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Influence of the solvent on the conformational-dependent properties of random-coil polypeptides

I. The mean-square of the end-to-end distance and of the dipole moment

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Conformational energies for the *N*-acetyl-*N'*-methylamides of the 20 natural amino acids were calculated, including the solvent effects, as functions of the angles ϕ and ψ for rotation of the main chain and for six positions χ^1 of the C^α–C^β bond in the side chain (fixed values for χ^2, χ^3,...). The computed energies were used to evaluate the mean-square end-to-end distance and mean-square dipole moment of homopolypeptides of the 20 natural amino acids. Ten proteins and three enzymes of current interest were also studied. Slight differences in both properties are found on taking the effects of solvent into consideration. Comparison with other computational and experimental results is made.

1. Introduction

Polypeptides and proteins are biological macromolecules currently attracting an enormous amount of interest, and therefore research that can provide information on the structure and function of these biomolecules is of justifiable importance.

Several techniques have been applied with varying degrees of success to the conformational study of polypeptides [1–5]. The present work consists of a theoretical conformational analysis, using a simplified semi-empirical potential function for the energy which, at the same time as providing an adequate description of the interactions that arise in these substances, can be rapidly evaluated.

To date, most studies have not taken into account interactions between these polymers and the solvent because of their complex nature. Calculations generally refer to the unperturbed state of the molecule [6–8]. Nevertheless, these forces evidently play a fundamental role in determining the conformations adopted, as demonstrated in recent investigations [9–13].

Our approach to the study of the different interactions is based on the construction of a potential function which takes into account not only the intramolecular contributions to the energy (electrostatic, from non-bonded atoms, hydrogen bonds, and torsion, corresponding to interactions that depend on the dihedral angles for rotation of the chain) but also certain polymer-solvent interactions of the type described by Scheraga and co-workers [14–16] that have been tested in molecules similar to ours with satisfactory results.

This study concludes with the calculation of diverse conformational properties that have been considered previously only in the absence of

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solvent [17–20] among which are the dimensions and dipole moments of the hydrated polypeptides in the random-coil state. As well as the necessity of knowing the geometry (distances and bond angles) and conformational energy of each given polymer, the calculation requires knowledge of the contribution from each repeat unit to the magnitude of the whole chain.

We have used the Rotational Isomeric State model [21] (RIS) to study these properties: this is a relatively simple model that replaces integrals over the entire conformational space available to the molecule by summations over discrete sets of rotational states. To evaluate the summations of distinct contributions from bonds or groups of bonds to the average magnitude of the complete chain, we employed the matrix calculus technique developed by Flory [22,23]; this is an exact mathematical procedure and has been applied successfully by different groups in recent years [24–26].

2. Calculation

2.1. Conformational energies

Despite the complexity of these substances, it is well known that their structures have in common certain characteristic features allowing the structures to be appreciably simplified. Fig. 1 shows schematically the structure of an α-L-polypeptide in its planar *all-trans* conformation [27,28]. The subscripts i, $i+1$,... represent the position of each repeat unit in the whole chain.

As well as the directional nature of the amino acid residue and the presence of an asymmetric centre (-CHR-), with the exception of glycine, there exists experimental evidence that the peptide linkage is planar and in a *trans* conformation. As a result, the distance between consecutive α-carbon atoms is constant and can be represented by a hypothetical virtual bond (dashed line in fig. 1). Another important consequence is that the separation between two consecutive side chain groups R_i and R_{i+1} is large for any given conformation of the molecule, such that one can take the conformational energy of peptide unit i to be independent of neighbouring units, to a satisfactory degree of approximation. Therefore, one can consider carrying out the determination of a polypeptide's conformational energy from results obtained for independent residues.

In calculating the energy, we took into account the intramolecular interactions that arise on the backbone and side chain, and also the effect of the solvent medium. In the present work, we have addressed the effect of hydration, since water is the solvent par excellence in which these substances are formed and exert their function. Nevertheless, with the aim of generalizing the model in the future to include other solvents, such as

