EXTENDED HÜCKEL THEORY APPLIED TO NUCLEOPHILIC SUBSTITUTION IN PYRIDINE, QUINOLINE AND ISOQUINOLINE

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Abstract—It is shown that localization energies and total electron densities ($\sigma + \pi$), calculated by the Extended Hückel Theory (EHT), for pyridine, quinoline, and isoquinoline, correlate quite conclusively with the experimentally observed site of predominant nucleophilic attack by amide ion (Chichibabin reaction).

PYRIDINE has received a great deal of attention in MO calculations, particularly in the π-electron approximation, because of its relationship to benzene. As Table 1 indicates, a variety of different methods suggest, on the basis of π-electron densities, that the predominant site of nucleophilic attack in the pyridine neutral molecule should be at the 2-position.[1-7] However, the work of Brown[3] shows that the π-electron densities in the simple Hückel approximation may accord with any position of substitution, depending on the initial assumptions of the values for the coulomb integral (α) and

TABLE I. π-ELECTRON DENSITY CALCULATIONS IN PYRIDINE

Method		π-Electron density			Difference
	Q(N)	Q(2)	Q(3)	Q(4)	Q(4) −Q(2)
HMO[1]	1·141	0·976	0·979	0·949	−0·027
HMO[3]	1·20	0·920	1·000	0·950	+0·030
VESCF[3]	1·029	1·011	0·984	0·982	−0·029
	1·107	0·952	1·004	0·981	+0·029
	1·020	1·006	0·988	0·982	−0·024
	1·150	0·900	1·054	0·938	+0·038
	1.095	0.964	0.996	0.984	+0.024
SESCF[4]	1·203	0·936	0·969	0·986	+0·050
CISCF[5]	1·100	0.951	1·010	0·979	+0·026
SCF[6]	1·194	0·881	1·052	0·941	+0·060
PP[7]	1·151	0·916	1·030	0·958	+0·042
IPP[7]	1·166	0·904	1·037	0·952	+0·048

Abbreviations: HMO = Hückel MO, VESCF = Variable Electronegativity Self-Consistent Field, SESCF = Semiemperical Self-Consistent Field, CISCF = Self-Consistent Field with Configuration Interaction, SCF = Self-Consistent Field, PP = Pariser-Parr, IPP = Improved Pariser Parr.

[1] A. Barnes, J. Amer. Chem. Soc. 81, 1935 (1958).

[2] R. Daudel, R. Lefebvre, and C. Moser Quantum Chemistry p. 532. Interscience, New York, N.Y. (1959).

[3] R. D. Brown and M. L. Heffernan, Austr. J. Chem. 12, 554 (1959).

[4] M. S. De Giambiagi, M. Giambiagi, and R. Ferreira, J. chim. Phys. 61, 697 (1964).

[5] R. McWeeny and T. E. Peacock, Proc. Phys. Soc. A70, 41 (1957).

[6] R. L. Miller, P. G. Lykos, and H. N. Schmeising, J. Amer. Chem. Soc. 84, 4623 (1962).

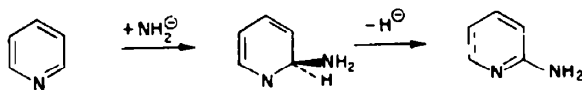[7] G. Leroy, J. chim. Phys. 60, 1270 (1963).

the exchange integral (β) for nitrogen. It is thus not surprising to find a great deal of conflicting data from HMO calculations on heterocyclic systems. For example the π-electron densities quoted by Daudel[2] show the 2-position to have the lower density, while the results of Barnes[1] give the 4-position as having the lower π-electron density.

