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Molecular Orbital Calculations on the Conformation of Polypeptides and Proteins

III. Conformational Maps of Amino-Acid Residues: A Preliminary Comparison of Empirical, Quantum-Mechanical and Experimental Results*

BERNARD PULLMAN, BERNARD MAIGRET, and DAVID PERAHIA
Institut de Biologie Physico-Chimique, 13, rue P. et M. Curie, Paris 5è, France

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An extensive comparison of empirical and quantum-mechanical computations on the conformation of the glycyl and alanyl residues indicates substantial differences between the two. The quantum-mechanical computations impose less restrictions upon the "allowed" or "preferred" conformational space than do the empirical ones. In the case of the alanyl residue they even introduce new zones of conformational stability, overlooked by the majority of the empirical computations. The experimental data coming from crystallographic studies on lysozyme, myoglobin and a number of smaller compounds are in better agreement with the quantum-mechanical results than with the empirical ones. Recent quantum-mechanical calculations on the conformational maps of the four aromatic residues of proteins having shown that these maps are, as far as their general contours are concerned, very similar to those of the alanyl residue, the conformational map for this last residue is considered as typical, roughly, for all C^{β} containing residues. It is shown that practically all experimentally known conformations for *all* the different amino-acid residues in lysozyme, myoglobin and a number of smaller compounds, fit into this scheme, the agreement being much better with the quantum-mechanical conformational map than with a typical empirical one.

Une comparaison détaillée des résultats des calculs empiriques avec ceux des calculs quantiques sur la conformation des résidus glycyle et alanyle indique l'existence des divergences profondes entre les deux. Les calculs quantiques, menés par la méthode PCILO, imposent nettement moins de restrictions que ne le font les calculs empiriques sur l'espace conformationnel préféré de ces résidus. Dans le cas du résidu alanyle les calculs quantiques introduisent même des nouvelles zones de stabilité conformationnelle qui ont échappé à la majorité des calculs empiriques et dont la signification paraît essentielle. Les données expérimentales provenant des études cristallographiques sur le lysozyme, la myoglobine et un certain nombre de molécules plus petites sont en meilleur accord avec les résultats des calculs quantiques qu'avec ceux des calculs empiriques. Des calculs quantiques récents sur les cartes conformationelles des quatre résidus aromatiques des protéines ayant montré que ces cartes sont, pour autant que l'on s'intéresse à leurs contours généraux, très semblables à celle du résidu alanyle, la carte conformationelle de ce dernier a été considérée comme représentant, *grosso modo*, tous les résidus à carbone β. On montre que pratiquement toutes les conformations connues expérimentalement de *tous* les acides aminés du lysozyme, de la myoglobine et d'un certain nombre de molécules plus petites sont en accord avec cette représentation, l'accord étant bien meilleur avec la carte conformationnelle résultant des calculs quantiques qu'avec celle représentant un calcul empirique typique.

Ein detaillierter Vergleich der Resultate empirischer und quantenmechanischer Rechnungen für die Konformation des Glycyl- und Alanyl-Restes zeigt große Divergenzen. Die nicht empirischen, nach der PCILO-Methode durchgeführten Rechnungen ergeben weniger Beschränkungen als die

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empirischen. Im Fall des Alanylrestes führen erstere sogar zu neuen Bereichen der Stabilität, die bei der Mehrzahl der empirischen Rechnungen nicht auftreten, obwohl sie wesentlich zu sein scheinen. Die experimentellen Angaben aus kristallographischen Studien über Lysozym, Myoglobin und eine Anzahl kleinerer Moleküle sind in besserer Übereinstimmung mit den Resultaten der quantenmechanischen als mit denen der empirischen Rechnungen. Kürzlich haben quantenmechanische Berechnungen für die Konformation von vier aromatischen Proteinresten gezeigt, daß sie im großen und ganzen der des Alanylrestes sehr ähnlich sind. Deshalb wurden dessen Konformationen als in den Grundzügen typisch für alle C^{β} enthaltenden Reste angesehen. Schließlich wird gezeigt, daß praktisch alle bekannten Konformationen für die verschiedenen Aminosäure-Reste in Lysozym, Myoglobin und einer Anzahl kleinerer Verbindungen in dieses Schema passen, wobei die Übereinstimmung mit den quantenmechanischen Ergebnissen besser als mit denen rein empirischer Rechnungen ist.

