



THE ELECTROSTATIC MOLECULAR POTENTIAL FOR IMIDAZOLE

The protonation process of the imidazole molecule is studied by the electrostatic molecular potential method. Calculations are made at different levels of approximation within the CNDO/2 method. Conclusions are drawn on the validity of this method for the study of protonation processes.

1 — INTRODUCTION

There has been a steady increase in the use of the methods of Quantum Mechanics for studying molecules with pharmacological activity. Most of the applications deal with the conformational and electronic requirements that a set of drugs must exhibit when interacting with a receptor, in order to display pharmacological activity.

The conformational space of a set of drugs with similar molecular structure and linked to the same receptor must be examined in order to find out the active conformation shared by this family of drugs [1].

The electronic structure requirements are established by drawing correlations between the pharmacological activity and some molecular parameters, such as bond orders, atomic charge densities, free valency indices, etc. However, the results obtained are not very trustworthy, both because it is difficult to get reliable pharmacological data and because some rather crude approximations are made when the methods of Quantum Mechanics are used for calculations on large molecules [2]. There is an alternative way for studying the electronic structure requirements which is based on the electrostatic molecular potential, i.e., the molecular wave function is used to calculate the electrostatic potential created around the molecule by the nuclei and the electronic distribution. Within the LCAO-MO approximation, the electrostatic potential created by a molecule at point \underline{r}_i of space is given by [3]:

$$V(\underline{r}_i) = \sum_{\alpha} \frac{Z_{\alpha}}{r_{i\alpha}} - \sum_{r,s} P_{rs} \int \frac{\chi_r(\underline{r}_i) \chi_s(\underline{r}_i)}{r_{il}} d\underline{r}_i \quad (1)$$

where Z_{α} is the effective nuclear charge of atom α , P_{rs} is the density matrix element related to AO's χ_r and χ_s and $r_{i\alpha}$, r_{il} are the distances to point \underline{r}_i of the nucleus α and of the monoelectronic charge density $\chi_r(\underline{r}_i) \chi_s(\underline{r}_i)$.

The energy of interaction between the molecular charge distribution and a charge q placed at \underline{r}_i may be evaluated from (1) as:

$$E(\underline{r}_i) = qV(\underline{r}_i) \quad (2)$$

The calculation of the energy of interaction between a drug and its receptor — simulated by a set of point charges adequately located — will be very

easy within this approximation, as the calculation of $V(\underline{r}_i)$ depends only on monocentric integrals. However, as equation (1) refers to an unperturbed charge distribution, $E(\underline{r}_i)$ given by (2) is only the first order energy of interaction between the molecule and the charge q , because all the other contributions to E — namely from polarization, charge transfer and deformation of the molecular geometry — which increase as the charge approaches the molecule, are neglected within this approximation.

With this work we intend to make an evaluation of the accuracy of the electrostatic potential method (within the framework of the CNDO/2 approximation) for the calculation of the energy of interaction between a molecule and a point charge.

2 — THE MOLECULAR ELECTROSTATIC POTENTIAL [4]

i) Within the CNDO/2 approximation [5] all the nuclear attraction integrals depending on the overlap of different AO's are neglected, while all the other integrals are approximated as:

$$V_{H,\pi} = V_{HA} = \gamma_{HA} \quad (3)$$

where γ_{HA} is the Coulomb repulsion integral between s type AO's centered on the hydrogen atom H and atom A. The interaction between a molecule and a proton is evaluated as:

$$E_H = \sum_A \left[\frac{Z_A}{R_{HA}} - P_{AA}(ns\ 1s | \frac{1}{R_{HA}} | ns\ 1s) \right] \quad (4)$$

where P_{AA} is the atomic charge density on A, $n=1$ if A is a hydrogen atom, or $n=2$ if A is a first row atom, and the summation extends over all the atoms of the molecule.

ii) Another possibility is to calculate the nuclear attraction integrals, V_{HA} , between s orbitals (in order to maintain the rotational invariance) instead of using the γ approximation. E_H is given by

$$E_H = \sum_A \left[\frac{Z_A}{R_{HA}} - P_{AA}(ns | \frac{1}{R_{HA}} | ns) \right] \quad (5)$$

iii) Alternatively, all the bicentric nuclear attraction integrals are calculated exactly;