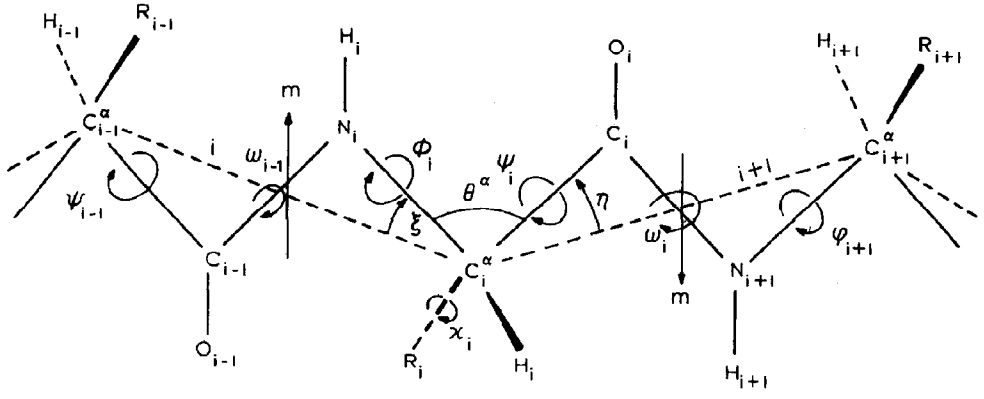

Fig. 1. Segment of an α-L-polypeptide shown in its planar *all-trans* conformation. Virtual bonds connecting consecutive α-carbons are shown as dashed lines.

methanol, ethanol and formic acid, we have introduced suitable parameters.

We used the geometry and charge distribution put forward by Scheraga and co-workers [29,30] as most suitable for these kinds of compounds.

The expression of conformational energy as a function of the angles for rotation of the main chain (ϕ,ψ) and side chain (χ^1) has the form:

$$E_{\text{total}}(\phi,\psi,\chi^1) = \sum_{i,j}\left[\frac{q_i q_j}{\epsilon' r_{ij}}\right] + \sum_{i,j}\left[e\left(\frac{r_0}{r_{ij}}\right)^{12} - 2e\left(\frac{r_0}{r_{ij}}\right)^{6}\right] + \sum_{\text{H,X}}\left[e'\left(\frac{r_0'}{r_{\text{HX}}}\right)^{12} - 2e'\left(\frac{r_0'}{r_{\text{HX}}}\right)^{10}\right] + \sum_{\theta}\left[\left(\frac{E^0}{2}\right)(1 \pm \cos n\theta)\right] + \sum_{i}\left[E_{\text{hy},i}\right] + \sum_{i}\left[E_{\text{sp},i}\right] \quad (1)$$

The first term represents the electrostatic energy which is computed as a coulombic potential between atom-centred monopole partial charges q. The second is a Lennard-Jones-type potential which corresponds to the steric non-bonding interactions. The third represents the additional energy due to intramolecular hydrogen bond formation. The fourth represents a torsional contribution to reproduce experimental rotational barriers. The last two terms correspond respectively to non-specific hydration of the uniform interaction produced by the water molecules of the hydration shell on each atom of the solute, and specific hydration, which is the additional energy caused by the formation of hydrogen bonds between polar solute atoms and water molecules of the hydration shell. These terms that correspond to the interaction with the solvent have been adopted from the hydration shell models of Hopfinger [31] and from the hydrated peptides of Scheraga and co-workers [14], regarding the CH_3, CH_2 and CH groups as simple interaction centres (i.e., not considering the non-polar hydrogens explicitly).

Instead of using energy-minimization procedures in the calculations, we scanned the whole conformational space available to the molecule systematically, since average conformations are employed in the calculations.

We calculated the conformational energies for the *N*-acetyl-*N'*-methylamides of the 20 hydrated natural amino acids, in which there are two rotational degrees of freedom on the backbone (ϕ, ψ) and rotation over the angle (χ^1) of the side chain when the radical R is not a hydrogen atom. We varied χ^1 from 0 to 360° in steps of 60°, and for each value of χ^1 we varied ϕ and ψ from 0 to 360° in steps of 18°. We thus obtained the energies of 2400 conformations for each amino acid with the exception of glycine and proline due to their special structural characteristics.

The program ECEPP/2 [32] was modified to carry out the sweep of the angles ϕ and ψ producing maps of the energy. Suitable corrections were introduced with regard to the solvent energy terms.

The resulting energy values were used to calculate the partition function of the molecules being studied [22]:

$$Z = \sum_{\chi^1}\sum_{\phi}\sum_{\psi} \exp\left[-E(\chi^1,\phi,\psi)/RT\right] \quad (2)$$

and all the average magnitudes needed in carrying out Flory's matrix calculus techniques for evaluation of the properties under study, as described in the following section.