1. Introduction

Because of the widely accepted idea that the conformation of a residue in a polypeptide chain is in general largely independent of the nature and conformation of the neighbour residues, a particular importance has been paid in theoretical studies of these problems to the units designated as "dipeptides", which correspond to the span of the chain in Fig. 1 (which indicates also the standard conventions utilized in such studies, following Ref. [1]).

These theoretical studies have until recently been carried out essentially by *empirical* methods, first in the so called "hard sphere" approximation, which by evaluating on the basis of Van der Waals (or similar) radii the "allowed" contacts between the constituent atoms, yielded the simplest *conformational maps* ("allowed" limits as a function of the angles of rotation Φ and Ψ) and later in a more refined, approximation which consisted of partitioning the potential energy of the system into several contributions (such as non-bonded and electrostatic interactions, barriers to internal rotations, hydrogen bonding etc.) and of evaluating these contributions with the help of empirical formulas deduced from studies on small model compounds (for excellent reviews of these studies see Refs. [2–5]).

More recently, the problem has been reinvestigated by a more fundamental quantum-mechanical approach [6–8]. The recent development of molecular orbital methods towards treating simultaneously all-valence (σ and π) and even all

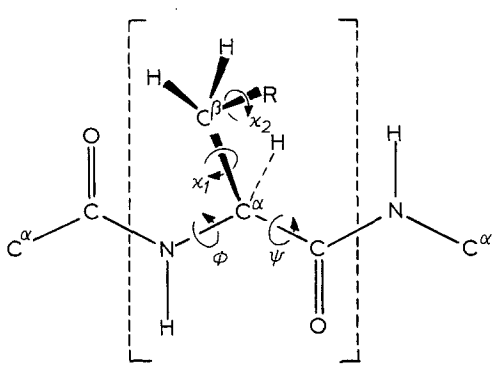


Fig. 1. A dipeptide and standard conventions [1] for the study of polypeptide conformations. [ ] limits of a residue

electrons of a system makes it possible nowadays to calculate directly the total energy of a molecule, corresponding to any given configuration of its constituent atoms and enables therefore to choose the preferred ones. It avoids thus the *a priori* division of the potential energy into constituent parts and eliminates the somewhat artificial character and possible incompleteness of the empirical procedures. In our quantum-mechanical calculations [6–8], the method used is the so-called PCILO procedure [9–12] recently developped in our laboratory. It is an all valence electrons procedure, rather refined, as it goes beyond the self-consistent molecular orbitals scheme by incorporating a part of the correlation energy.

Although our quantum-mechanical calculations have so far been carried out for a limited number of amino-acid residues (the glycyl, alanyl, phenylalanyl, tyrosyl, histidyl, tryptophanyl and prolyl residues), it appears already that the results obtained have a sufficiently general outlook and enough significance with respect both to the results of the earlier empirical computations and to the available experimental information in these fields, to justify and even urge a general critical confrontation of these different data. Such a confrontation is the subject of this paper.

2. The Case of the Glycyl Residue

The glycyl residue, the simplest one, in which C^{α} carries two hydrogens and which is thus the only residue devoid of a C^{β}, constitutes obviously a special case. Its examination is already significant as to some essential trends of our confrontation.

Fig. 2 presents a conformational map for the glycyl residue (as deduced from the study of the glycyl-L-glycine dipeptides) in which are indicated:

a) The limits of the "allowed" conformational space as obtained in the "hard sphere" approximation of the empirical methods [13]. The allowed space consists of four separated areas: A, B, C, and D. The results of more refined empirical calculations using potential energy functions [3, 4] are in general very similar to the preceeding ones. In some "hard sphere" computations regions A and B (or C and D) are joined together by a "corridor" around $\Psi = 180$, by a "relaxation" of the imposed contact conditions [13]. As, however, the contours indicated on Fig. 2 correspond already to the "outer limits" of the "hard sphere" calculations, the introduction of the supplementary "corridors" appears arbitrary and unjustified in this procedure. The regions A and B (or C and D) are also united by a "saddle" in some of the more refined empirical potential energy computations, but the "saddle" is there of relatively high energy: about 9 Kcal/mole above the deepest minimum [14].

b) The contours of the quantum-mechanical PCILO computations [6], limited at the reasonable value of 6 Kcal/mole *(vide infra)* above the deepest minimum. (The numbers 6 are placed on the figure on the side of the regions of higher energies).

c) The deepest (±) and local (+) minima obtained in the quantum mechanical computations.