E_H is given by (6) where P_{rr} is the density matrix element for orbital r on atom A:

$$E_H = \sum_A \left[\frac{Z_A}{R_{HA}} - \sum_{r \in A} P_{rr}(r | \frac{1}{R_{HA}} | r) \right] \quad (6)$$

All the terms containing the density matrix elements P_{rs} are neglected, as they have no physical meaning within the CNDO/2 approximation [6].

iv) All the above approximations use a CNDO/2 density matrix built from coefficients taken as Slater orbital coefficients, despite the fact that a ZDO approximation has been used. However, the CNDO coefficients \underline{C}^λ may be deorthogonalized by means of a Löwdin transformation [7]:

$$\underline{C}^x = \underline{S}^{-1/2} \underline{C}^\lambda \quad (7)$$

and a density matrix \underline{P}^x can be built from the new coefficients:

$$\underline{P}^x = \underline{S}^{-1/2} \underline{P}^\lambda \underline{S}^{-1/2} \quad (8)$$

where \underline{P}^λ is the CNDO/2 density matrix.

As the bicentric contributions are no longer zero, all the nuclear attraction integrals are retained for the calculation of the electrostatic potential:

$$E_H = \sum_A \frac{Z_A}{R_{HA}} - \sum_{r,s} D_{r,s}^x(r | \frac{1}{R_{HA}} | s) \quad (9)$$

$D_{r,s}^x$ being Mulliken's density matrix [6]:

$$\left. \begin{aligned} D_{rr}^x &= P_{rr}^x \\ D_{rs}^x &= 2P_{rs}^x S_{rs} \end{aligned} \right\} \quad (10)$$

3 — ASSESSMENT OF THE METHOD

The protonation of a molecule, besides changing its geometry, will give rise to a large polarization of its electronic charge. At small distances there will be also some charge transfer towards the proton. However, as none of these effects are accounted for by the electrostatic potential method, its application to a protonation process may be questioned.

In order to test the method at the level of a CNDO/2 approximation, some calculations were made for the system imidazole-proton which

performs a very important role in biological systems [8]. Three kinds of calculations were made:

- Calculations with geometry optimization for several interatomic distances N_8-H (fig. 1) in order to evaluate the influence of the approaching proton on the geometry and charge distribution of the molecule.
- Calculations without geometry optimization, in order to evaluate the effect of protonation on the charge distribution of the molecule.
- Calculation of the molecular electrostatic potential around the molecule; this is equivalent to the calculation of the first order energy of interaction between the molecule and the proton, thus neglecting the effects of polarization, charge transfer to the proton and changes of the molecular geometry.

The results of these calculations will provide an assessment of the validity of the electrostatic potential method at the level of a CNDO/2 approximation for studying the protonation of molecules.

4 — RESULTS

4.1 — CALCULATIONS WITH GEOMETRY OPTIMIZATION

The calculated geometry for imidazole (fig. 1) is in very good agreement with the experimental geometry obtained by SHERIDAN *et al* [9].

The calculated values of the total charge densities and of the π charge densities are given in Table 1, together with the values found in the literature. An analysis of the values obtained for the nitrogen atoms leads to the conclusion that the total charge distribution is dominated by the polarization of the σ electrons in such a way that both nitrogen atoms behave as electron acceptors, although the pyridinic nitrogen (N_8) is a π acceptor and the pyrrolic nitrogen (N_9) is a π donor.

All the carbon atoms are weak π acceptors (KONSKI *et al* [14] with a STO-3G basis set *ab initio* calculation have obtained a value of 1.607 for the C_6 π density, but this value appears to be grossly exaggerated and is in disagreement with all the other published values). Carbon 5 is consistently found to be an electron donor, but carbons 6 and 7 are found to be weak electron donors in some of the calculations and weak electron acceptors in other calculations; however, all the values are very similar (3.92-4.08 for carbon 6 and 3.95-4.10 for carbon 7).

