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Molecular Orbital Treatment of Some Amino Acids

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INDO-molecular orbital calculations have been performed on a number of amino acids, namely, alanine, phenylalanine, some tyrosines and histidine. Computations on *N*-acetylhistidine are included for comparison. The results obtained for the charge densities and dipole moments were used to get a "structure-function" correlation.

Proteins perform virtually all types of work in an organism. The standard amino acids, constituting proteins, differ only with respect to their side chain. Each side chain is so specific that it cannot be replaced by another one.

Several CNDO/2 calculations predict that the neutral form of glycine is more stable than the ionic form.[1-3] Conformational analysis performed with CNDO/2[4-7] and INDO[8] as well as the corresponding ab initio calculations,[9-11] reveals a number of interesting results. CNDO/2 calculations on systems of two, three, and four members (-$CONHCH_2$-) were carried out and the most stable conformation of glycine trimer was predicted.[5] Cooperative conformational studies have been carried out on glycine.[12]

Luke et al.[13] have studied the STO-3G and STO-3G* optimized structures of glycine and found that it has three or four low-lying stable conformations. The molecule can easily rearrange to any of them. Intermediate water structures in the solution of alanine dipeptide were investigated.[14] With the ST2 water model, the solute, alanine dipeptide, is hydrated.

Ladik et al.[15] have presented some new results on the quantum mechanical investigation using localized orbitals of DNA. The results show an excellent localization of the occupied orbitals and a rather good one for the virtuals (both for the σ- and π-orbitals) of the four nucleotide bases. Interaction energy calculations between a polyglycine chain in different conformations and polynucleotide chain were performed.

In the last years, substantial progress has been achieved in the quantum mechanical investigation of DNA including the water and ion structure around it,[16] and band structure calculations using a whole nucleotide as a unit cell.[17] Pilot calculations have been performed to assess the effect of water structure on a nucleotide base stack[18] for the investigation of polynucleotide-polypeptide (polyglycine) interaction[19] and for the treatment of a periodicity in DNA macromolecules.[20]

The negative factor counting technique in its ab initio form[21] was used to calculate the total density of states of nonperiodic polynucleotides and polypeptides.[22] Computations were performed on a periodic and nonperiodic poly(-gly-cys-asp-ser-) chain.

A number of theoretical investigations have been devoted to the determination of the energy band stuctures and of the possible pathway for electron delocalization in proteins.[23] All calculations were represented by the very simple periodic models, mostly poly(gly) with the exception of MINDO/3 all-valence electron crystal orbital calculations of aperiodic β-polypeptide.[24] The effect of some factors on the energy band structure on some protein models was calculated with the aid of the CNDO/2 crystal orbital method.[25]

In this work INDO-molecular orbital calculations have been carried out on a number of amino acids in an attempt to understand the "structure-function" relationship for them. Such a study has not been reported before.

Method of Calculations. INDO-CI procedures have been followed, details and parameterization of the procedures are found elsewhere.[26] Interaction was considered between nine configurations which correspond to electronic transitions between the three highest occupied molecular orbitals and the three lowest unoccupied molecular orbitals.

Results and Discussion

A. Alanine and Phenylalanine. Alanine is considered as the α-amino acid with the smallest nonpolar side chain whereas phenylalanine is the amino acid with the largest nonpolar side chain. Figure 1 shows the configuration used in MO calculations with the INDO values of total charge in units of 10^{-3} e. Table 1 gives the values of some of the calculated parameters. It can be seen that phenylalanine has a weaker dipole than alanine indicating that the polarization of the benzene ring is in the opposite direction to that of the -COOH group. The total charge densities on the groups: -NH_2, -OH, and -COOH are only slightly higher than they are in alanine. This result explains the fact that phenylalanine is a stronger acid (K_a=6.7×10^{-3}) than alanine (K_a=4.89×10^{-3}).[27] The built up of a slight negative charge on the benzene ring (0.052) suggests that phenylalanine can act as electron donor as well as an electron acceptor.