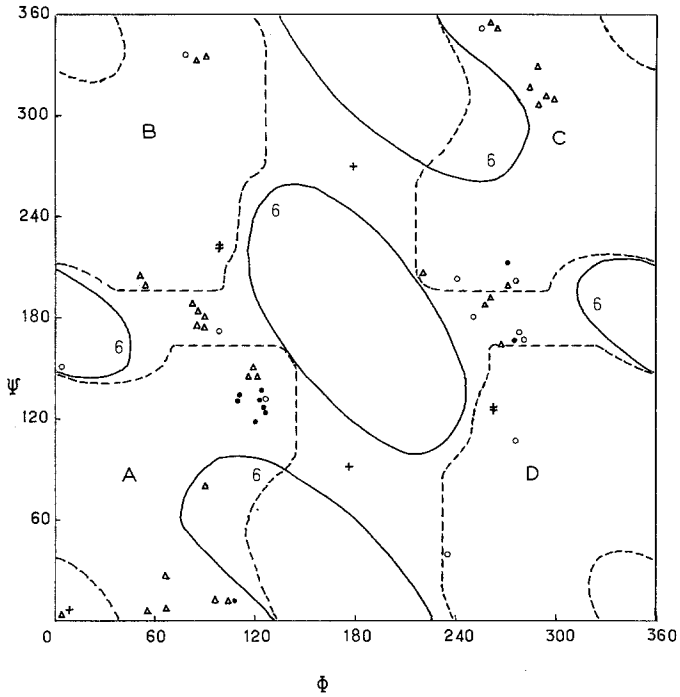


Fig. 2. Conformational maps for the glycyl residue. ---- Allowed limits of the "hard sphere" approximation. —— Limits of the quantum-mechanical computations within 6 Kcal/mole above the deepest minimum (∔). + Local minima in the quantum mechanical calculations. ○ Values found in lysozyme [16]. ● Values found in myoglobin [18]. △ Values found in small compounds [13]

d) The experimental conformations of the glycyl residues as found in a series of small compounds (following the complication of [15]) and in the two proteins, lysozyme [16, 17] and myoglobin [18].

For the two last cases we have plotted (in this figure and in the two following ones) the representative points of not only their random coil sections for which our calculations are directly appropriate but also those of their helical fragments. We did so because, although we do not posses yet quantum-mechanical results on the conformational maps of long enough helical polypeptides, we had the strong impression, based partially on the analysis of the available empirical computations on both dipeptides and the corresponding polypeptides, that our *contour* for the dipeptide embodies a large fraction of the possibilities available to the polypeptides. The positioning and the relative values of the different local minima will, with no doubt, vary, maybe even appreciably, on passing from the dipeptides to polypeptides, but we do not expect the general limits of the contour to undergo too drastic transformations. As will be seen later on this paper this point of view seems quite substantiated by the very evidence coming from the study of lysozyme and myoglobin.

Let us thus first compare the empirical and the quantum-mechanical results. It is immediately seen that although there is a general resemblance between the

two groups of results, the quantum-mechanical calculations impose less restrictions on the allowed (or preferred) conformational space than do the empirical ones. In particular in the quantum mechanical calculations the four regions A, B, C, and D communicate between themselves by large (relatively low energy) corridors. It is particularly important to stress for the further discussion that not only do these corridors unite A with B and C with D but that they unite also transversally B with D (and less directly A with C). These general results remain valid when the contours of the preferred conformations are reduced to 5 Kcal/mole above the deepest minimum (see the complete map in Ref. [6]). When they are further reduced to 4 and 3 Kcal/mole the corridors between A and B or between C and D tend to disappear but the two corridors between B and D, on both sides of the central plateau (which, in fact, raises rapidly to a very high mountain) persist.

