Theoret. chim. Acta (Berl.) 19, 121—134 (1970)
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Molecular Orbital Calculations on the Conformation of Polypeptides and Proteins

VI. The Conformational Energy Maps and Stereochemical Rotational States of the Seryl and Threonyl Residues*

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Received April 30, 1970

Quantum-mechanical calculations, by the PCILO method, on the conformations of the amino-acid residues of proteins have been extended to the seryl and threonyl residues. The conformationally stable regions, within 5 Kcal/mole above the global minima, represent 57% of the total available space for the seryl residue and 27% for the threonyl one. They are appreciably wider than those permitted by the "empirical"studies. The quantum-mechanical calculations account much more satisfactorily for the limiting contour of the distribution of the experimental conformations, as observed in lysozyme, myoglobin and α-lactalbumin, than do the "empirical" computations. The situation is less satisfactory as concerns the position of the global minima which imply two intramolecular hydrogen bonds. This may be attributed to the fact that this position is more sensitive to the model employed in the calculations than the general contours. Experiments made on a seryl-containing dipeptide agree completely with our prediction on the two most stable conformations of that residue. The calculations indicate also that the seryl and threonyl residues should have a reduced tendency to assume the R_α conformation, which, however, is not forbidden to any of them.

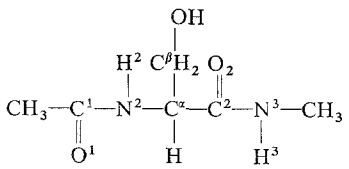
Les calculs quantiques par la méthode PCILO sur les conformations des résidus amino-acides des protéines ont été étendus au cas des résidus séryle et thréonyle. Les zones conformationnelles stables, dans la limite de 5 Kcal/mole au dessus du plus bas minimum, représentent 57%, de l'espace disponible pour le résidue séryle et 27% de cet espace pour le résidu thréonyle. Elles sont nettement plus larges que celles permises par les calculs «empiriques». Les calculs quantiques rendent compte d'une façon beaucoup satisfaisante que les calculs «empiriques» des limites de la répartition sur la carte conformationnelle des points représentatifs des conformations des résidus séryle et thréonyle dans le lysozyme, la myoglobine et l'α-lactalbumine. La situation est plus délicate en ce qui concerne la position du plus bas minimum qui comporte deux liaisons hydrogène intramoléculaires. Ceci peut être attribué au fait que cette position parait être plus sensible au modèle utilisé dans les calculs que ne le sont les contours généraux. Les expériences effectuées sur un dipeptide à résidu séryle confirment complètement nos prédictions sur les conformations les plus stables de ce résidu. Les calculs indiquent aussi que les résidues séryle et thréonyle devraient avoir une tendance réduite pour assumer la conformation R_α sans que celle-ci leur soit toutefois interdite.

Die quantenmechanischen Berechnungen von Aminosäure-Anteilen in Proteinen mit Hilfe der PCILO-Methode wurden auf den Seryl- und Threonyl-Anteil ausgedehnt. Die Gebiete stabiler Konformation — innerhalb 5 Kcal/mol über dem absoluten Minimum — stellen 57% des insgesamt möglichen Bereichs für den Seryl-Anteil und 27% für den Threonyl-Anteil dar. Diese Gebiete sind beträchtlich größer als diejenigen, die auf Grund „empirischer" Verfahren möglich sind. Die quantenmechanischen Rechnungen genügen dem Bereich der experimentellen Verteilung der Konformationen besser als die „empirischen" Rechnungen. Im Hinblick auf die Lage der absoluten Minima, die zu innermolekularen Wasserstoffbindungen gehören, ist die Beschreibung weniger

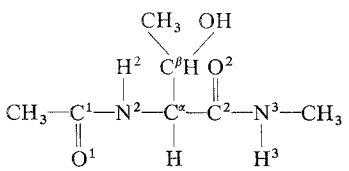
* This work was supported by grant n° 67-00-532 of the Délégation Générale à la Recherche Scientifique et Technique (Comité de Biologie Moléculaire).

befriedigend. Dies kann der Tatsache zugeschrieben werden, daß diese Werte empfindlicher bezüglich der verwendeten Modellverbindung sind als dies bei der allgemeinen Stabilitätskarte der Fall ist. Die Experimente mit einem Dipeptid mit Seryl-Anteil stimmen völlig mit unseren Voraussagen der stabilsten Konformation dieses Anteils überein. Die Berechnungen zeigen weiterhin, daß sowohl der Seryl- als auch der Threonyl-Anteil eine verhältnismäßig geringe Tendenz zur Aufnahme der R_α-Konformation haben sollten; sie ist jedoch für beide Anteile nicht verboten.