The hydrogen atoms 2 and 3 are found to be electron donors and the hydrogen atoms 1 and 4 are very weak electron acceptors (charge densities 1.01); however, all the values found in the literature foresee that all the hydrogen atoms are electron donors.

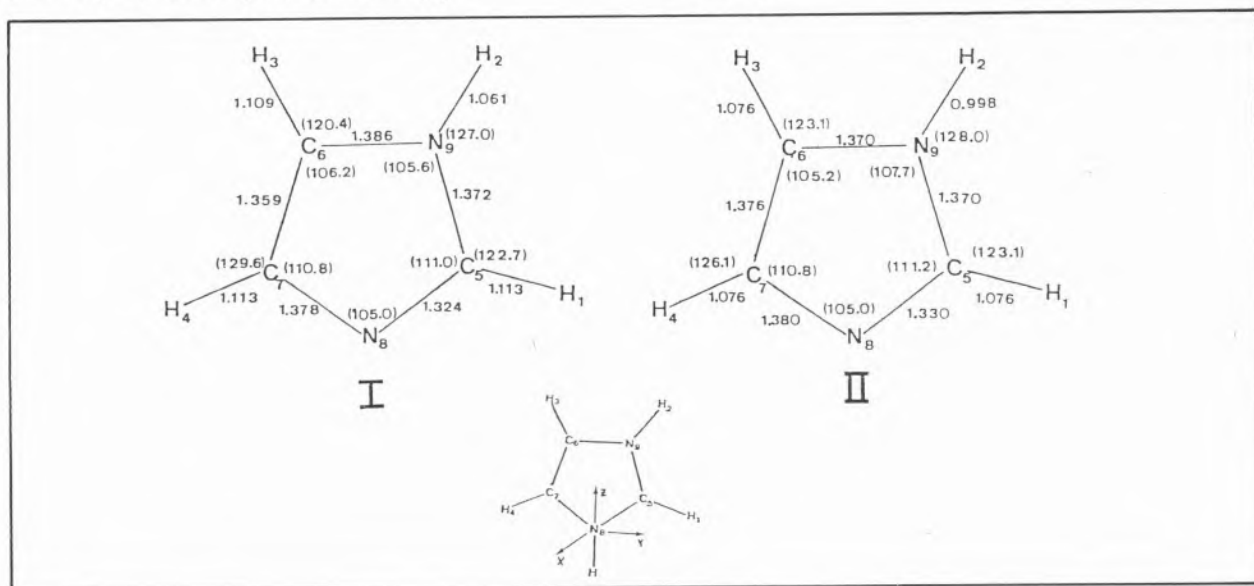


Fig. 1

Bond lengths (in Å) and bond angles (inside brackets) for imidazole. The calculated results obtained with geometry optimization (I) are compared against the experimental values (II) obtained by Sheridan *et al* [9] using rotational spectroscopy

Table 1
Imidazole-Electronic densities

		Total densities							
		Method of calculation		Atom					
				N ₈	N ₉	C ₅	C ₆	C ₇	H ₁ H ₂ H ₃ H ₄
This calculation	CNDO			5.195	5.091	3.851	3.984	3.966	1.011 0.893 0.999 1.010
Konski <i>et al</i> [10]	<i>ab initio</i> (STO-3G)			5.269	5.312	3.881	3.887	4.019	0.914 0.766 0.920 0.931
Konski <i>et al</i> [10]	<i>ab initio</i> (4-31G)			5.548	5.880	3.659	3.916	3.951	0.772 0.608 0.773 0.795
Berthier <i>et al</i> [11]	CNDO			5.159	5.842	3.915	4.026	4.059	0.782 0.624 0.788 0.799
Roche <i>et al</i> [12]	CNDO			5.26	5.07	3.98	4.08	4.10	0.90 0.77 0.96 0.92

π electronic densities

	Method of calculation	Atom				
		N ₈	N ₉	C ₅	C ₆	C ₇
This calculation	CNDO	1.175	1.615	1.022	1.118	1.070
Konski <i>et al</i> [10]	<i>ab initio</i> (STO-3G)	1.129	1.996	1.108	1.607	1.141
Konski <i>et al</i> [10]	<i>ab initio</i> (4-31G)	1.201	1.643	0.998	1.092	1.066
Fischer <i>et al</i> [13]	CNDO	1.142	1.651	1.037	1.072	1.094

