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# EXTENDED HÜCKEL THEORY APPLIED TO ELECTROPHILIC SUBSTITUTION IN IMIDAZOLE

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**Abstract**—The $\sigma$-complex energies and total electron densities of the imidazole cation, neutral molecule, and anion have been calculated by the Extended Hückel Theory. Where the mechanism of electrophilic substitution is believed to involve a $\sigma$-complex, good agreement is obtained with the experimentally observed site of substitution.

IMIDAZOLE is one of the very few heterocyclic molecules for which detailed observations are available on the orientation in electrophilic substitution under a wide range of acidity conditions.[1] In some instances these observations include detailed kinetic analysis of the particular conjugate acid-base form of the substrate undergoing attack. Thus it has been shown that for nitration and sulfonation carried out in strongly acid solutions exclusive 4,(5)-substitution* occurs.[2,3] Similarly, deuterium substitution in concentrated sulfuric acid occurs initially at the 4,(5)-position.[4] For nitration it has been established by kinetic measurements that the substitution occurs in the imidazole cation, and the same is probably true for sulfonation and deuteration.[5] Bromination in organic solvents may be an electrophilic substitution in the neutral molecule and preferential attack at the 4,(5)-position is observed.[2] Finally, it has been established that iodination[6] and diazocoupling,[7] presumably also deuterium substitution in alkaline media,[8] involve electrophilic attack on the anion. In this case, however, the orientation is not quite as clear-cut as for the cation and neutral molecule. While for iodination substitution is initially at the 4,(5)-position, diazo-coupling and deuterium exchange occur at the 2-position. However, for iodination the proton loss is rate-determining, as shown by the large deuterium isotope effect.[9,10] This implies that in the transition state for iodination the attacking species has already been localized at the reaction site, and the carbon-hydrogen bond to the leaving proton is being stretched. The transition state for iodination is thus known to have many of the characteristics of a $\sigma$-complex. The absence of an isotope effect in diazo-coupling[9,10] implies a mechanism different from that observed in iodination.

The experimental results cited above, together with more recent evidence on the

* In the cation and the anion the 4- and 5-positions are completely equivalent. In the neutral molecule they are equivalent in a time-averaged sense, because of facile tautomeric proton shift between the two nitrogens.

[1] J. H. Ridd, *Physical Methods in Heterocyclic Chemistry* (Edited by A. R. Katritzky), Academic Press, New York, N.Y. (1963) Vol. 1; pp. 109–160.
[2] I. E. Balaban and F. L. Pyman, *J. Chem. Soc.* **121**, 947 (1922).
[3] R. G. Fargher and F. L. Pyman, *J. Chem. Soc.* **115**, 217 (1919).
[4] T. D. Breese and J. H. Ridd, personal communication.
[5] M. Brickman, M. W. Austin, J. H. Ridd and B. V. Smith, *Chem. & Ind.* 1057 (1962).
[6] R. D. Brown, H. C. Duffin, J. C. Mayhard and J. H. Ridd, *J. Chem. Soc.* 3937 (1953).
[7] J. H. Ridd, *J. Chem. Soc.* 1238 (1955).
[8] R. T. Gillespie, A. Grimison, J. H. Ridd and R. F. White, *J. Chem. Soc.* 3228 (1958).
[9] A. Grimison and J. H. Ridd, *Proc. Chem. Soc.* 256 (1958).
[10] A. Grimison and J. H. Ridd, *J. Chem. Soc.* 3019 (1959).

involvement of $\sigma$-complexes in electrophilic substitution by iodine and bromine,[11,12] suggested a possible correlation between 4,(5)-substitution and a $\sigma$-complex mechanism. It was decided to investigate this correlation by comparison of theoretically calculated electronic properties of imidazole model systems with the very detailed experimental data for substitution.

The most extensive calculations on the imidazole system have been those of Brown and Heffernan.[13] Using the variable Electronegativity Method (VESCF), these authors conclude that the 2-position is the more reactive site for attack by an electrophile, since this position was calculated to have the highest electron density (Table 1). However, the difference in the $\pi$-electron densities between the 2- and 4,(5)-positions is 0·007, 0·003 and 0·007 electron for the cation, neutral molecule, and anion, respectively. If, for reasons of later comparison, we consider this difference as superimposed on a constant $\sigma$-electron density of 3·0 for each position, there is less than a 0·2% difference in total electron density. As pointed out by Ridd,[1] due to the difficulty in estimating parameter values, the uncertainty in the VESCF electron densities is greater than their difference at the various positions. At best one expects no discrimination between the 2- and 4,(5)-positions on the basis of $\pi$-electron densities.

The localization energies calculated by the VESCF method indicate that the localization of the electrophile at the 4,(5)-position results in the more stable intermediate and thus the 4,(5)-position should be the preferred site of attack in the cation, neutral molecule, and anion. The two reactivity indices are thus in complete disagreement.