Continuing our series of quantum-mechanical studies on the conformational energy maps and the stereochemical rotational states of the amino acid residues of proteins [1–6] we have now extended the computations to the two residues with an aliphatic OH terminal group: seryl and threonyl. Explicitly the calculations have been performed, as previously, on the two "dipeptides", N-acetyl-N′-methyl-serylamide I and N-acetyl-N′-methyl-threonylamide II:



(I)



(II)

The method utilized is, also as in the previous papers of this series, the PCILO method [7–10], which constitutes a rather refined molecular orbital all-valence-electrons procedure going beyond the self-consistent field approximation by incorporating an appreciable fraction of the correlation energy and which has been presented in this journal. The abbreviation PCILO stands for Perturbative Configuration Interaction using Localized Orbitals.

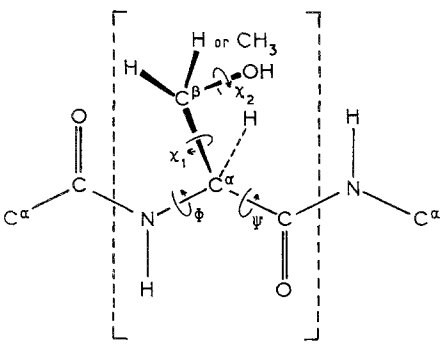


Fig. 1. Standard conventions [11] for the study of polypeptide conformations
[ ] limits of a residue

The general conventions for the description of the conformations [11] are illustrated in Fig. 1. The geometrical input data (bond length and bond angles) for the residues have been taken from the compilation of Gurskaya [12], the configuration adopted for the peptide group being planar-*trans*. Moreover, a number of simplyfying assumptions have been made as concerns the rotational states of the aliphatic groups. Thus, in agreement with the conclusions of part I of these series of papers [1], the angles of rotation of the two backbone terminal methyl groups are fixed in such a manner that the N – H and C = O terminal bonds are each eclipsed by one of the C – H bonds of these groups. Moreover, for the threonyl residue, the C^{β} methyl group was assumed to be staggered with respect the $C^{\alpha}H$ group. Because it seems established [13, 14] that in the case of aliphatic-type side chains, the staggered configurations characterized by $\chi = 60°$ (gauche), 180° (trans) and 300° (gauche) are preferred we have limited our calculations to the combinations of such values for the two rotational angles χ_1 and χ_2 under consideration (Figs. 2 and 3). The hydroxyl group was also assumed to be staggered with respect to the $C^{\beta}H$ group.

For each of the two residues, we have then constructed the conformational maps in increments of 30° for the rotational angles Φ and Ψ, the side-chain rotational angles being considered as selected parameters following the indications above. The resulting map is obtained for each residue from the superposition of the corresponding nine sub-maps by taking the lowest energy points from each map individually. As in the previous papers of this series, we have limited the presentation of the energy contours on the final conformational maps to 5 Kcal/mole above the deepest minimum for each residue.

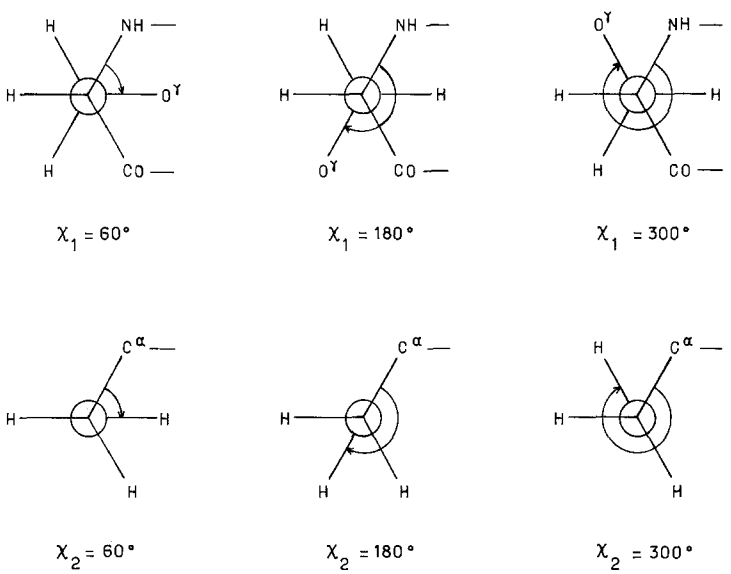


Fig. 2. Newman projections of the most stable rotamers about the $C^{\alpha} - C^{\beta}$ bond (rotational angle χ_1) and the C^{β}–OH bond (rotational angle χ_2) for serine