As concerns the minima, the deepest and the local ones, some of the empirical calculations (e.g. [19]) place the deepest minimum in the same region than we do around $\Phi = 260$ $\Psi = 140$ and $\Phi = 100$ $\Psi = 220$ but others place them in quite different places (e.g. [20]) and, in fact their location depends in such calculations appreciably on the adopted potential functions and the selected parameters in these functions. We may already say that while the location of this minimum in glycyl-L-glycine dipeptides is not yet established with certainty, recent experimental evidence coming from NMR and IR spectroscopy is strongly in favor of the location of this deepest minimum, in some of them, at the coordinates which we have calculated *(vide infra* the discussion on the alanyl residue).

The comparison of the theoretically delimited "allowed" or "preferred" conformational zones with the experimentally observed conformation of the glycyl residue in a number of small compounds and in proteins is highly revealing with respect to the precision of the two modes of calculation. Thus, it may be observed that while a large number of representative points are located outside the limits of the "hard sphere" approximation, and are situated in particular in the disallowed or at least dubious regions between A and B and between C and D, all the experimental points with only two narrow exceptions fall between the limits of the quantum-mechanically preferred zones. It may be added that this situation holds to a large extent even when the limits of the quantum-mechanical preferred zones are reduced to 5 or 4 Kcal/mole, the experimental points situated between the "hard sphere" regions A and B or C and D remaining embodied in the transversal corridors uniting A and C.

3. The Alanyl Residue

This residue is of particular significance being the smallest residue with a C^{β} carbon.

Fig. 3 presents the empirical, quantum-mechanical and experimental results for that residue.

The examination of these data leads to the following principal remarks and conclusions:

1. As regards the conformational zones allowed by the "hard sphere" approximation [13, 21] they are greatly reduced with respect to those allowed for the

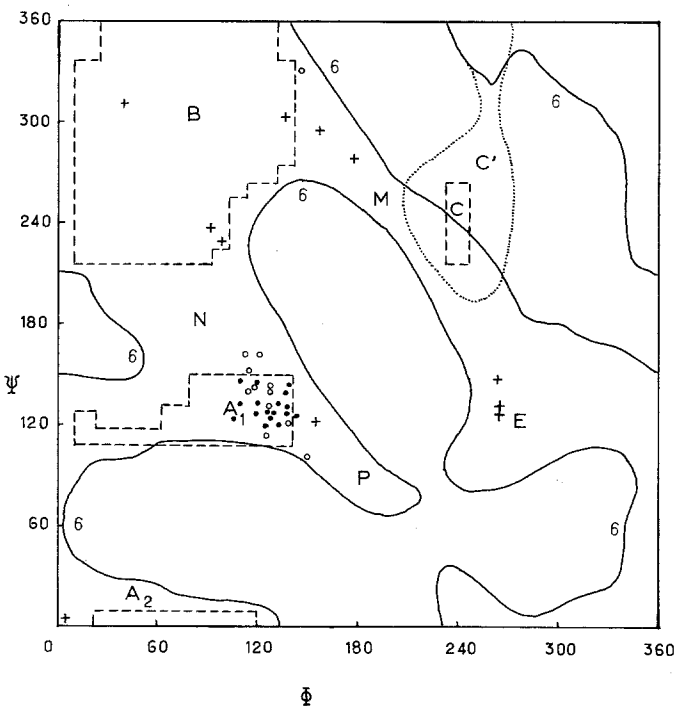


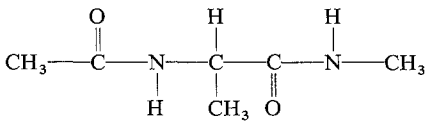
Fig. 3. Conformational maps for the alanyl residue. – – – – Allowed limits of the "hard sphere" approximation. ..... Enlarged limits of the C region of the "hard sphere" approximation in calculations with empirical potential functions. —— Limits of the quantum-mechanical computations within 6 Kcal/mole above the deepest minimum (∓). + Local minima in the quantum-mechanical calculations. ○ Values found in lysozyme [16]. ● Values found in myoglobin [18]

glycyl residue. The allowed zones comprise now: regions A_1 and A_2 (which constitute the upper and lower fragments of glycyl's region A), region B and the small region C, a remnant of the large C region of the glycyl residue. Glycyl's region D disappears completely. More refined empirical computations, using potential energy functions give practically the same results. with only the C region being generally enlarged into C′ [14, 19, 20]. In some of the empirical computations [14], but not others, regions A_1 and B are jointed together by a narrow high energy (8 Kcal/mole) corridor.

