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EHT and CNDO/2 Calculations on Amino Terminal Peptides

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Quantum Mechanical investigations have been performed by means of EHT and CNDO/2 methods on the three amino terminal peptides: $NH_3^+-CH_2-CONHCH_3$, $NH_3^+-CH(CH_3)-CONHCH_3$ and $NH_3^+-CH_2-CON(CH_2)_4$. The resulting energy maps compare satisfactorily with the distribution of the experimental X-rays data.

Molecular orbital computations on model compounds of interest for the biologically important field of polypeptide conformations have recently appeared. Different procedures have been used but particularly the Extended Hückel [1–4] and the PCILO [5–7] have gained preference with results in reasonable agreement with the classical ones as derived from the contact criteria and the potential energy formulae [8–10]. In spite of the rather reduced dimensions of the molecules

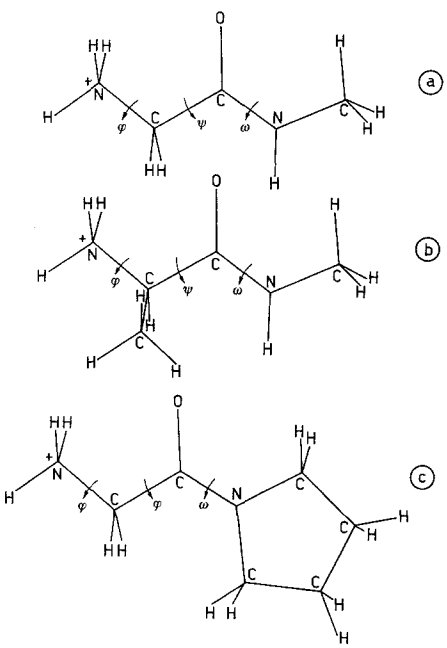

Fig. 1a–c. Schematic view of the $NH_3^+-CH_2-CONHCH_3$, (a) $NH_3^+-CH(CH_3)-CONHCH_3$, (b) and $NH_3^+-CH_2-CON(CH_2)_4$, (c) sequences in the initial conformation corresponding to φ, ψ and ω internal rotation angles equal to zero

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that quantum mechanical methods are able to handle in reasonable computer time, the possibility to check with independent procedures some of the more or less "classical results" has been welcomed by several authors.

Simple biologically interesting systems are, among the others amino terminal segments that are likely to be present in proteins. We undertook therefore a rather systematic analysis, both with classical and quantum mechanical procedures on some protonated sequences. A detailed comparison of the derived results will be published elsewhere but we wish to report here some quantum mechanical conclusions for the three sequences $NH_3^+-CH_2-CONH-CH_3$, $NH_3^+-CH(CH_3)-CONH-CH_3$, and $NH_3^+-CH_2-CON(CH_2)_4$ (Fig. 1).

To save computer time we carried out an exploratory analysis with the classical partition energy method (PEM) and then the more expensive quantum mechanical techniques were used to investigate mainly the low energy conformational regions. From this approach it turned out a reasonable factorization

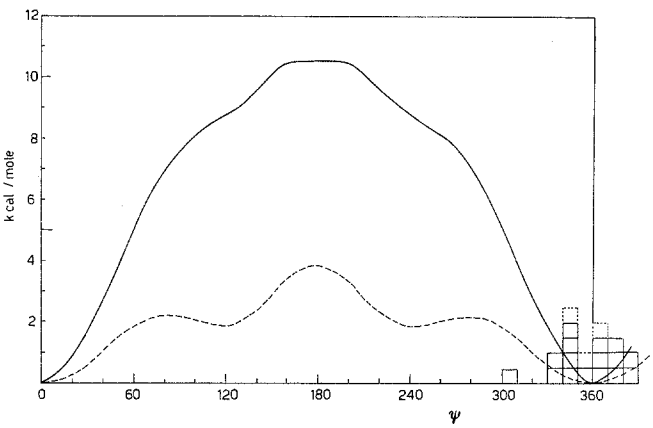

Fig. 2. EHT ——— and CNDO/2 ——— energy curves for the glycyl fragment $NH_3^+-CH_2-CONHCH_3$