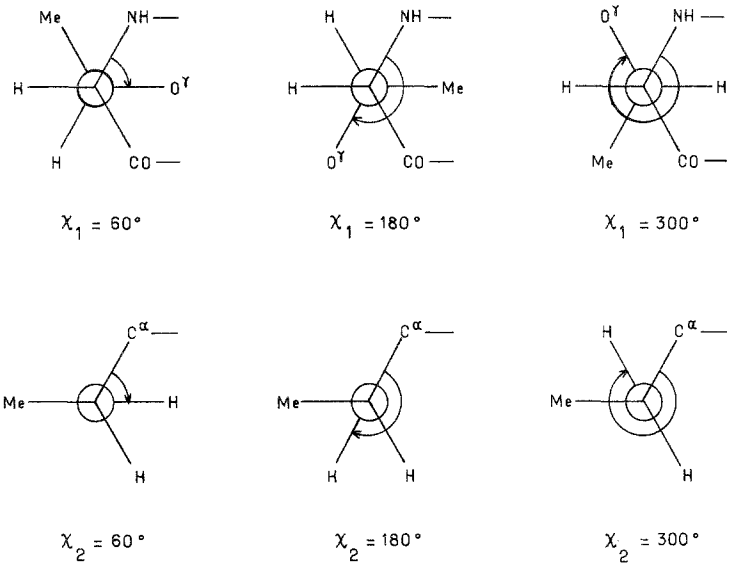


Fig. 3. Newman projections of the most stable rotamers about the $C^{\alpha} - C^{\beta}$ bond (rotational angle χ_1) and the C^{β}–OH bond (rotational angle χ_2) for threonine

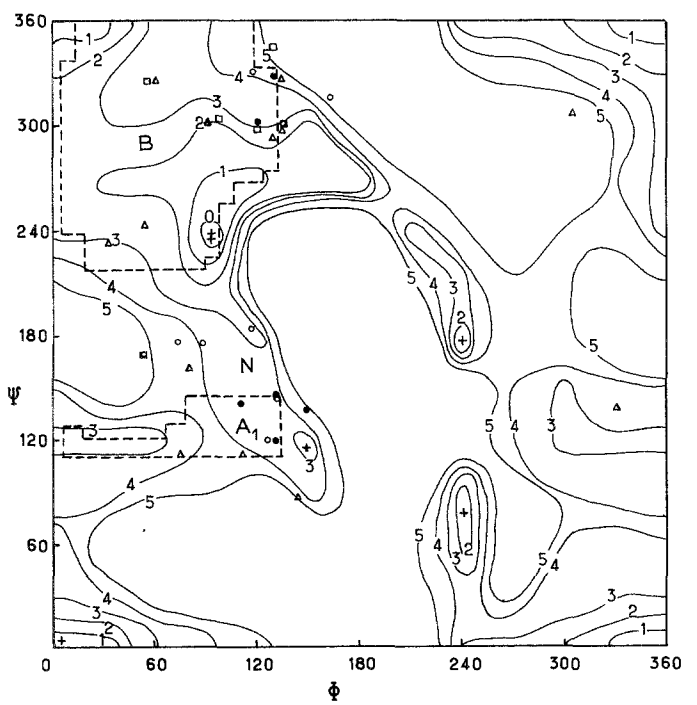


Fig. 4. Calculated energy curves for the ground state of N-acetyl-N′-methyl-serylamide. The contours are in kilocalories per mole relative to a zero at the absolute minimum of the calculation (∓). + local minima, ○ values found in crystalline lysozyme, ● values found in myoglobin, □ values found in α-lactalbumin. △ values found in ribonuclease S (see Appendix)

Results

A) N-acetyl-N'-methyl-serylamide I

The conformational energy map of this compound is presented in Fig. 4 and the map of its side chain rotational states in Fig. 5. The most stable conformation (global minimum) occurs at $\Phi = 90°$, $\Psi = 240°$ (with $\chi_1 = \chi_2 = 60°$) and corresponds closely to Mizushima's seven-membered hydrogen-bonded conformation called H'-7 in the notation of paper II of this series [2]. In this particular case this conformation contains also a *second* hydrogen bond formed between the hydroxyl group of the side chain and the carbonyl group $C^2 = O^2$ (Fig. 6) and it is to this situation that this conformation owes to be the global minimum. A number of local minima are found: 1) at $\Phi = \Psi = 0$ (and for $\chi_1 = \chi_2 = 180$) corresponding to the fully extended form (FE) at about 1 Kcal/mole above the global minimum; 2) at $\Phi = 150°, \Psi = 120°$ (and $\chi_1 = 60°$, $\chi_2 = 180°$) corresponding to the right handed α helix region (R_α), at about 3 Kcal/mole above the global minimum; 3) at $\Phi = 240°$, $\Psi = 180°$ (and $\chi_1 = 60°$, $\chi_2 = 300°$), in a region which may be considered as intermediate between a left-handed α-helix (L_α) and the E region of paper III, stabilized by a possible formation of a second hydrogen-bond between the side-chain hydroxyl group and the carbonyl