In the more sophisticated calculations there is more accord about the position of π-electron density. However, as with the Hückel method, the calculations show that the electron density difference between the 2- and 4-positions is always very small, less than 0·06 electron (Table 1). If, for reasons of later comparison, we consider this difference as superimposed on a constant σ-electron density of 3·0 for each position, this is less than a 1·5% difference in total electron density. Thus, either total or π-electron density calculations do not suggest a great deal of discrimination between the positions for which nucleophilic attack is considered. The experimental results show, on the contrary, that the amination of pyridine by amine ion (Chichibabin reaction) leads almost uniquely to C-2 substitution.[8,9]

A similar situation exists for quinoline and isoquinoline, except that few calculations have been made above the level of the simple Hückel approximation.[10] Again a variety of positions of substitution are indicated, and the differences in electron densities between these positions are small.

On the basis of the HMO calculation of Barnes,[1] the recent communication by Jones and Beveridge[11] proposes the formation of an aryne intermediate during nucleophilic attack. Since this aryne intermediate would be expected to show equal reactivity at the C-2 and C-3 positions, Jones and Beveridge postulated an interaction of the nitrogen lone pair with the two coplanar sp^2 hybrids of the aryne bond. A Hückel calculation then predicted predominant attack at the C-2 positions of pyridine and quinoline and the C-1 position of isoquinoline. Such lone pair delocalization in the respective aryne intermediates no longer involves the π-electrons of the aromatic system, but rather the σ-electrons. This suggested to us that direct calculations on pyridine, quinoline, and isoquinoline, including σ- as well as π-electrons, might lead to results more in agreement with the experimental facts without the postulation of an aryne intermediate.[12] This seemed particularly attractive since the nucleophilic attack on pyridine is believed to.involve the formation of a σ-complex during the addition-elimination mechanism.[13]

DETAILS OF THE CALCULATION

The LCAOMO method recently developed by Hoffmann,[14] called the Extended Hückel Theory (EHT), is particularly suitable for this purpose, since it simultaneously calculates σ- and π-electron distributions. In this method, the basis set for the linear

[8] J. Eisch and H. Gilman, *Chem. Revs.* **57**, 525 (1957).

[9] M. T. Leffler, *Organic Reactions* (Edited by R. Adams) Vol. I, p. 91.

[10] J. H. Ridd, *Physical Methods in Heterocyclic Chemistry* (Edited by A. R. Katritzky) Vol. I, [a] p. 131, [b] p. 127. Academic Press, New York, N.Y. (1963).

[11] H. L. Jones and D. L. Beveridge, *Tetrahedron Letters* 1577 (1964).

[12] R. A. Abromovitch, F. Helmer, and J. G. Saha, *Tetrahedron Letters* 3445 (1964).

[13] C. K. Ingold, *Structure and Mechanism in Organic Chemistry* p. 809. Bell, London (1953).

[14] R. Hoffmann, *J. Chem. Phys.* **39**, 1397 (1963).

combination of atomic orbitals, $\psi_i = \sum_j c_{ij}\phi_j$ is extended to include all valence shell atomic orbitals. Thus, in the case of pyridine the 1s Slater orbitals for hydrogen, the 2s and the three 2p Slater orbitals for carbon and nitrogen, are used. Minimization of the total energy, in the Hückel approximation of the total Hamiltonian as a sum of one-electron effective Hamiltonians, gives the secular determinant:

$$\det |H_{ij} - ES_{ij}| = 0$$

where i, j go from 1 to n, i.e. through the total number of atomic orbitals. All overlap integrals S_{ij} are retained, and are calculated from standard sources.[15] The exchange integrals H_{ij} are computed using the approximation:

$$H_{ij} = 0.5 K(H_{ii} + H_{jj})S_{ij} \text{ where } K = 1.75$$

A Mulliken population analysis[16] finally yields the σ- and π-electron densities. A program for carrying out these calculations on the IBM 7094 computer has been described,[17] and this program is available.[18]

This method was applied to pyridine, quinoline, and isoquinoline. In all cases idealized geometries were assumed, all bond angles being taken as 120°. All carbon-carbon and carbon-nitrogen distances were taken as 1·40 Å, and the carbon-hydrogen bond distances as 1·10 Å. The following values of the valence state ionization potentials were used:[14,19] H(1s) = −13·6 ev, C(2s) = −21·4 ev, C(2p) = −11·4 ev, N(2s) = −26·0 ev, and N(2p) = −13·4 ev.