2.2. Dimensions

The dimensions of a polymer chain are usually expressed by means of the end-to-end distance, whose square can be obtained as [22,23]:

$$r^2 = \prod_{i=1}^{x} \boldsymbol{G}_i \quad (3)$$

where $\boldsymbol{G}_i$ is a 5×5 matrix defined in the form:

$$\boldsymbol{G}_i = \begin{vmatrix} 1 & 2\boldsymbol{l}_i^T T & l_i^2 \\ 0 & T & \boldsymbol{l}_i \\ 0 & 0 & 1 \end{vmatrix} \quad (4)$$

$\boldsymbol{l}_i$ being a column vector representing the length of virtual bond i in the coordinate system whose x-axis runs in the direction of the bond (see fig. 1). In the case of the substances under study here,

these vectors provide a complete description of the conformation of the chain. We have taken a value of 3.81 Å for the virtual bond [1]. The 3×3 matrix T_i transforms the coordinates defined on the virtual bond $i+1$ into those corresponding to bond i, and is given by [22,23]:

$$T_i = R(\xi,0) \cdot R(\theta, \Pi - \phi_i) \cdot R(-\eta, \psi_i) \qquad (5)$$

One can see that T_i depends on the geometry of the molecule through the angles ξ, θ, η and the rotational angles ϕ_i, ψ_i (see fig. 1).

The average of r^2 over all possible configurations of a polypeptide is calculated by averaging T_i over the rotational angles [22]:

$$\langle T \rangle = Z^{-1} \sum_{\phi} \sum_{\psi} T(\phi,\psi) \times \sum_{\chi^1} \exp[-E(\chi^1,\phi,\psi)/RT] \qquad (6)$$

the mean square end-to-end distance then being expressed as:

$$\langle r^2 \rangle = \prod_{i=1}^{x} \langle G_i \rangle \qquad (7)$$

2.3. Dipole moment

The application of the RIS model to the calculation of the average of the unperturbed polypeptide dipole moment has been explained in detail by López Piñeiro and Saiz [18]. One can use equations that are formally identical to those used for the dimensions (eqs. 3 and 4) replacing only l_i by μ_i, the repeat unit's dipole moment. However, in this case μ_i is not constant and must be averaged over all conformations of the unit.

The average for a given unit is calculated from the equation [18]:

$$\langle \mu_i \rangle = \mu_S + \langle \mu_R \rangle_i \qquad (8)$$

Where μ_S denotes the dipole moment of the skeleton, which we have supposed as being equal to that of *N*-methylacetamide and constant for all the amino acids. The term μ_R corresponds to the dipole moments of the side chain groups, calculated using the charge distribution yielded by the MINDO/3 [33] method, with the geometry proposed by Scheraga et al. [29,30] for these substances. One then performs the transformations needed to express μ_R in the same coordinate system as that for the dipole moment of the skeleton and, averaging over the different conformations as a function of the rotational angles, one obtains $\langle \mu_R \rangle$ which, when substituted into eq. 8, yields the value of $\langle \mu_i \rangle$. Table 1 summarizes our results for μ_i, in comparison with those obtained in the absence of hydration. In general, these vectors are roughly parallel to C = O bond. The most significant differences between non-hydrated and hydrated species occur in the cases of aspartic and glutamic acids, arginine, glutamine and histidine. Such results are due to stabilization of regions with greater values of the dipole moments.

Table 1

Averaged dipole moments (in units of C m, $\times 10^{-30}$) of the peptide units (H_3C-CO-NH-CH_2R) referred to the virtual bond coordinate system