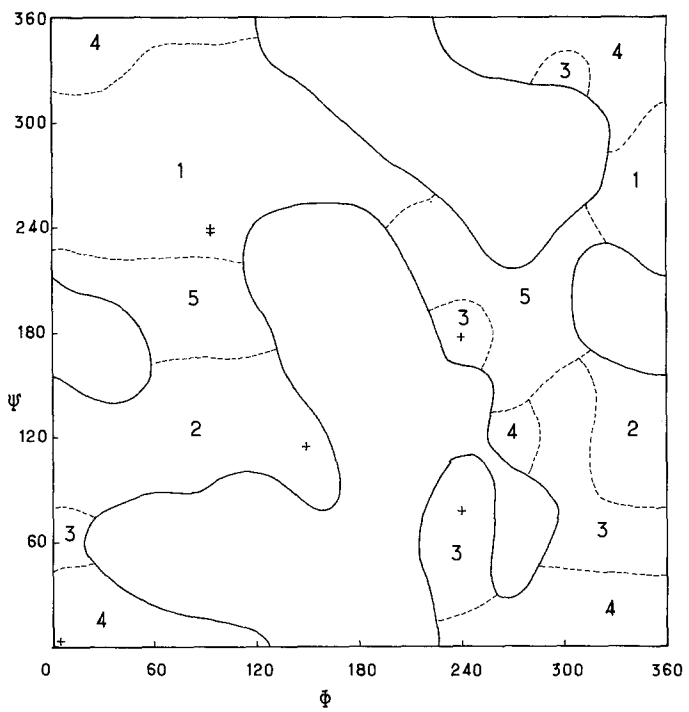


Fig. 5. Map of the preferred conformations for the rotational angles χ_1 and χ_2 for the ground state of N-acetyl-N'-methyl-serylamide. The outside contour is that of 5 Kcal/mole above the absolute minimum in accordance with the energy map of Fig. 4. ∓ global minimum, + local minima. Zone 1: $\chi_1 = 60$, $\chi_2 = 60$, Zone 2: $\chi_1 = 60$, $\chi_2 = 180$, Zone 3: $\chi_1 = 60$, $\chi_2 = 300$, Zone 4: $\chi_1 = 180$, $\chi_2 = 180$, Zone 5: $\chi_1 = 180$, $\chi_2 = 300$

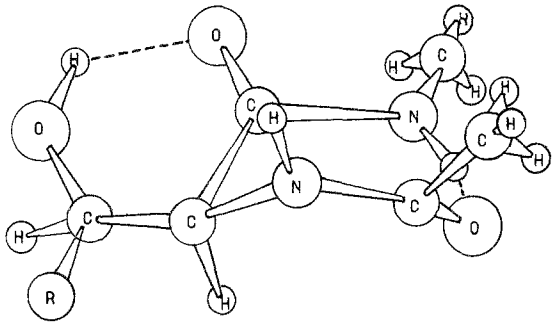


Fig. 6. The most stable conformation predicted for N-acetyl-N′-methyl-serylamide (R = H) and N-acetyl-N′-methyl-threonylamide ($R = CH_3$) ($\Phi = 90°$, $\Psi = 240°$)

group $C^1 = O^1$; this local minimum is nevertheless about 2 Kcal/mole above the global one; 4) at $\Phi = 240°$, $\Psi = 80°$ (and $\chi_1 = 60°$, $\chi_2 = 300°$), in a region in which no local minimum has so far been observed in the previously studied amino-acid residues and which we shall call region M'. It shows again the possibility of an intramolecular hydrogen bond between the side chain hydroxyl group and the $C^1 = O^1$ group and is also about 2 Kcal/mole above the global minimum.