2. The quantum-mechanical calculations, truncated again at 6 Kcal/mole above the deepest minimum, agree with some aspects of this situation but impose much less restrictions than do the empirical ones, so that altogether they give a picture which is *substantially different*. It may be noted in the first place that the A_1 and B regions, separated in most of the empirical calculations are united by a corridor, N, in the quantum mechanical ones. But moreover *the quantum-mechanical calculations introduce three features absent in the empirical ones:* a) They indicate the existence of a new zone of conformational stability, E, in which they even place the deepest minimum for the alanyl residue; b) they maintain a corridor, M, between regions B and E and, finally, 3) they enlarge somewhat the region A_1 by a "peninsula" P, a remnant of the second corridor

which in the conformational map of the glycyl residue united (through N) its zones B and D. On the other hand, the region C of the empirical computations is absent as such in the molecular orbital calculations and is only present, in its lower part, as a portion of the bridge M, at about 4–5 Kcal/mole above the deepest minimum.

3. As concerns the comparison of the theoretical computations with the available experimental results, it may again be remarked that the agreement is somewhat better with the quantum-mechanical calculations than with the empirical ones. To this must be added the very recent finding by Bystrov *et al.* [22], who on the basis of NMR and IR studies on I, which is the very "glycyl-L-alanine dipeptide" used in the quantum-mechanical computations, proposed for



I

its most stable conformation the very one predicted by us and which corresponds to a seven-membered hydrogen bonded structure (see Refs. [6, 7]). This possibility, as already stated, was totally overlooked by the earlier empirical computations (which also differred greatly among themselves as to the nature of the most stable conformer (see [9])) with the exception of some very recent ones, carried out by Popov *et al.* [20] with the help of improved potential functions. It is these experimental studies that suggest also a similar stable conformation for the glycyl residue in the corresponding dipeptide.

Another particular result of the quantum-mechanical calculations, also overlooked by the empirical ones, is the prediction of the existence of a local minimum, about 2 Kcal/mole above the deepest one, at coordinates $\Psi = \Phi = 0$, which corresponds thus to the fully extended form of the dipeptide. Here again it is gratisfying to quote that recent IR evidence is in favor of the existence of such a conformer of I in dilute solutions in carbon tetrachloride [24].

4. Beyond the Alanyl Residue

The quantum-mechanical calculations have recently been extended to the four aromatic amino acid residues of proteins. A detailed account of this work is given in part II of this series [7]. The result essential for the considerations developped in this paper is that, as already considered by some of the authors engaged in empirical computations [2–4], *the general allowed conformational space, within a fixed limit above the individual deepest minima, is very similar in all these residues and very similar to the general contour obtained for the alanyl residue.* Naturally, there are differences among the individual residues but they all conform to the pattern obtained for alanyl. What essentially distinguishes these residues from alanyl (and among themselves) are variations in the rotational states (angles χ_1 and χ_2) of the side chains and the fact that they have many more local minima than alanyl, although for all of them the most stable conformation, or at least one of the most stable ones, is predicted to lie in the E region, at or