Residue	Non-hydrated [a]			Hydrated [b]		
	μ_x	μ_y	μ_z	μ_x	μ_y	μ_z
Glycine	−0.03	13.84	0.00	−0.03	13.84	0.00
Alanine	−0.03	13.84	0.00	−0.03	13.84	0.00
Valine	0.00	13.84	0.00	0.00	13.84	0.00
Isoleucine	−0.22	13.64	0.07	−0.22	13.64	0.07
Leucine	−0.06	13.84	0.00	−0.06	13.84	0.00
Serine	0.10	14.84	−1.97	0.06	14.81	−1.63
Threonine	2.54	14.31	−3.94	2.30	13.17	−3.93
Aspartic acid	−3.27	10.81	4.34	−3.27	11.21	4.90
Glutamic acid	−1.74	13.64	4.00	−0.80	15.24	3.97
Lysine	−0.23	14.01	0.17	−0.13	14.08	0.17
Arginine	0.70	16.78	3.94	3.03	18.64	3.53
Cysteine	1.63	16.41	−2.07	1.60	15.84	−2.00
Methionine	−0.87	9.47	0.57	−0.77	9.57	1.03
Phenylalanine	−0.03	13.88	0.00	−0.03	13.91	−0.03
Asparagine	−6.60	7.24	5.94	−6.87	6.84	5.60
Glutamine	−3.63	14.48	5.74	−0.30	16.84	6.60
Tyrosine	−1.97	12.94	3.94	−1.93	13.14	4.14
Histidine	0.50	16.31	−2.54	−1.03	17.81	−3.27
Tryptophan	1.93	15.44	−3.47	2.00	15.71	−3.33
Proline	1.07	13.81	6.00	1.07	13.81	0.00

[a] From ref. 18.
[b] Present work.

3. Results and discussion

We analysed the conformational energy maps obtained for the *N*-acetyl-*N'*-methylamides of the

20 hydrated natural amino acids, locating the conformations with minimum energy and determining the degree of stabilization regions differing in energy. We found the locations of the energy minima generally to be close to those reported by others [34–39] in similar studies and to those we obtained in the absence of hydration [17]; however, the relative stability of the minima was significantly changed on hydration. In this investigation, we do not discuss the detailed treatment of the effects of the hydration term on the conformational energy in the non-hydrated species *. However, in all cases, we observed the appearance of new minimum energy regions and the predominance of extended conformations, such as α-helix and C_5, over non-hydrated compounds.

3.1. Homopolypeptides

On analysis of the variation in the dimensions, expressed by means of the characteristic relation $C_x = \langle r^2 \rangle / xl^2$, with changes in the degree of polymerization or molecular weight of the 20 homopolypeptides, we observed the same trend as that when they were studied in the absence of hydration [17].

As an example, fig. 2 shows the variations in C_x for the polymer of aspartic acid under both conditions, noting the same feature of behaviour: a rapid rise with x for low values of the degree of polymerization, reaching practically the asymptotic limit for values of $x \geq 150$. The polypeptide chains studied approach rigid or flexible behaviour according to the rigidity of each individual structure and the corresponding molecular weight, attaining different absolute values for the characteristic relation. The limiting values for both species are indicated by the arrows in fig. 2.

The values of C_∞ for the homopolypeptides of the 20 hydrated natural amino acids are listed in table 2. The data were obtained from calculations of C_x as a function of x (for $x \geq 300$) and extrapolated to $x \to \infty$ by plotting C_x vs. $1/x$ and extrapolation of the linear part. If one compares

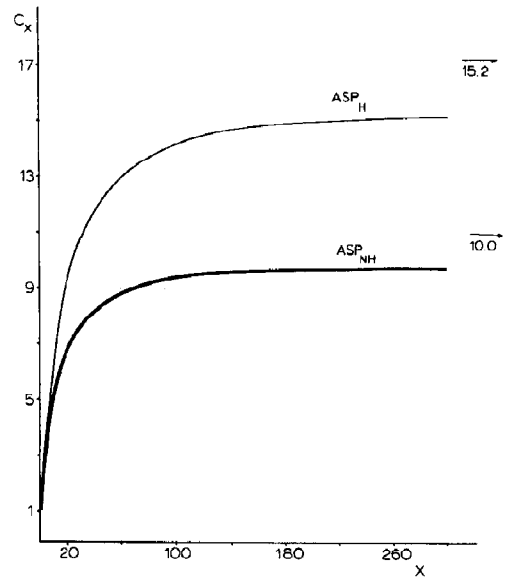

Fig. 2. Variation of C_x vs. x for the aspartic acid polypeptide: hydrated form $(ASP)_H$ and non-hydrated form $(ASP)_{NH}$.

these results with the dimensions obtained for these species without hydration [17], when 15 of the 20 substances had a characteristic relation within the interval $C_\infty = 8 \pm 3$, one observes that, although C_∞ for some particular systems decreases with hydration, generally there is a rise. This increase remains within the limits noted above and reproduces reasonably well the scarce available theoretical and experimental results [17,40–42].

We can summarize the above by stating that, in general, the behaviour observed in the absence of solvent is reproduced satisfactorily although in a few cases differences do occur as a result of a shift in the global energy minima and due to the greater statistical weight of some more or less extended structures (see footnote, below left).