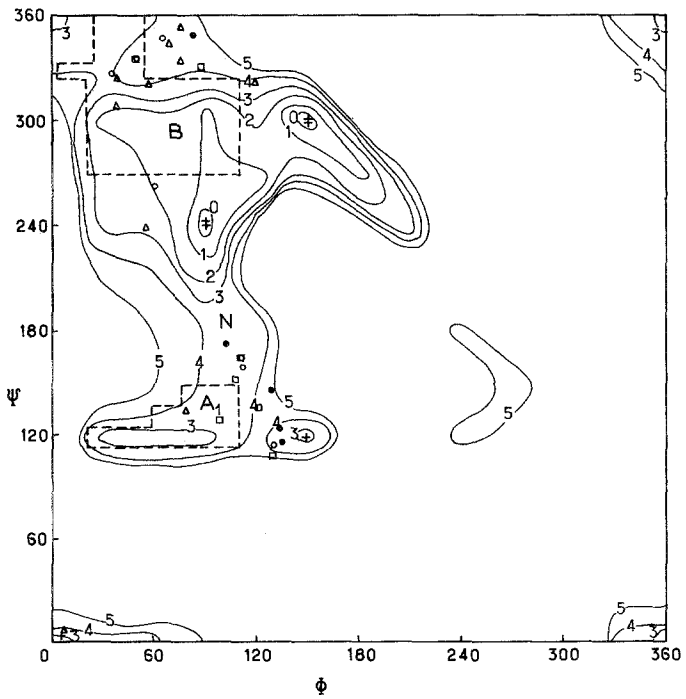


Fig. 7. Calculated energy curves for the ground state of the N-acetyl-N′-methyl-threonylamide. The contours are in kilocalories per mole relative to a zero at the absolute minimum of the calculation (∔). + local minima, ○ values found in cristalline lysozyme, ■ values found in myoglobin, □ values found in α-lactalbumin. △ values found in ribonuclease S (see Appendix).

As concerns the rotational angles of the side chain it is thus observed that the value $\chi_1 = 60°$ is associated with all the minima, except with that of the FE region for which its value is 180°. More generally speaking these two values of χ_1 divide among themselves the allowed rotational areas in the proportion of 36% for $\chi_1 = 60°$ and 21% for $\chi_1 = 180°$. In connection with this result we may recall the previous contradictory theoretical claims of Sarathy and Ramachandran [15] on the one hand and of Birshtein and Ptitsyn [16] on the other as to the preeminence of one of these values of χ_1 (60° or 180°, respectively) for the seryl residue.

B) N'acetyl-N'-methyl-threonylamide II

The conformational energy map for this compound is shown in Fig. 7 and the map of its side chain rotational states in Fig. 8. The first thing to be observed is the strong decrease of the energetically allowed area (within the fixed limit of 5 Kcal/mole above the global minimum) when passing from the seryl residue to the threonyl residue. The drop is from 57% to 27%, more pronounced thus than when passing from the alanyl (56%) to the valyl (40%) residue. Practically all the area between $\Phi = 220° - 360°$ appears as an energetically unfavorable one for the threonyl residue.

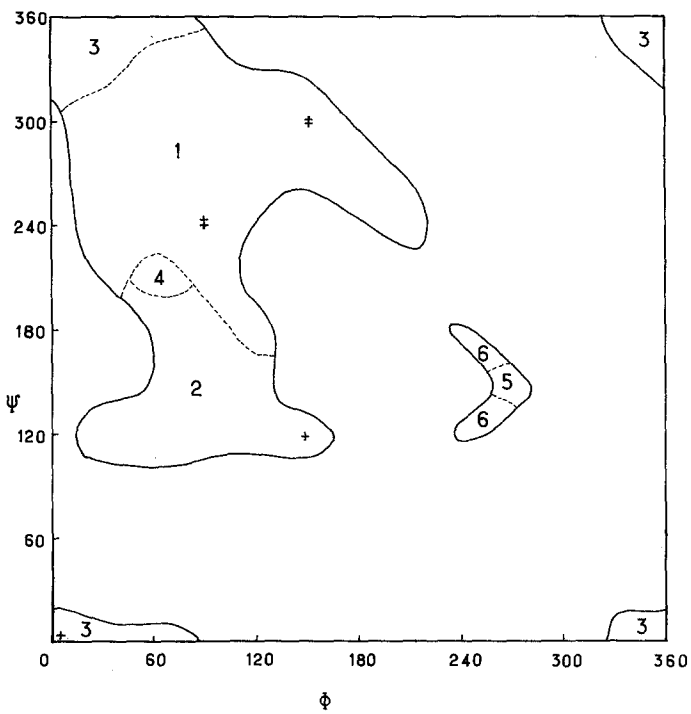


Fig. 8. Map of the preferred conformations for the rotational angles χ_1 and χ_2 for the ground state of N-acetyl-N'-methyl-threonylamide. The outside contour is that of 5 Kcal/mole above the absolute minimum in accordance with the energy map of Fig. 7. ‡ global minimum, + local minima, Zone 1: $\chi_1 = 60$, $\chi_2 = 60$, Zone 2: $\chi_1 = 60$, $\chi_2 = 180$, Zone 3: $\chi_1 = 180$, $\chi_2 = 180$, Zone 4: $\chi_1 = 180$, $\chi_2 = 300$, Zone 5: $\chi_1 = 300$, $\chi_2 = 60$, Zone 6: $\chi_1 = 300$, $\chi_2 = 180$