The problem of the validity of $\pi$-electron calculations in heteroatomic systems, where polarization of the $\sigma$-bond framework must occur has been discussed recently.[14] In the $\pi$-electron approach, parameters are adjusted in such a way that the overall molecular properties, which actually represent all electrons present in the molecule, give the best fit with either $\pi$-electron densities, $\pi$-electron energies, or $\pi$-bond orders.[15] In this way, $\sigma$-effects are absorbed into the parameters used to represent the heteroatom perturbation. Thus, in the specific case of imidazole, different parameters are used for the "pyrrole" nitrogen atom and the "pyridine" nitrogen atom. It is interesting to note that Longuet-Higgins and Coulson[16] suggest that in heteroatomic systems the polarization of the $\sigma$-bond framework should be accompanied by a back-polarization of the $\pi$-electrons. An application of the Extended Hückel Theory (EHT) to pyridine, taking into account all valence electrons, indeed shows that the fractional $\sigma$-charge and $\pi$-charge distributions can be different from one another.[17] This has nothing to do with the actual breakdown of the $\sigma$–$\pi$ separation of the molecular wave function, but rather to the procedure in most $\pi$-electron calculations of correlating gross molecular properties solely with the $\pi$-electron system. Such an approach is only valid in homoatomic systems like benzene, where the $\sigma$-bond framework is indeed unpolarized.

[11] E. Grovenstein and N. S. Aprahamian, *J. Amer. Chem. Soc.* **84**, 212 (1962).

[12] [a] M. Christen and H. Zollinger, *Helv. Chim. Acta* **45**, 2057, 2066 (1962); [b] M. Christen, W. Koch, W. Simon and H. Zollinger, *Ibid.* 2077 (1962).

[13] R. D. Brown and M. L. Heffernan, *Austr. J. Chem.* **12**, 543 (1959).

[14] G. Del Re and R. G. Parr, *Rev. Mod. Phys.* **35**, 604 (1963).

[15] A. Streitwieser *Molecular Orbital Theory for Organic Chemists*, J. Wiley, New York, N.Y. (1961). Chap. 5; pp. 117–135.

[16] H. C. Longuet-Higgins and C. A. Coulson, *J. Chem. Soc.* 971 (1949).

[17] W. Adam and A. Grimison, *Tetrahedron.*

With these difficulties in mind, we felt that only total electron densities ($\sigma + \pi$) would be significant in a theoretical investigation of the $\sigma$-complex mechanism. Furthermore a calculation treating all valence electrons, such as EHT, provides a means of calculating directly the energies of the various possible $\sigma$-complexes. Both, total electron densities and $\sigma$-complex energies, calculated by EHT, successfully correlated the observed site of nucleophilic substitution in pyridine, quinoline and isoquinoline.[17] The Extended Hückel Theory was therefore applied to the imidazole cation, neutral molecule and anion.

*Details of the calculation*

The Extended Hückel Theory, an LCAOMO method recently developed by Hoffmann,[18] simultaneously calculates $\sigma$- and $\pi$-electron distributions. In this method, the basis set for the linear combination of atomic orbitals, $\psi_i = \sum_r C_{ir}\phi_r$, is extended to include all valence shell atomic orbitals. Thus, in the case of imidazole the 1s Slater orbitals for hydrogen and the 2s and 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 valence atomic orbitals. All overlap integrals $S_{ij}$ are retained, and calculated from standard sources.[19] The exchange integrals $H_{ij}$ are computed using the approximation.

$$H_{ij} = 0{\cdot}5\,K\,(H_{ii} + H_{jj})\,S_{ij}, \text{ where } K = 1{\cdot}75$$

The Coulomb integrals $H_{ii}$ are taken as the valence state ionization potentials. A Mulliken Population Analysis[20] finally yields the $\sigma$- and $\pi$-electron densities. A program for carrying out these calculations on the IBM 7094 computer has been described.[21]

The geometries of the imidazole systems were approximated as ideal regular pentagons. All ring bond lengths were taken as 1·40 Å and all carbon—and nitrogen hydrogen bond lengths as 1·10 Å. The valence state ionization potentials, were those previously used for pyridine, quinoline and isoquinoline,[17] 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. The Slater orbital exponents were H: 1·00, C: 1·625 and N: 1·950.

As a first approximation, the model for the $\sigma$-complexes consisted of localizing a proton rather than the actual electrophile at the various ring positions in the imidazole system. Identical input data was used except that the site at which the proton was localized in the substrate was changed from a trigonal to a tetrahedral center.