RESULTS AND DISCUSSION

The results are summarized for pyridine, quinoline, and isoquinoline in Table 2. The σ- and π-electron densities indicate that in pyridine and quinoline the C-2 atom, and in isoquinoline the C-1 atom, should be the most reactive towards nucleophilic substitution. This is in excellent agreement with the experimental results of nucleophilic attack by amide ion and hydroxide ion.[10b] A significant difference in electron density is found between the C-2 and C-4 positions in pyridine (0·27 electron or 6·8 %). It can be seen that this is predominantly a σ-effect, the π-electron density difference being much smaller (0·03 electron), of the order of magnitude of the previous π-electron calculations. Similar results have been obtained in the examples of quinoline and isoquinoline.

Although the total electron density distributions are in excellent accord with the experimental results of nucleophilic substitution, it seemed advisable, since the σ-complex appears to be the accepted intermediate for this reaction,[18] to calculate the stability of the various σ-complexes involved in the Chichibabin reaction. The total energy content of these complexes were calculated by localizing a hydride ion at the various sites under examination using the Extended Hückel Method. Such a calculation capitalizes on one of the principal successes of the Extended Hückel Method, namely the assessment of molecular geometries. Employing the same set of parameters

[15] R. S. Mulliken, C. A. Rieke, D. Orloff, and H. Orloff, *J. Chem. Phys.* **17**, 1248 (1949).
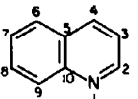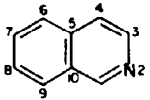[16] R. S. Mulliken, *J. Chem. Phys.* **23**, 1833, 2338, 2343 (1955).
[17] R. Hoffmann and W. N. Lipscomb, *J. Chem. Phys.* **36**, 2179, 3489 (1962); **37**, 2872 (1962).
[18] *Quantum Chemistry Program Exchange.* Chemistry Department, Indiana University, QCPE #30.
[19] R. Hoffmann, *J. Chem. Phys.* **40**, 2745 (1964).

TABLE 2.—ELECTRON DENSITIES IN PYRIDINE, QUINOLINE AND ISOQUINOLINE
BY EXTENDED HÜCKEL THEORY

Molecule	Position	Electron density (Q)		
		π	σ	$\sigma + \pi$
Pyridine	1	1·43	3·49	5·92
	2	0·84	2·86	3·70
	3	1·01	3·11	4·12
	4	0·87	3·09	3·96
Quinoline	1	1·48	4·50	5·98
	2	0·79	2·87	3·66
	3	1·02	3·12	4·14
	4	0·85	3·11	3·96
	5	0·97	2·99	3·96
	6	0·98	3·11	4·09
	7	1·01	3·11	4·12
	8	0·97	3·11	4·08
	9	1·04	3·12	4·16
	10	0·89	2·74	3·63
Isoquinoline	1	0·78	2·87	3·65
	2	1·45	4·49	5·94
	3	0·91	2·86	3·77
	4	1·03	3·12	4·15
	5	0·90	2·98	3·88
	6	1·02	3·12	4·14
	7	0·96	3·11	4·07
	8	1·01	3·11	4·12
	9	0·97	3·11	4·08
	10	0·97	2·99	3·96

quoted above, but changing the site at which the hydride ion is localized in the substrate from a trigonal to a tetrahedral centre (considering idealized geometries again), the energies for the σ-complexes in question were calculated for pyridine, quinoline, and isoquinoline. In the case of pyridine, for example, the σ-complex at positions C-2 and C-4 were considered. The results are summarized in Table 3. In each case, the σ-complex formed by the nucleophilic attack at the 2-position for pyridine and quinoline and the 1-position for isoquinoline appears to be the more stable. These energy values should only be used to point out general trends in stability rather than in an absolute sense. The results are in excellent harmony with those obtained from total electron distributions and we feel that both criteria taken together, i.e. energies of the σ-complexes and total electron distributions, conclusively correlate the preferred site of nucleophilic attack.