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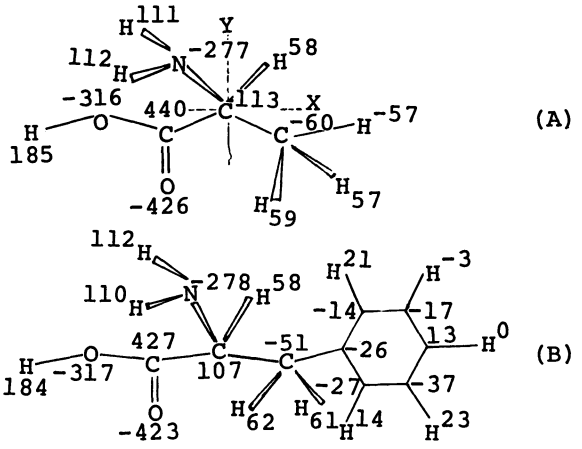

Fig. 1. Configuration and total charge density($\times 10^3$) on: (A) alanine, (B) phenylalanine.

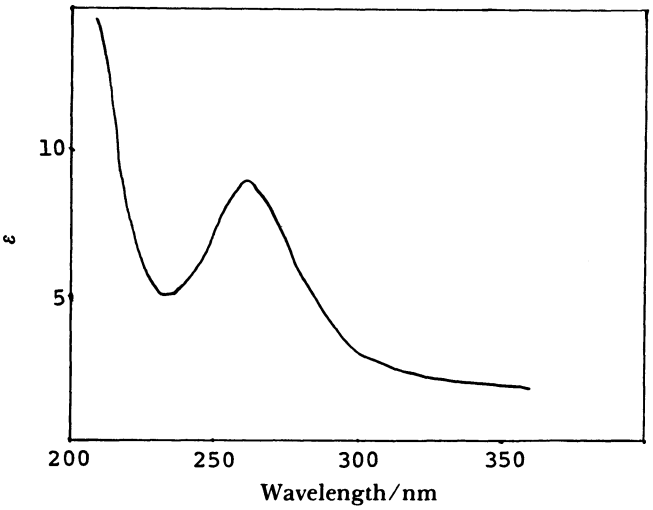

Fig. 2. Electronic absorption spectrum of alanine in methanol.

Figures 2 and 3 show the electronic absorption spectra of alanine and phenylalanine using methanol as a solvent. A weak band appears in the spectrum of alanine (240—290 nm) which agrees satisfactory with the calculated transition energy (3.88 eV). The spectrum of phenylalanine shows two absorption bands, the lower energy one (ca. 260 nm) shows the characteristic vibrational components of the $^1L_b \leftarrow {}^1A$ transition of the benzene nucleus. The correspondance between the calculated (4.91, 5.70 eV) and the experimental (4.81, 5.90 eV) transition energies is satisfactory.

B. Tyrosine and Hydroxytyrosines. Figures 4A,B and 5 show the configurations of the molecules and the calculated total charge density in units 10^{-3} e. Table 2 gives the values of the calculated parameters. It can be seen that tyrosines have strong dipoles and hence their position and sequence in proteins is totally different from those of alanine and phenyl-

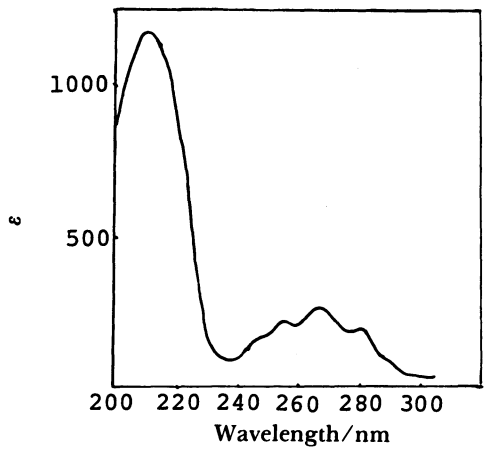

Fig. 3. Electronic absorption spectrum of phenylalanine in methanol.