## RESULTS AND DISCUSSION

The $\sigma$- and $\pi$-electron densities are summarized in Table 1, and the $\sigma$-complex energies in Table 2. The total electron densities suggest the 4,(5)-position as the most

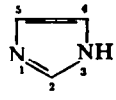
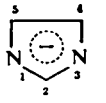
[18] R. Hoffmann, *J. Chem. Phys.* **39**, 1397 (1963).
[19] R. S. Mulliken, C. A. Rieke, P. Orloff and H. Orloff, *J. Chem. Phys.* **17**, 1248 (1949).
[20] R. S. Mulliken, *J. Chem. Phys.* **23**, 1833, 2338, 2343 (1955).
[21] R. Hoffmann and W. N. Lipscomb, *J. Chem. Phys.* **36**, 2179, 3489 (1962); **37**, 2872 (1962).

reactive site for electrophilic substitution in all three species. The difference in the total electron densities between the 2- and 4,(5)-position is 0·44, 0·45 and 0·46 electron respectively for the cation, neutral molecule and anion. This substantial difference corresponds to approximately 10% in the two positions as compared to 0·2% in the VESCF $\pi$-electron densities. The polarization of the molecules may be somewhat exaggerated. However, application of the EHT method to a large number of five-membered oxygen and nitrogen heterocycles has yielded a good linear correlation between proton chemical shifts and total electron densities,[22] indicating that the relative ordering of electron densities is reliable.

The $\sigma$-complex energies also indicate that localization of the electrophile is preferred at the 4,(5)-position for all three substrates at imidazole. Thus total electron densities and $\sigma$-complex energies are in agreement in predicting preferential substitution at the 4,(5) position over the 2-position for the cation, neutral molecule and anion. If the transition state for the electrophilic substitution at the 4,(5)-position indeed is structurally similar to the $\sigma$-complexes considered, the localization of the incoming electrophile should be guided by the position of highest total electron density and $\sigma$-complex of lowest energy. The model chosen here is admittedly a crude one, but the experimental results of preferred attack at the 4,(5)-position for nitration, sulfonation, deuteration in concentrated sulfuric acid, bromination and iodination are reproduced.

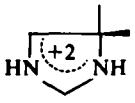
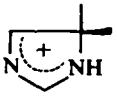
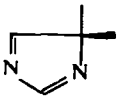
These calculations do not account for the electrophilic attack at the 2-position during diazo-coupling and deuteration under basic conditions. But here the experimental evidence implies a mechanism different from that considered as our model, possibly a loosely bound $\sigma$-complex or even a $\pi$-complex. To settle this point the energy surface for the formation of a $\pi$-complex which subsequently rearranges to a $\sigma$-complex should be calculated. Because of the structural complexity of imidazole,

TABLE 1. ELECTRON DENSITIES IN THE IMIDAZOLE SYSTEM

| Molecule | Position | VESCF $\pi$ | EHT $\pi$ | EHT $\sigma$ | EHT $\sigma + \pi$ |
|---|---|---|---|---|---|
|  | 1 | 1·512 | 1·52 | 3·74 | 5·25 |
| | 2 | 0·997 | 0·85 | 2·66 | 3·51 |
| | 3 | 1·512 | 1·52 | 3·74 | 5·25 |
| | 4 | 0·990 | 1·06 | 2·89 | 3·95 |
| | 5 | 0·990 | 1·06 | 2·89 | 3·95 |
|  | 1 | 1·650 | 1·52 | 3·74 | 5·26 |
| | 2 | 1·100 | 0·85 | 2·64 | 3·48 |
| | 3 | 1·101 | 1·52 | 4·50 | 6·01 |
| | 4 | 1·037 | 1·06 | 2·86 | 3·92 |
| | 5 | 1·112 | 1·06 | 2·89 | 3·95 |
|  | 1 | 1·197 | 1·52 | 4·50 | 6·02 |
| | 2 | 1·207 | 0·85 | 2·61 | 3·46 |
| | 3 | 1·197 | 1·52 | 4·50 | 6·02 |
| | 4 | 1·200 | 1·06 | 2·86 | 3·92 |
| | 5 | 1·200 | 1·06 | 2·86 | 3·92 |

[22] W. Adam and A. Grimison, data unpublished.

TABLE 2. ENERGIES OF σ-COMPLEXES BY EXTENDED HÜCKEL THEORY

| σ-Complex | Structure | Energy (ev) |
|---|---|---|
| Cation-2 |  | −484·14 |
| Cation-4 |  | −484·28 |
| Neutral molecule-2 |  | −478·27 |
| Neutral molecule-4 |  | −478·43 |
| Anion-2 |  | −472·38 |
| Anion-4 |  | −472·54 |

such a lengthy calculation has not yet been carried out. Smaller systems, e.g. the protonation of a heteroatomic double bond need to be investigated before attempting π-complexes in the imidazole system.

In conclusion, the results indicate that the one-parameter EHT method is capable of giving a reasonable electron distribution in heteroatom systems. Its advantage of including σ-electrons, and success in calculating molecular geometries[18] make it particularly useful for discussing the orientation of substitution reactions where σ-complexes are believed to be involved. For the cases studied so far, i.e. imidazole cation, neutral molecule and anion, pyridine, quinoline and isoquinoline, we find that the total electron densities are in accord with the σ-complex energies, and when taken together provide a useful index for reactions proceeding through a σ-complex intermediate.

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