Finally, a good linear correlation is observed between the total electron densities $(\sigma + \pi)$ and the chemical shifts (δ) for pyridine,[20] quinoline and isoquinoline[21] as shown in Fig. 1. Specifically, the magnitude of the chemical shifts within a particular molecule are quantitatively correlated with the total electron density of the carbon to which the proton is attached. The corresponding π-electron densities do not show

[20] I. C. Smith and W. G. Schneider, *Canad. J. Chem.* **39**, 1158 (1961).
[21] J. A. Pople, W. G. Schneider, and H. T. Bernstein, *High-resolution Nuclear Magnetic Resonance* p. 269, McGraw-Hill, New York, N.Y. (1959).

TABLE 3. ENERGIES OF THE σ-COMPLEXES OF PYRIDINE, QUINO-
LINE, ISOQUINOLINE

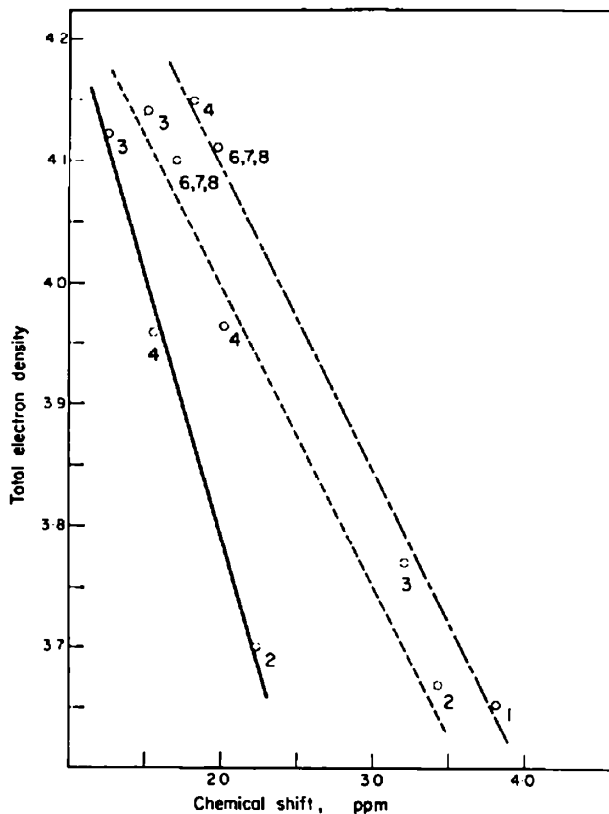| Molecule	Position	Energy (ev)
Pyridine	2	−561·00
	4	−560·76
Quinoline	2	−878·36
	4	−878·12
Isoquinoline	1	−878·24
	3	−877·12

FIG. 1. Correlation of Total Electron Densities with Chemical Shifts (ppm) for Pyridine
—O—O—, Quinoline ---O---O---, and Isoquinoline –·-O·-O-·. (Averaged
values used for 6, 7, and 8 positions.)

such a linear relation, but rather badly scattered points. Since the chemical shift is a
direct measure of the electron environment of the proton,[23] we feel that the total
electron densities within a particular molecule, as calculated by the Extended Hückel
Theory, provide a realistic assessment of the electron distribution.

On the basis of these calculations, we suggest that this simple, one parameter
technique allows correlation of the predominant site of nucleophilic attack in nitrogen
heterocyclics without recourse to an aryne intermediate with lone pair delocalization.

[23] T. K. Wu and B. P. Dailey, J. Chem. Phys. 41, 2796 (1964).

In this respect, it is interesting to note Hoffmann's conclusion[19] that in pyridine itself the classical lone pair on nitrogen is more than 40% delocalized over the entire sigma framework. Similarly, our calculations indicate that the nitrogen lone pair is considerably delocalized over the sigma framework in quinoline and isoquinoline.