems considered, the electronegativity parameter for nitrogen was taken as $h_N = 0.5$, and

$$h_{C_x} = \frac{h_N}{3^n} \qquad (3)$$

where n is the number of positions between carbon x and the nitrogen atom. For the nonzero off-diagonal matrix elements,

$$k_{C=N} = k_{C=C} = 1.0 \qquad (4)$$

In the calculations on the aryne-sp^2 systems, the electronegativity parameter for nitrogen was chosen as $h_N = 1.0$, relative to a carbon α_{sp^2} of 0.0. The carbon atom coulomb integrals perturbed by the proximity of the nitrogen atom in the molecule were then computed from equations (3) and (1). The off-diagonal elements were estimated from the equations

$$\beta_{ij} = 0.5\,(I_i + I_j)\,S_{ij} \qquad (5)$$

$$k_{ij} = \beta_{ij}/2.39\,\text{ev} \qquad (6)$$

where I represents the valence state ionization potential[13] and S_{ij} is the weak overlap integral[14] between sp^2 hybrids on centers i and j. The relative energies of the aryne-sp^2 systems are defined analogous to the relative pi-electron energies in the Hückel theory,

$$E_{sp^2} = \sum_j n_j \varepsilon_j \qquad (7)$$

where n_j is the occupation number of the j^{th} molecular orbital of energy ε_j, the sum being taken over all occupied orbitals.

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