Table 1. Values of Calculated Parameters of Alanine and Phenylalanine

Calcd parameter	Alanine	Phenylalanine
Dipole moment, *D*		
atomic[a]	1.6555	1.5009
polarization[b]	2.0866	1.9098
total	2.5622	2.2909
Total charge density ($\times 10^3$ e)		
$-NH_2$	−56	−57
-OH	−130	−133
-COOH	−126	−130
Ph ring	—	−52
Energy/eV		
HOMO	−10.2289	−9.3201
LUMO	−0.3975	−0.8001
Transition energy and Osc. str.	3.88(0.01)	4.90(0.12)
	7.80(0.08)	5.70(0.54)

a) $\vec{\mu}_{ch}$. b) $\vec{\mu}_{hyb}$ (Ref. 26).

Table 2. Values of Calculated Parameters of the Studied Tyrosines

Parameter	Tyrosine	3-Hydroxytyr	3,5-Dihydroxytyr
Dipolemoment, *D*			
atomic	1.9437	2.1552	2.2027
polarization	2.7567	3.5154	4.6785
total	4.1873	5.1414	6.6757
Total charge density ($\times 10^3$ e)			
$-NH_2$	−57	−57	−57
-OH	−134	−134	−133
-COOH	−131	−132	−131
-OH(a)[a]	−136	−131	−125
-OH(b)	—	−96	−95
-OH(c)	—	—	−136
-Ph ring	89	184	256
-Side Chain[b]	−47	−43	−100
Energy/eV			
HOMO	−9.4268	−9.3141	−9.2292
LUMO	−0.8692	−0.9555	−1.0378
Trans. energy and Osc. str.	5.04(0.01)	4.70(0.03)	4.79(0.01)
	5.48(0.56)	5.51(0.50)	5.36(0.60)
	6.17(0.45)	6.15(0.50)	6.18(0.50)

a) See Figs. 4A, B and 5. b) Net total charge on the side chain.

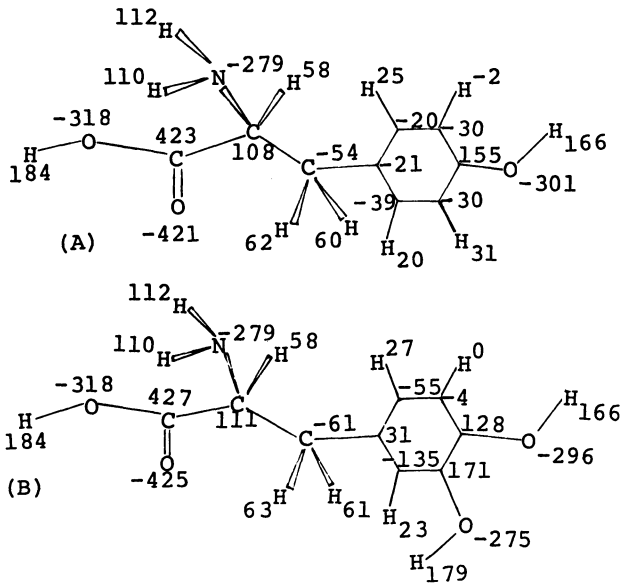

Fig. 4. Configuration and total INDO charge density($\times 10^3$ e): (A) tyrosine, (B) 3-hydroxytyrosine.

alanine. The charge densities on different functional groups ($-NH_2$, -OH, and -COOH) did not differ significantly from tyrosine to hydroxytyrosines. However, a net negative charge is built up on the side chain and increases in the order: 3,5-dihydroxytyrosine>tyrosine>3-hydroxytyrosine. On the other hand a net positive charge is built on the benzene ring and increases in the order: 3,5-dihydroxytyrosine>3-hydroxytrosine>tyrosine. Tyrosine is a much stronger acid ($K_{a_1}=6.7\times10^{-3}$) than 3-hydroxytyrosine ($K_{a_1}=1.32\times10^{-5}$).