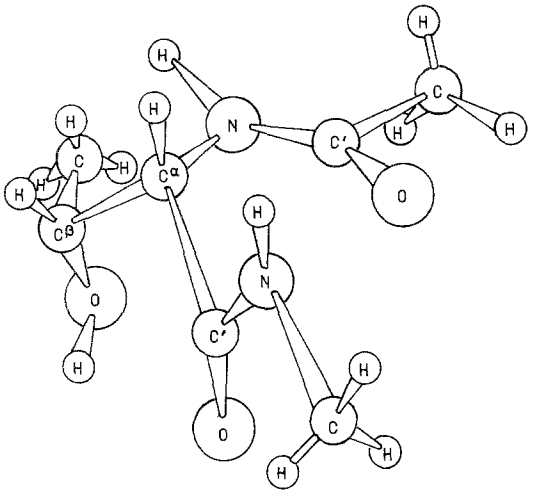


Fig. 9. Conformation of N-acetyl-N'-methyl-threonylamide at one of its global minimum: the M region ($\Phi = 150°$, $\Psi = 300°$)

Two equivalent global minima are observed in this case. The first one located at $\Phi = 90°, \Psi = 240°$ (and for $\chi_1 = \chi_2 = 60°$) is analogous to the corresponding minimum for the seryl residue (H′ – 7). The second one, at $\Phi = 150°$, $\Psi = 300°$ (and for $\chi_1 = \chi_2 = 60°$) is located in the M region and corresponds to the conformation of Fig. 9. Two local minima, both at about 3 Kcal/mole above the global one, are found, one at $\Phi = 150°, \Psi = 120°$ (R_α region) and the other at $\Phi = \Psi = 0°$ (the FE region).

As in the case of the seryl residue one observes for the threonyl one a predominance of the rotational zone of $\chi_1 = 60°$ (21%). The proportion of the zone with $\chi_1 = 180°$ drops to 4,5% and $\chi_1 = 300°$ appears in the proportion of 1%.

Discussion

The discussion of the results of the quantum-mechanical calculations is particularly instructive when considered for the double viewpoint of comparison with: 1. the results of the previous "empirical" computations on the same residues, 2. the available experimental information.

As concerns the "empirical" computations those available for the individual residues considered here have been carried out only in the "hard-sphere" approximation [17] and we have indicated in Fig. 4 and 7 by dashed lines the "allowed" conformational space for each residue following this approximation. (That for the threonyl residue corresponds directly to the one indicated in Ref. [17]. As concerns the seryl residue, this reference does not contain an explicit map for it but states that it is intermediate between those for the alanyl and leucyl residues. As the two are very close there is no difficulty in drawing, based upon this indication, an approximate contour-map for the

seryl residue). The hard sphere conformational maps consist in both cases of two regions A_1 and B, both regions being much more restricted for the threonyl residue as compared with the seryl one (6,5% and 14% respectively). A particular point worth stressing is the presence of the R_α region (centered around $\Phi, \Psi = 130°$, 120°) in the allowed zone for the seryl residue and its elimination from the allowed zone for the threonyl one. This result suggest that, following the "hard sphere" approximation, the two residues should have intrinsically different aptitudes with respect to the possibility of assuming the conformation appropriate for an α-helix.

The quantum-mechanical results are substantially different from the empirical ones in a number of respects. In particular, although they englobe the A_1 and B regions of the "hard sphere" in their zones of conformational stability they enlarge them substantially and consider the region placed between the two zones (region N) as one of comparable and appreciate stability, too. Similarly, although the quantum-mechanical calculations, just as the empirical ones, ascribe a much more restricted conformational space to threonine than to serine they do so essentially by eliminating in the case of the former the regions placed at $\Phi > 180°$. In particular the area of the right handed α-helix is an allowed one in the quantum-mechanical calculations for both residues and even constitutes, in both of them, a local minimum, which is, however, situated at about 3 Kcal/mole above the global minimum.