4.2 — THE EFFECT OF PROTONATION ON THE MOLECULAR PARAMETERS

The changes of some molecular parameters as a proton approaches the pyridinic nitrogen (N₈) are given in Table 2. It can be seen that protonation decreases the strength of the N₉—H₂ bond, as there is an increase of its bond length. The total electronic charge density and the π electronic charge density at the pyrrolic nitrogen both decrease with protonation, but the σ electronic charge density increases; this means that the protonation of the pyridinic nitrogen will increase both the π donating and the σ accepting capacities of the

pyrrolic nitrogen, but as the π effect is more pronounced, the net effect is an increase of the accepting capacity. This shows that the protonation of the pyridinic nitrogen has a marked influence on the behaviour of the other nitrogen.

The energy minimum for the imidazole-proton system was found by optimizing the coordinates of all the atoms and gives the following coordinates for the proton: Z_H = -1.065 Å, Y_H = 0.005 Å; this means that the proton approaches the nitrogen atom along a direction that is slightly displaced towards the pyrrolic nitrogen relative to the bisecting line of the C₅—N₈—C₇ angle (fig. 1).

Table 2
Change of some of the molecular parameters of imidazole with the distance N₈—H (with geometry optimization)

R _{N₈-H} (Å)	E _{Total} (eV)	ΔE (eV)	R _{N₉-H₂} (Å)	P _{N₉}	P _{N₉} ^{π}	P _{N₉} ^{σ}	P _{H₂}
0.800	-1304.629	-9.875	1.066	5.027	1.488	3.539	0.799
0.900	-1308.003	-13.249	1.066	5.028	1.492	3.537	0.790
1.000	-1309.412	-14.658	1.066	5.029	1.494	3.535	0.791
1.025	-1309.548	-14.794	1.066	5.029	1.494	3.535	0.791
1.045	-1309.560	-14.846	1.066	5.030	1.494	3.535	0.791
1.065	-1309.617	-14.863	1.066	5.030	1.495	3.535	0.792
1.150	-1309.368	-14.614	1.066	5.030	1.496	3.534	0.793
1.250	-1308.498	-13.744	1.066	5.032	1.503	3.529	0.794
∞	-1294.754	0	1.061	5.091	1.615	3.475	0.893

4.3 — CALCULATIONS WITHOUT GEOMETRY OPTIMIZATION

The changes of some molecular parameters of imidazole as a proton approaches the pyridinic nitrogen N_8 along the direction defined above, are given in Table 3 for calculations without geometry optimization.

Table 3

Changes of some of the molecular parameters of imidazole with the distance N_8-H (without geometry optimization)

$R_{N_8-H}(\text{\AA})$	$\Delta E(\text{eV})$	P_{N_9}	$P\pi_{N_9}$	$P\sigma_{N_9}$
0.700	-3.276	5.040	1.508	3.532
0.900	-13.189	5.036	1.502	3.534
1.000	-14.535	5.042	1.515	3.527
1.025	-14.725	5.042	1.516	3.526
1.045	-14.733	5.042	1.516	3.526
2.000	-2.074	5.074	1.554	3.520
∞	0	5.091	1.615	3.475

When these values are compared against those obtained with geometry optimization, it becomes obvious that the results are very similar for the same N_8-H distance; it is also important to notice that the positions of the energy minimum, calculated with and without geometry optimization, are almost coincident and that the value of the minimum only differs by 0.130 eV.

This result means that without appreciable loss of accuracy we can use the calculations without geometry optimization, thus saving quite a large amount of computer time.

4.4 — CALCULATIONS OF THE MOLECULAR ELECTROSTATIC POTENTIAL

The electrostatic potential created by an imidazole molecule was calculated using approximations i) to iii) from paragraph 2 and the results are given in figs. 2 to 4. The results are qualitatively rather similar and the most important differences, from a quantitative point of view are the location and the value of the minimum (Table 4).