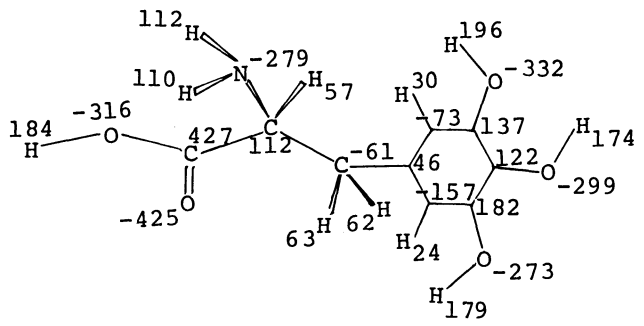

Fig. 5. Configuration and total INDO charge density($\times 10^3$ e) for 3,5-dihydroxytyrosine.

Figure 6 shows the absorption spectrum of tyrosine in methanol. Two electronic transitions are observed and correspond to the $^1L_b \leftarrow {}^1A$ and $^1L_a \leftarrow {}^1A$ of the perturbed benzene nucleus. The correspondance between the observed transition energies (4.51, 5.51 eV) and the calculated (5.04, 5.48) seems to be satisfactory.

C. Histidine and *N*-Acetylhistidine. The presence of imidazole ring in the side chain of histidine is a determining factor in the properties of histidine. Table 3 gives the calculated parameters and Fig. 7 shows the total charge density on the different atoms of the molecule. Computations on *N*-acetylhistidine are included for comparison. Acetylation led to a pronounuced increase in the dipole moment and a decrease of charge density on the imidazole ring compared to histidine.

The results of calculations (Table 3) show that histidine has a much stronger dipole than tyrosine or

Table 3. Numerical Values of the Calculated Parameters of Histidine and *N*-Acetylhistidine

Parameter	Histidine	*N*-Acetylhistidine
Dipole moment, *D*		
atomic	4.2880	6.8581
polarization	2.5580	3.1215
total	6.3829	9.8934
Total charge density ($\times 10^3$ e)		
$-NH_2$	−157	−158(-NH)
-OH	−167	−175
-COOH	−226	−242
Imidazole ring	−147	−35
Energy/eV		
HOMO	−9.1263	−9.0382
LUMO	−2.3710	−2.4539
Trans. Energy and Osc. Str.	3.97(0.003)	4.01(0.02)
	4.87(0.001)	5.19(0.37)
	5.21(0.37)	5.86(0.02)
	6.09(0.01)	5.99(0.02)
	6.22(0.39)	6.70(0.05)

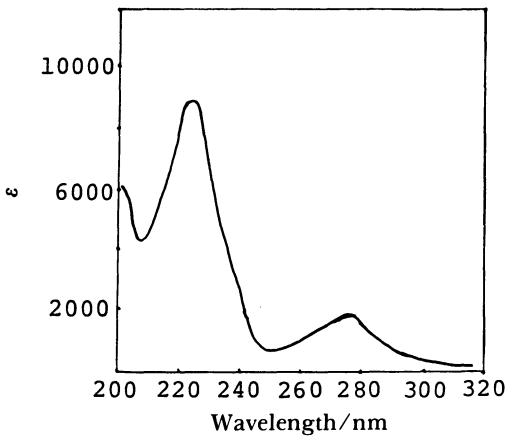

Fig. 6. Electronic absorption spectrum of tyrosine in methanol.