We may now consider the comparison between the theoretical results and the available experimental data. With the obvious restrictions which we have already underlined in the previous papers of this series (and to some aspects of which we shall come back later in this paper) about the generalization of the results obtained for the individual residues to the situation in polypeptides, we shall refer essentially in this respect to the data from the crystallographic studies on hen's egg white lysozyme [18, 19] and sperm whale myoglobin [20]. As concerns the first of these molecules we shall utilize recently refined data on the conformational angles kindy communicated to us by Dr. Blake. Moreover, we shall also use the data proposed recently by Browne *et al.* [21] for the three-dimensional structure of bovine α-lactalbumin based upon that of the hen's white egg lysozyme. These last data are necessarily somewhat less reliable [22].

The Figs. 4 and 7 contain the indications about the experimentally found conformations of the corresponding residues in the three above-mentioned globular proteins. They are presented in more details in Table 1. The confrontation of these data with the theoretical predictions clearly indicates both an excellent agreement between the quantum-mechanically computed zones of conformational stability and the observed conformations of the residues and the manifest superiority of the quantum-mechanical results over the indications of the empirical treatments. Thus, for the seryl residues, 8 representative points (out of a total of 21, the coordinates of one serine residue in α-lactalbumin remaining undetermined) fall outside the zone permitted by the empirical computations while all of them, with the exception of three situated very close to the borderline, fall within the quantum-mechanical contour. The situation is still more striking for the threonyl residues, for which 13 out of the total of

Table 1. *Theoretical and experimental results on preferred conformations of the seryl and threonyl residues*

Residue	Region	Theory				Experiment				
		Φ	Ψ	χ_1	χ_2	Values found in	Residue n°	Φ	Ψ	χ_1
Ser	H′−7	90	240	60	60	Lysozyme	24	120.1	327.4	
							36	54.4	171.8	
	Extended H−7	240	180	60	180		50	162.4	318.0	
							60	87.1	177.3	
	R_α	150	120	60	180		72	135.0	301.9	
							81	131.5	145.5	
	M'	240	80	60	300		85	118.6	331.7	
							86	117.3	186.5	
	Fully extended	0	0	180	180		91	122.1	119.7	
							100	73.4	179.1	
						α-Lactalbumin	22	130.0	345.0	
							34	54.4	171.8	
							47	120.0	300.0	
							69	135.0	301.9	
							70	56.2	325.8	
							76	96.8	304.5	
						Myoglobin	3	130	329	82
							35	110	141	292
							58	120	303	198
							92	131	120	69
							108	131	146	298
							117	148	128	331
Thr	H′−7	90	240	60	60	Lysozyme	40	110.4	162.2	
							43	37.8	330.3	
	M	150	300	60	60		47	113.8	159.6	
							51	49.0	337.2	
	R_α	150	120	60	180		69	58.2	263.1	
							89	128.1	114.3	
	Fully extended	0	0	180	180		118	61.7	348.9	
						α-Lactalbumin	4	88.0	330.8	
							29	119.1	136.0	
							30	108.4	150.8	
							33	98.7	129.1	
							48	49.0	337.2	
							86	128.1	114.3	
						Myoglobin	39	128	146	82
							51	62	350	59
							67	134	117	279
							70	132	125	311
							95	101	173	77

16 representative points fall outside the limits of stability allowed by the empirical approximations, while all the 16 with no exception are included within the limits allowed by the quantum-mechanical calculations.

While it is thus obvious that, just as it was the case with all the previously studied residues [1-6], the general contours of conformational stability established

by the quantum-mechanical calculations reproduce very satisfactorily the large range of conformations observed for these residues in a variety of biomolecules, the situation is more delicate as concerns the precise location of the observed conformations with respect to the predicted global and local minima, which frequently involve one or even two hydrogen bonds. Thus, it may be observed from Figs. 4 and 7 that the experimental points are generally distant from the predicted global minima and largely scattered, sometimes quite far from local minima too. This situation must certainly be attributed to the fact that the calculations are performed for "dipeptides" in which no side chain-side chain interactions occur while the experimental points correspond to larger polypeptides. In the particular case of the seryl and threonyl residues the hydrogen-bonding capacity of the OH groups of the side chain leads, as we have seen, to specific intra-residue hydrogen-bondings which are characteristic of the stable forms of the dipeptides and which need not be found in polypeptides, in which obviously different arrangements may be preferred. Very recently a striking confirmation to the correctness of this view-point and of the correctness of the calculations has been provided by the experimental investigation, using infra-red and NMR techniques, of the stable conformations of the very dipeptide I, for which we have carried out the calculations. Drs. Neel and Marraud (private communication) have informed us that their experimental studies lead to admit that the most stable conformation for the seryl residue in I is the H'-7 one predicted by our computations and that a secondary stable conformation corresponds to the fully extended one, in complete agreement thus with our predictions.