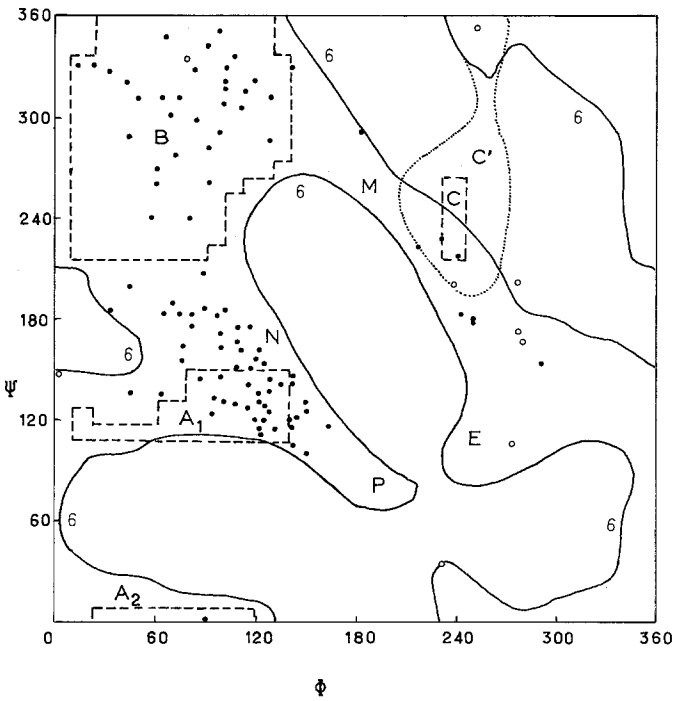


Fig. 4. The general significance of the conformational map for the alanyl residue. – – – – Allowed limits of the "hard sphere" approximation. ..... Enlarged limits of the C region of the "hard sphere" approximation in calculations with empirical potential functions. —— Limits of the quantum-mechanical computations within 6 Kcal/mole above the deepest minimum (+). ● Conformations of *all* the amino acid residues in lysozyme, with the exception of glycyls indicated by o [16]

near the coordinates $\Phi = 260°$ $\Psi = 140°$. The local minima are also more diversified and up till now have been found around the coordinates $(\Phi, \Psi) = (90°, 240)$, corresponding to a different seven-membered hydrogen bonded system, considered in particular by Mizushima *et al.* [25] for some simple dipeptides, at $(\Phi, \Psi) = (150°, 120°)$, around the well-known α-helix region, at $(\Phi, \Psi) = (40°, 320°)$, around the antiparallel pleated-sheat region, at $(\Phi, \Psi) = (140°, 300°)$ (significance not clear) and at $(\Phi, \Psi) = (0°, 0°)$ corresponding to the fully extended form.

Under these conditions and although the calculations for the remaining amino acids are under way it seems already highly reasonable to assume that *the conformational map of alanyl residue may be considered as representing to a large extent the conformational map of all* C^β *containing residues*, it means of all residues with the exception of glycine. In fact another exception is offered by proline, which because of the special features of the pyrrolidine ring represents a special case, which will be discussed in details in part IV of this series [8].

In order to check the validity of this proposition we have confronted the theoretical predictions based on this assumption with the available experimental data on *all* the amino-acid residues. This confrontation is presented in Figs. 4, 5 and 6, in which the experimental data refer again respectively to those of lysozyme [16, 17], myoglobin [18] and a few small molecules (from the compilation of Lakshminarayanan *et al.* [15]).

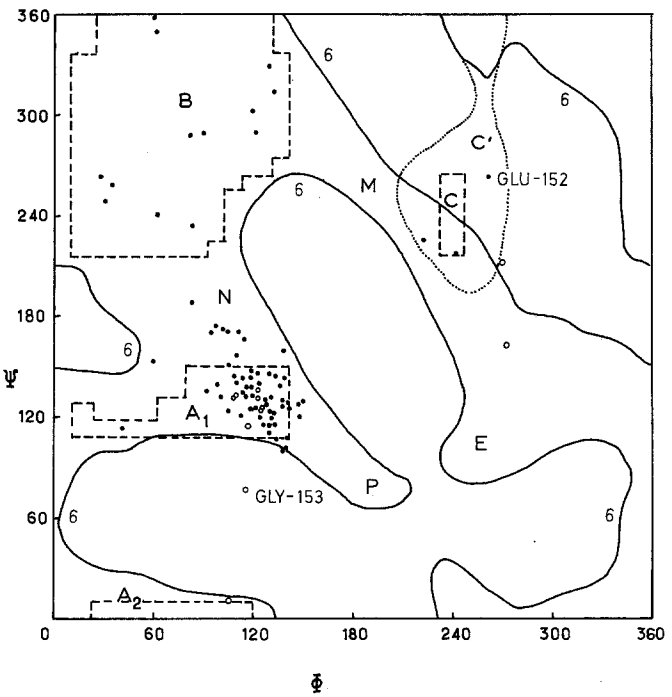


Fig. 5. The general significance of the conformational map for the alanyl residue. – – – – Allowed limits of the "hard sphere" approximation. ..... Enlarged limits of the C region of the "hard sphere" approximation in calculations with empirical potential functions. —— Limits of the quantum-mechanical computations within 6 Kcal/mole above the deepest minimum (+). ● Conformations of all the amino acid residues in myoglobin, with the exception of glycyls indicated by o [18]

The results of this confrontation are most striking:

1. The 6 Kcal/mole quantum-mechanical contour of the alanyl residue accounts excellently for the position of practically all the representative points in the three Figs. 4, 5, and 6. The only noticeable exceptions are the points representative of Gln 152 and Gly −153 of myoglobin, which are the two terminal residues of this protein, subject perhaps to some special conditions[1].