The results on dipole moments are demonstrated in fig. 3 and table 2. Firstly, we examine the behaviour of methionine which represents the most general case. There is a sharp fall in $D_x = \langle \mu^2 \rangle / x\mu_i^2$ for low values of x and stabilization at intermediate degrees of polymerization. The explanation of this behaviour, following the work of Weiler-Feichenfeld [43], is that for small x there are more extended conformations that imply lower values of the dipole moment, stabilization being

* Energy maps (functions of ϕ and ψ) available from the authors on request (not reproduced herein for reasons of space).

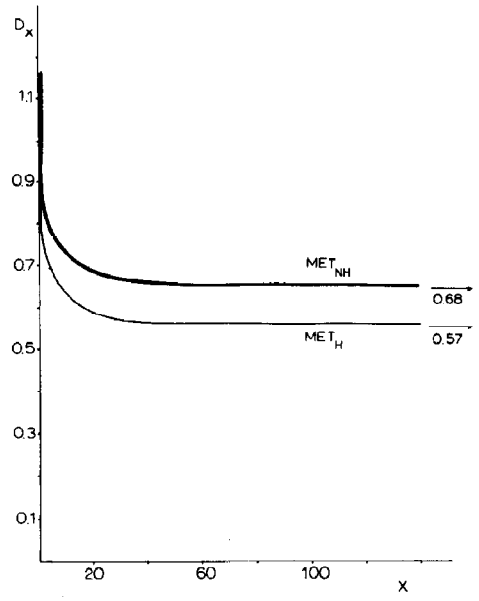

Fig. 3. Variation of D_x vs. x for the methionine polypeptide: hydrated form $(MET)_H$ and non-hydrated form $(MET)_{NH}$.

Table 2

Calculated values of C_∞ and D_∞ for homopolypeptides of the 20 natural α-amino acids

Residue	Non-hydrated [a]		Hydrated [b]	
	C_∞	D_∞	C_∞	D_∞
Glycine	2.17	0.36	2.65	0.65
Alanine	8.24	0.27	9.79	0.24
Valine	11.12	0.31	7.05	0.28
Isoleucine	7.21	0.61	4.10	0.54
Leucine	6.60	0.28	6.10	0.31
Serine	5.38	0.42	10.16	0.31
Threonine	6.02	0.47	5.81	0.43
Aspartic acid	10.03	0.24	15.21	0.19
Glutamic acid	6.83	0.34	6.53	0.32
Lysine	6.55	0.41	4.90	0.52
Arginine	8.10	0.37	8.77	0.79
Cysteine	10.41	0.45	11.72	0.35
Methionine	8.10	0.68	9.04	0.57
Phenylalanine	13.29	0.37	18.86	0.41
Asparagine	8.68	0.67	11.68	0.96
Glutamine	7.03	0.56	5.84	0.53
Tyrosine	13.28	0.27	16.08	0.33
Histidine	7.81	0.45	6.94	0.64
Tryptophan	13.33	0.17	12.84	0.16
Proline	18.62	0.15	18.62	0.15

[a] From refs. 17 and 18.
[b] Present work.

the result of folding in the chain for higher degrees of polymerization which causes the more extended conformations to lose their influence. The trend in behaviour is similar for hydrated and non-hydrated species, as can be seen in fig. 3.

Table 2 lists the values of D_∞ extrapolated in the same way as C_∞. The range of variation found in our calculations $0.15 < D_\infty < 0.96$ is in agreement with studies carried out in our laboratory in the absence of solvent [18] and with the range proposed by others for similar chains (0.58 and 0.35 for polyglycine and polyalanine [44] and 0.49 for polyphenylalanine [45]). On comparison with the values in the absence of hydration, one observes an appreciable degree of sensitivity of the magnitude to hydration. Regarding the possible relation between $\alpha_r 2$ $(\langle r^2\rangle_H/\langle r^2\rangle_{NH})$ and $\alpha_\mu 2$ $(\langle \mu^2\rangle_H/\langle \mu^2\rangle_{NH})$, our results confirm those of other authors [26,46–48] on synthetic polymers.

3.2. Heteropolypeptides

Eq. 3 and the analoguous expression for the case of dipole moments can also be used to calculate the magnitudes for heteropolypeptides provided their amino acid sequence is known, as the contribution of each residue is different in these cases. In our work we have calculated the dimensions and dipole moments of various enzymes and proteins with known sequences, and the end-to-end distances for some hexapeptides of alanine and glycine for which published data are available.