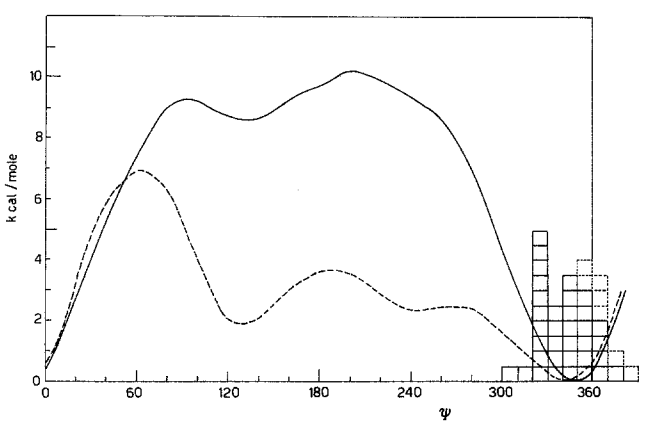

Fig. 3. EHT ——— and CNDO/2 ——— energy curves for the alanyl fragment $NH_3^+-CH(CH_3)-CONHCH_3$

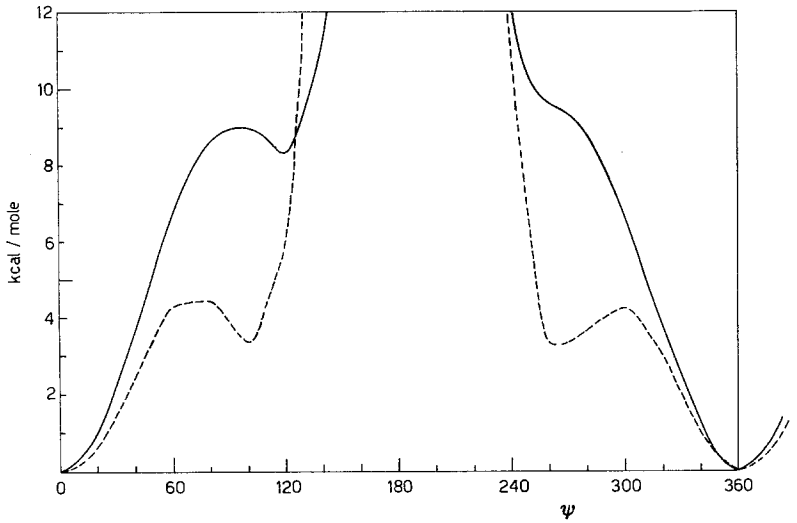

Fig. 4. EHT ——— and CNDO/2 ——— energy curves for the glycyl-prolyl fragment $NH_3^+-CH_2-CON(CH_2)_4$

to fix the $N-C_\alpha$ internal rotation angle to an ethane-like staggered position ($\varphi = 0°$). In fact in the investigated sequences a variation of the φ angle from this starting value seldom produced any significant lowering of the energy, on the contrary an increase of about 1–2 kcal/mole was observed for rotations of 20° in the conformationally important regions. These findings are also in satisfactory agreement with the distribution of the experimental values as derived from the crystal data of amino acids and small peptide sequences.

The methods used for the QM calculations are the well known EHT and CNDO/2 in the original form and parametrization suggested by Hoffmann [11] and Pople and Segal [12]. Programs from the QCPE organization [13] have been used in the computations.

In Figs. 2, 3 and 4 are reported the EHT and CNDO/2 energy curves for the three sequences and the histograms of the experimental data. The ψ internal rotation angles derived from metal peptide complexes are marked in the histograms with broken lines.

From the figures the position of the lowest energy minima as derived with the two methods are in good agreement and the experimental data fit the minima rather well, but the slope of the CNDO/2 energy curves are generally steeper and therefore only one conformation should be populated according to this procedure. The excitation energy of a number of subsidiary minima are on the contrary in an acceptable range (2–3 kcal/mole) in the EHT computations. Lack of experimental data corresponding to these excited conformations prevents more defined conclusions on the reliability of the energy values, nevertheless the energy difference between the lowest and the first excited conformations, computed with the EHT and the CNDO/2 methods, supports an extended conformation of the glycyl residue in the last investigated sequence for which no crystal data are available.

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