As the method of calculation becomes more sophisticated the minimum of the potential becomes more negative but, in any case, far less negative than the minimum obtained by CNDO2/CFF [15]

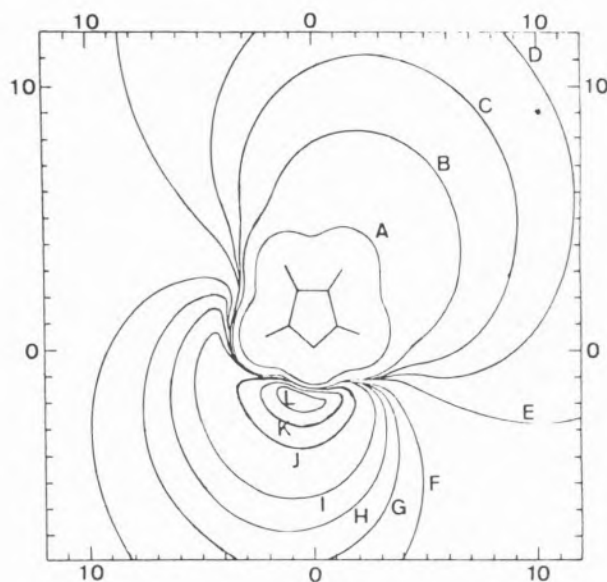


Fig. 2

The electrostatic molecular potential for imidazole; approximation 1 Contour values in eV; distances in \AA .

0.70(A); 0.10(B); 0.05(C); 0.03(D); 0.01(E)
-0.03(F); -0.05(G); -0.07(H); -0.10(I); -0.20(J)
-0.30(K); -0.40(L)

(even with the most favourable approximation the value obtained is only 8% of the CNDO2/CFF value); this is a direct consequence of neglecting the polarization of the electronic cloud and the

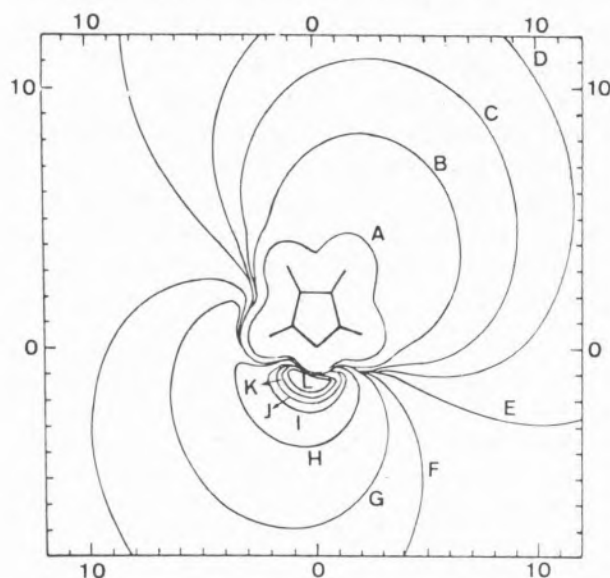


Fig. 3

The electrostatic molecular potential for imidazole; approximation 2 Contour values in eV; distances in \AA .

0.70(A); 0.10(B); 0.05(C); 0.03(D); 0.01(E);
-0.03(F); -0.07(G); -0.20(H); -0.40(I); -0.50(J);
-0.60(K); -0.70(L)

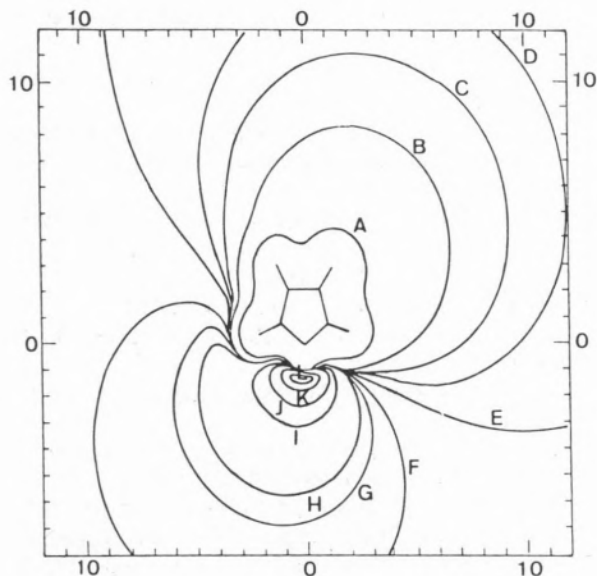


Fig. 4

The electrostatic molecular potential for imidazole; approximation 3. Contour values in eV; distances in Å.