We present the values obtained for these oligopeptides in table 3, in comparison with those of Hagler et al. [49] calculated by Monte Carlo simulation of a great number of chains. We also

Table 3

End-to-end distances (in units of m, $\times 10^{-10}$) of several hexapeptides

Peptide	$\langle r\rangle$ [a]	Non-hydrated $\langle r^2\rangle 1/2$ [b]	Hydrated $\langle r^2\rangle 1/2$ [c]
-Ala_6-	20.84	18.96	19.77
-Gly-Ala_5-	19.15	18.06	18.94
-Ala_5-Gly-	19.12	18.03	18.93

[a] From ref. 49.
[b] From ref. 17.
[c] Present work.

provide a comparison with our results in the absence of hydration [17]. The values are seen to be very similar (in the last two substances the differences are of the order of 1%), and an appreciable improvement is obtained for those of hydration. This confirms the accuracy of our set of conformational energies.

Tables 4 and 5 summarize the results for C_x and D'_x of the enzymes and proteins considered. These tables also list the data in the case where solvent is not taken into account. One observes that the C_x values are greater for the hydrated species as compared to the non-hydrated as expected from the expansion of the macromolecule due to hydration. The fact that $\alpha^2 > 1$ in 12 out of the 13 biomolecules studied confirms this effect. The effect determined for dipole moments is practically the same as that found for the non-hydrated species [18]. The small differences between particular substances are indicated by the variation in dipole moments of individual residues or by their presence in greater or lesser amounts in the molecule.

In conclusion, we believe that the improvements introduced into the molecular potential by taking into account interactions with the solvent signify that the present results provide more realistic information about the conformational properties of polypeptides than other calculations performed previously. Unfortunately, the lack of experimental results for comparison means that it is difficult to estimate the accuracy of our calculations. Assuming, however, that the RIS model gives a good account of the conformational properties of polypeptides, these are two possible sources of inaccuracy in the calculations: the conformational energies and the contributions l_i and μ_i. The set of energies we used provides a good description of the end-to-end distances of these polymers, and we are therefore confident of their suitability. The method of calculation for μ_i yields satisfactory results [18], therefore, we expect our results to be reasonably accurate, at least with regard to the relative values for the different peptides.

Table 4

Characteristic relation C_x of several enzymes and proteins

Peptide	$C_x = \langle r^2 \rangle / x \cdot l^2$		$\alpha^2 = \langle r^2 \rangle_H / \langle r^2 \rangle_{NH}$
	Non-hydrated [a]	Hydrated [b]	
Myoglobin	5.89	5.84	0.992
Lysozyme	5.48	6.19	1.129
Chymotrypsinogen	5.54	6.00	1.083
Ribonuclease	6.48	7.26	1.120
Human hemoglobin α	6.44	6.91	1.073
Human hemoglobin β	5.59	5.98	1.070
Human hemoglobin γ	5.50	5.86	1.065
Human hemoglobin δ	5.58	6.02	1.079
Horse hemoglobin α	5.92	6.44	1.088
Horse hemoglobin β	5.53	5.85	1.058
Bradykinin	3.60	4.05	1.125
Bovine oxytocin	4.10	4.25	1.037
Bovine vasopressin	4.40	4.80	1.091

[a] From ref. 17.
[b] Present work.

Table 5

Dipole moment ratios, $D'_x = \langle \mu^2 \rangle / x$ (in units of C^2 m^2, $\times 10^{-59}$) of several enzymes and proteins

Peptide	D'_x		Repeat units (x)
	Non-hydrated [a]	Hydrated [b]	
Myoglobin	8.03	7.45	152
Lysozyme	8.94	9.11	130
Chymotrypsinogen	8.14	8.38	246
Ribonuclease	8.67	9.56	125
Human hemoglobin α	7.13	6.83	142
Human hemoglobin β	7.28	6.63	147
Human hemoglobin γ	7.89	7.32	147
Human hemoglobin δ	7.92	7.34	148
Horse hemoglobin α	7.10	6.75	142
Horse hemoglobin β	7.59	6.83	147
Bradykinin	7.64	7.30	9
Bovine oxytocin	12.75	13.00	9
Bovine vasopressin	12.08	11.20	9

[a] From ref. 18.
[b] Present work.

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