2. The agreement between theory and experiment is appreciably better with the results of the quantum-mechanical computations than with those of the empirical ones. In particular one may notice the obvious significance in this respect of the regions E, M, P and N of the quantum-mechanical computations. Although the density of the representative points certainly is smaller in these regions than in the A_1 and B regions, their total omission by the empirical computations (with the exception of those of Popov *et al.* [20]) represents a significant defect. It may be worthwile stressing e.g. that, in distinction to the empirical calculations which indicate the existence of the low energy region C and which introduce

[1] For the C-terminal groups in the small compounds of Ref. [15], there are two possible rotational angles Ψ_1 and Ψ_2 instead of Ψ. There are therefore two possible combinations Φ, Ψ_1 and Φ, Ψ_2. In each case at least one of these combinations falls inside the preferred contour and this is the one marked on Fig. 6. It may be supposed that if the group would become engaged in a growing chain, it would assume preferentially this conformation.

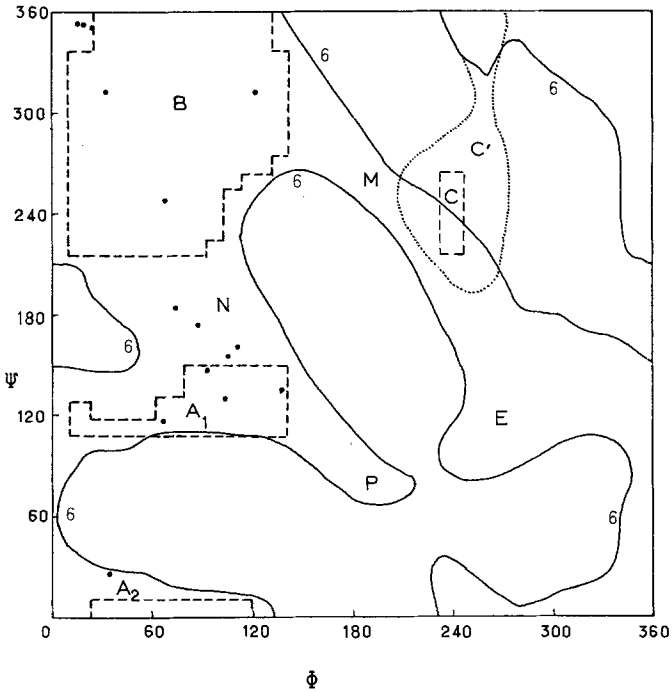


Fig. 6. The general significance of the conformational map for the alanyl residue. ---- Allowed limits of the "hard sphere" approximation. ..... Enlarged limits of the C region of the "hard sphere" approximation in calculations with empirical potential functions. —— Limits of the quantum-mechanical computations within 6 Kcal/mole above the deepest minimum (+). + local minima in the quantum-mechanical computations. ● Available conformations of different amino acid residues in small molecules (from the complication in [15])

at most a high energy "saddle" between regions A_1 and B, the quantum-mechanical calculations place the "corridor" between B and E (which embodies the lower part of C) and the region N at the same level of moderate (≈ 4 Kcal/mole above the minimum) energy, a situation in better agreement with the distribution of the experimental points. The quantum-mechanical calculations introduce also a more pronounced distinction between the stabilities of the conformations located around the coordinates of the right-handed and left-handed α-helices, (with the former appreciably more stable) than do the empirical ones, a situation also closer to the general experimental occurrence of α-helical polypeptides in the right-handed form.