0.70(A); 0.10(B); 0.05(C); 0.03(D); 0.01(E);
-0.03(F); -0.07(G); -0.10(H); -0.30(I); -0.50(J);
-0.80(K); -1.00(L)

Table 4

Minimum of the interaction energy for the system imidazole-proton and its location relative to the pyridinic nitrogen

Approximation	$Y_{N_8-H}(\text{\AA})$	$Z_{N_8-H}(\text{\AA})$	E(eV)
1	-0.60	-2.00	-0.48
2	-0.60	-1.25	-0.88
3	0.00	-1.25	-1.18
CNDO2/CFF	0.005	-1.065	-14.863

charge transfer to the proton; there will be also some minor effects from geometry changes.

The first two approximations also give a direction of approach of the proton lying to the left of the bisecting line of the $C_5-N_8-N_7$ angle, in disagreement with the CNDO2/CFF results. However, the results of the third approximation agree fairly well with the CNDO2/CFF results. In fig. 5 the energy of interaction for the system imidazole-proton is plotted against the distance N_8-H along the line containing N_8 and a point of coordinates ($Y_{N_8-H} = 0.005 \text{ \AA}$; $Z_{N_8-H} = -1.065 \text{ \AA}$). It can be seen that none of the approximations reproduces the CNDO/2 results close to the N_8 atom; however, for distances over 3 Å all

the results are similar because, at large distances, the main contribution for the interaction energy becomes purely electrostatic.

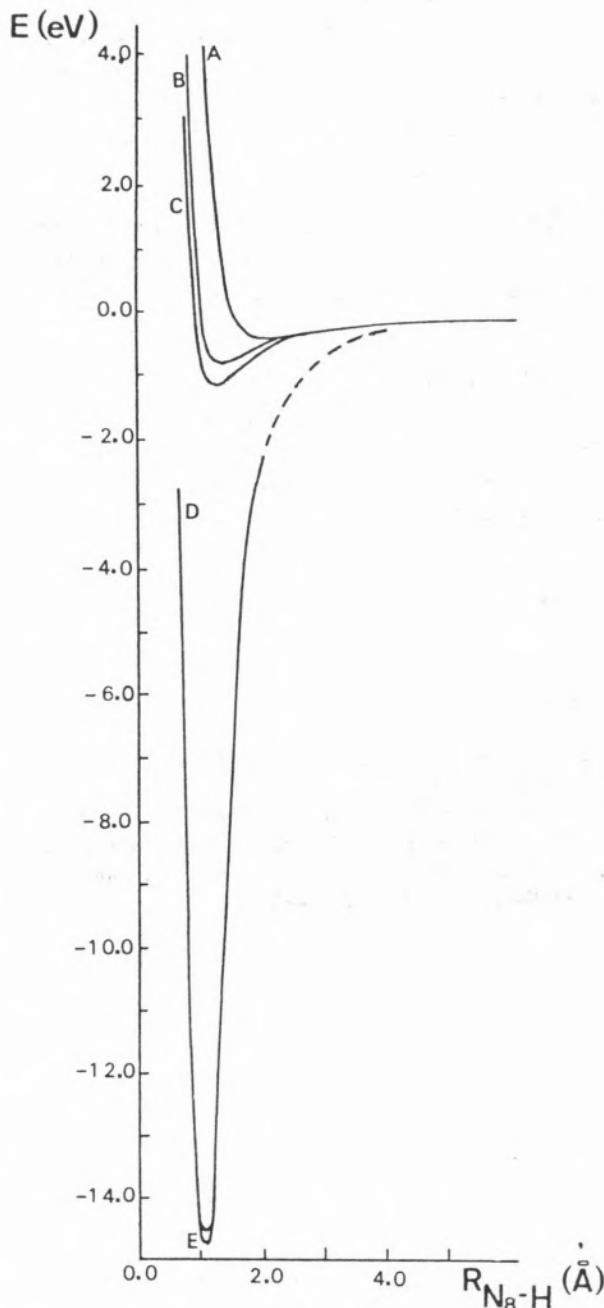


Fig. 5

The change of the energy of interaction imidazole-proton with the N_8-H distance.