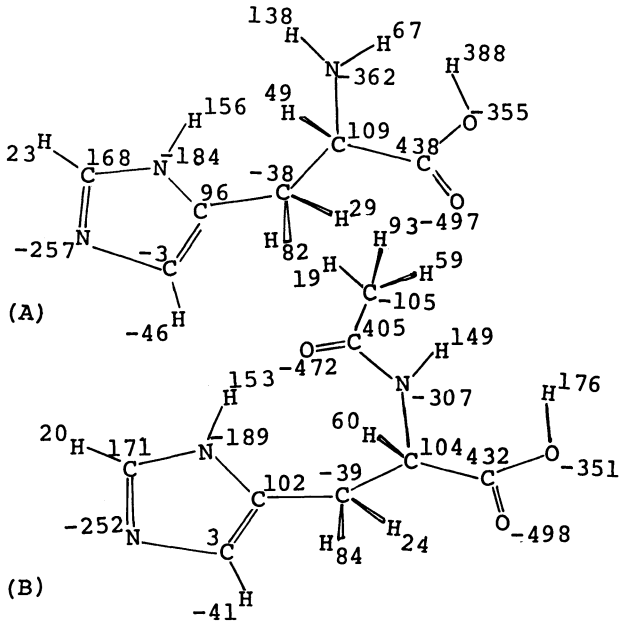

Fig. 7. Configuration and INDO total charge density($\times 10^3$ e): (A) histidine, (B) *N*-acetylhistidine.

hydroxytyrosine. This explains the activity of the acid and its existence in the most active center of the enzyme. The net negative charge built on the functional groups is higher than on the same groups in tyrosine and hydroxytyrosines. A net negative charge is built on the imidazole ring of histidine contorary to the net positive charge built on the benzene ring of phenylalanine and tyrosines. Histidine can act as an electron donor.

The electronic absorption spectrum of histidine (Fig. 8) shows two electronic transitions at 3.97 and 5.21 eV which corresponds nicely with the calculated (3.97 and 5.21 eV).

Conclusion

The position and function of the amino acid in the protein series is dependent on its electronic structure in addition to other properties as size, geometry and nature of its side chain. The results of this work explains many experimental observations. Calculations showed that phenylalanine has a weaker dipole than alanine. There is a weak built up of negative charge density on the benzene nucleus (−0.052) and this renders phenylalanine to act as an electron donor as well as an electron acceptor. Phenylalanine is a stronger acid than alanine which could be due to the higher charge densities of the functional groups in phenylalanine.

Tyrosines have strong dipoles and this determines their position in the protein series. A net positive charge is built on the benzene nucleus and tyrosines

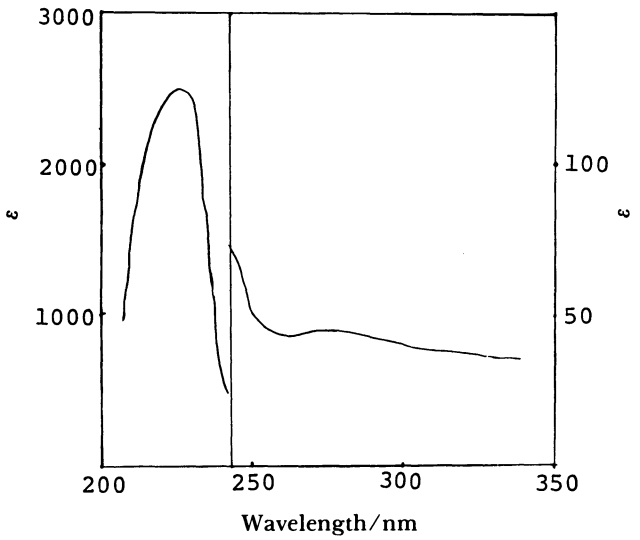

Fig. 8. Electronic absorption spectrum of histidine in methanol.

act as electron acceptors. The theoretical results account for the activity of histidine and its existence at the active center of the enzyme. Histidine can act as an electron donor, a net negative charge is built on its imidazole ring. Acetylation decreases this charge.

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