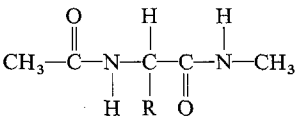
3. It may be noticed that the quantum-mechanical conformational maps of Figs. 4 and 5 even englobe the glycyl residues of these proteins, in spite of the fact that the individual conformational map for this residue is substantially wider than that for the alanyl residue (74% of the available space as against 50%, respectively, in the quantum-mechanical calculations, with the 6 Kcal/mole contour. The corresponding numbers are 55% and 17% in the "hard sphere" approximation, a situation which illustrates both the greater flexibility of the quantum-mechanical scheme and the less drastic restrictions in this scheme than in the empirical one,

upon passing from the glycyl to the alanyl residue). Curiously the glycyl residues of lysozyme show a tendency to cluster in the E region.

The quantum-mechanical contour for the alanyl residue appears thus as representing quite generally, as far as may be affirmed today, the preferred conformational arrangements for all the amino-acids in proteins.

The same conclusion would remain basically valid if the contour was limited to 5 Kcal/mole above the deepest minimum (see Ref. [6]). The preferred conformational space would have the same general shape but would, of course, be a little more restricted and a few marginal points would fall outside it. This evolution would continue, naturally, if the contour was still more restricted.

4. The particular importance of the region E as representing possibly one of the most stable conformers for a number of dipeptides of the type II, beyond



II

those with $R = H$ or $R = CH_3$, advocated by the theory, remains problematic although it may be interesting to quote in this respect some still more recent results of Bystrov *et al.* [26], who on the basis of NMR and IR studies on N-acetyl-alanyl-phenylalanine and N-acetyl-phenylalanine-alanyl propose again the seven membered hydrogen-bonded conformation at $\Phi = 240°$, $\Psi = 120°$ as the preferred one for the phenylalanyl residue.

5. Conclusions

The conclusions which may be drawn from this study appear particularly straightforward.

In the first place, it is obvious that the quantum-mechanical calculations are greatly succesful in designing the preferred conformational space of the amino-acid residues and that their success in this field is significantly superior to the achievements of the majority of the empirical procedures. This stems in large part from *the appearance in the quantum-mechanical calculations of new zones of conformational stability* such as the regions E, P, M and N, overlooked or even explicitly dismissed (as it was the case of the E region for C^β containing residues [13] in the empirical computations). It is not our intention to introduce here any *fundamental* opposition between the two types of computations: empirical and quantum-mechanical, although it is evident that the last ones are of more basic a nature. Both represent legitimate although different approximation approaches towards the same goal. As indicated by the already quoted work of Popov *et al.* [23] it is possible to parametrize the empirical procedures in such a way that they may yield results quite similar to those of the quantum-mechanical methods. On the other hand, too simple quantum-mechanical methods may frequently lead to as unsufficient (or partially sufficient) results as do the empirical ones. In fact, calculations carried out for the very glycyl-L-alanine dipeptide I by a much simpler quantum-mechanical method than PCILO, namely by the

Extended Hückel Theory, lead to results practically identical to those of the earlier empirical calculations [27] and are therefore only partially satisfactory.

It may be reasonably proposed that, in the present circumstances the superiority of the PCILO results could be utilized for the improvement of the empirical formulas and their parametrization, and that such formulas could thus be used with more confidence for computations on large polypeptide systems for which the empirical calculations will remain for a long time more rapid than the quantum mechanical ones. We shall present such an attempt in a future paper of this series.

Finally, the present status of our confrontation clearly indicates the limits of the success and suggest some of the most urgent refinements. Thus, while the present results apparently provide a satisfactory picture of the general contours of the preferred regions of the conformational map, they are probably more open to discussion as concerns the positions of the deepest and local minima. Taking into account the fact that the maps have been obtained with pre-selected values of the rotational angles for the side-chains, χ_1 and χ_2 [6, 7], this is not an astonishing situation. A more precise picture needs a minimization of these first results with respect to all the parameters involved and an appropriate complementary statistical treatment about the importance of the essential zones of conformational stability. While it is doubtful that these refinements would change in any appreciable degree the overall contours of the conformational map they will certainly improve the information about the position and the importance of the local minima. Our work is presently being developped in this direction.

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Professor Dr. B. Pullman
Institut de Biologie Physico-Chimique
13, rue P. et M. Curie
F-75 Paris 5è, France