- A — Electrostatic potential — approximation 1
- B — Electrostatic potential — approximation 2
- C — Electrostatic potential — approximation 3
- D — CNDO/2 calculations without geometry optimization
- E — CNDO/2 calculations with geometry optimization

5 — CONCLUSIONS

The results may be summarized as follows:

i) The main contributions to the protonation process are given by the electrostatic interaction and by the polarization of the electronic cloud. As the distance increases the effect of polarization becomes negligible. Geometry changes have only a minor effect.

ii) Approximations i) and ii) are not reliable, even from a qualitative point of view, because they don't give the right direction of approach for the proton.

iii) Approximation iii) (if not very good from a quantitative point of view) at least will give qualitatively reasonable results, mainly near the pyridinic nitrogen, the most important region in the protonation process.

Received 22 January 1982

REFERENCES

- [1] W. G. RICHARDS, *Quantum Pharmacology*, Butterworths, London (1977).
- [2] Z. SIMON, *Quantum Biochemistry and Specific Interactions*, Abacus Press, Tunbridge Wells, Kent (1976).
- L. B. KIER, *Molecular Orbital Theory in Drug Research*, Academic Press, New York (1973).

- [3] E. SCROCCO, J. TOMASI, *Topics in Curr. Chem.*, **42**, 95 (1973).
- [4] J. A. POPLE, D. P. SANTRY, G. A. SEGAL, *J. Chem. Phys.*, **43**, 5129 (1965).
- J. A. POPLE, G. A. SEGAL, *J. Chem. Phys.*, **44**, 3289 (1966).
- [5] C. GESSNER-PRETTRE, A. PULLMAN, *Theoret. Chim. Acta*, **25**, 83 (1972).
- [6] J. J. KAUFMAN, *Int. J. Quantum Chem.*, **4**, 208 (1971).
- R. CABALLOL, R. GALLIFA, M. MARTINS, R. CARBO, *Chem. Phys. Lett.*, **25**, 89 (1974).
- [7] P. O. LÖWDIN, *J. Chem. Phys.*, **18**, 365 (1950).
- P. O. LÖWDIN, *Advances in Quantum Chemistry*, **5**, 185 (1970).
- [8] C. A. MATUSAK, A. I. MATUSAK, *J. Chem. Ed.*, **53**, 280 (1976).
- [9] I. H. GRIFFITHS, A. WARELEY, V. E. WILLIAMS, N. L. OWEN, J. SHERIDAN, *Nature*, **216**, 1301 (1967).
- [10] C. T. O'KONSKI, I. W. JOST, *J. Mol. Struct.*, **58**, 475 (1980).
- [11] G. BERTHIER, L. PRAUD, I. SERRE, *The Jerusalem Symposia on Quantum Chemistry*, vol. 2, *Quantum Aspects of Heterocyclic Compounds* (1969).
- [12] M. ROCHE, L. PUJOL, *J. Chim. Phys.*, **68**, 465 (1971).
- [13] I. FISCHER-HJALMARS, I. NAG-CHAUDHURI, *Acta Chem. Scand.*, **23**, 2963 (1969).
- [14] E. STEINER, «The Determination and Interpretation of Molecular Wave Functions», University Press, Cambridge (1976).
- [15] V. MORAIS, A. A. AMARAL, J. GOMES, *Rev. Port. Quím.*, **22**, 38 (1980).

RESUMO

O Potencial Molecular Electrostático da Imidazola

Faz-se estudo da protonação da imidazola por meio do método do potencial molecular electrostático, usando aproximações a vários níveis dentro do método CNDO/2. Tiram-se conclusões quanto à validade do método para o estudo de problemas deste tipo.