It appears therefore that while our quantum-mechanical calculations are, generally speaking, quite satisfactory already at the present stage of their elaboration as long as the general contours of the conformationally stable regions are concerned they need to be handled with more caution as concerns the positions of the minima, these depending more tightly upon the precise compound studied.

In connection with this general problem a few words may be said also about the question of the ability or inability of the seryl and threonyl residues to assume the α-helical conformation. As we have already indicated the empirical "hard sphere" calculations of Leach *et al.* [17] while allowing such a conformation for the seryl residue, preclude it for the threonyl one. Other authors adopt sometimes a different or even an opposite standpoint. Thus Davies [23], Guzzo [24], and Havsteen [25] consider both these residues as helix-breaking while Kotelchuck and Scheraga [26] consider the threonyl residue as helix making and the seryl one as helix breaking. All these classifications seem to be too brutal. The best founded conclusion is probably the one reached recently by Ptitsyn [27, 28] as a result of the analysis of the distribution of amino-acid residues between the helical and non-helical areas in a group of seven globular proteins (including lysozyme and myoglobin) and bearing thus altogether upon over 1000 amino-acid residues. The conclusion reached by this author is that the seryl and threonyl residues have a somewhat reduced tendancy to be incorporated in inner helices and an increased tendancy to occur in non-helical areas, with these tendancies being somewhat more pronounced in the

former than in the latter of these residues. This moderate conclusion agrees very satisfactorily with our own results which indicate that both residues may assume the R_α conformation (as justified by the existence of a local minimum near Φ, $\Psi = 130°$, 120°) but that they cannot do it too easily, this local minimum being at about 3 Kcal/mole above the global one (while this same R_α region occurs, as a mean, only 1 Kcal/mole above the global minimum in the aliphatic amino-acid residues [6] and 2 Kcal/mole above the global minimum in the aromatic amino-acid residues [2]). The reality of such a situation is substantiated by the occurence of a few experimental points on Figs. 4 and 7 in the vicinity of the R_α local minimum, the population of this region being perhaps slightly greater for the threonyl residue than for the seryl one. The existence of poly-L-serine in the α-helical forms [29] and its preferential existence in solution and in the solid state in the β-structure [30] must therefore be looked for, at least to a large extent, rather in the particular factors stabilizing this last structure than in those basically destabilizing the former, although of course, a definite conclusion about the inherent aptitude of poly-L-serine to form an α-helix (whether right- or left-handed, the empirical calculations [15, 31] and to some extent also our own favoring somewhat a left-handed one) will only be ascertained after the extension of the theoretical calculations to at least a helical oligomer.

Acknowledgement. The authors wish to thank Dr. Blake for the communication of the refined conformational angles in lysozyme and Drs Neel and Marraud for the communication, prior to publication, of their results on the infra-red investigation of the conformations of N-acetyl-N′-methyl-serylamide.

Table 2. *Experimental results on the conformation of the seryl and threonyl residues in ribonuclease-S*

Residue	Residue N°	Φ	Ψ	χ_1
Ser	15	305	307	290
	16	36	233	300
	18	78	109	84
	22	135	298	162
	23	55	242	320
	32	111	110	60
	50	135	327	112
	59	81	162	110
	75	144	86	247
	77	62	327	164
	80	90	302	149
	89	332	138	169
	90	130	295	171
Thr	17	79	134	18
	36	5	8	345
	45	69	345	110
	70	55	241	181
	78	119	321	48
	82	58	321	275
	87	76	355	70
	99	36	310	10
	100	37	325	142

Appendix

This paper was terminated when an article appeared by Wyckoff *et al.* [32] presenting the results of a three-dimensional structure of ribonuclease-S at a nominal resolution of 2 Å. We have transformed the crystallographic coordinate data reproduced in this article into the dihedral angles Φ and Ψ.

Although these coordinates must be considered for the time being as preliminary and are subject to refinement we thought it useful to include in our paper the data corresponding to the seryl and threonyl residues. These data are summed up in Table 2 and the corresponding representative points have been added to Figs. 4 and 7.

It can be seen that the information from ribonuclease-S substantiates our previous conclusions based upon the study of lysozyme, myoglobin and α-lactalbumin and confirms the superiority of the quantum-mechanical energy contours over the "empirical" ones.

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