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Chemistry

Accessible surface areas as a measure of the thermodynamic parameters of hydration of peptides

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ABSTRACT **A method is described for the inclusion of the effects of hydration in empirical conformational energy computations on polypeptides. The free energy of hydration is composed of additive contributions of various functional groups. The hydration of each group is assumed to be proportional to the accessible surface area of the group. The constants of proportionality, representing the free energy of hydration per unit area of accessible surface, have been evaluated for seven classes of groups (occurring in peptides) by least-squares fitting to experimental free energies of solution of small monofunctional aliphatic and aromatic molecules. The same method has also been applied to the modeling of the enthalpy and heat capacity of hydration, each of which is computed from the accessible surface area.**

The free energy of folding of a protein consists of the sum of contributions from the energy of its intramolecular interactions (1, 2) and from the free energy of interaction of the molecule with the surrounding solvent water. Exact computation of the latter contribution still poses problems (3). As a practical approach, hydration-shell models have been used. In these models, the free energy of interaction of water molecules with the solute is expressed in the form of an averaged effective potential of interaction of atoms (and functional groups) of a solute molecule with a layer of solvent around each atom (4–10)—i.e., in terms of a potential of mean force (3). An empirical free energy of hydration is assigned to every atom and group. When the conformation of the protein changes, some water is eliminated from the hydration shell whenever groups on the protein approach each other. The free energy change accompanying this process depends on the total free energy of hydration of the groups and on the amount of water being eliminated from the hydration shells. This amount, in turn, depends on the size and distance of separation of the groups that approach each other, and it can be computed by geometrical methods from the volumes of overlapping spheres (4–6, 10, 11).

The hydration-shell model contains several approximations, which may be sources of error and also reduce the speed of computer-based numerical computations (8), such as the thickness of the shell, the apportioning of the free energy between overlapping hydration shells of covalently connected atoms, and the calculation of the volume of overlap of three or more hydration spheres that belong to nearby atoms. The latter problem can be overcome, however, by modifying the computing procedures (10, 11).

We have initiated an alternative approach, in order to avoid these problems. We assume that the extent of interaction of any functional group i of a solute with the solvent is proportional to the solvent-accessible surface area A_i of group i (12–14) because the group can interact directly only with the water molecules that are in contact with the group at this surface. Thus, the total free energy of hydration of a solute molecule is given by Eq. 1:

$$\Delta G_h^\circ = \sum_i g_i A_i, \qquad [1]$$

where the summation extends over all groups of the solute, and A_i is the conformation-dependent accessible surface area of group i. The constant of proportionality g_i represents the contribution to the free energy of hydration of group i per unit accessible area. It was obtained by applying Eq. 1 to a series of model compounds for which ΔG_h° can be obtained experimentally from the measured free energies of solution and for which A_i can be assumed to be constant because the model compound is sufficiently small so that it undergoes little conformational change in solution. In this case, A_i is set equal to A_i^{max}, the maximum accessible surface area of group i. If a peptide or protein molecule undergoes conformational changes, A_i for various groups will change as a result of the approach of other atoms in the molecule and, hence, ΔG_h° will be altered.

A similar approach to the evaluation of the solvation energy of proteins has been taken by Eisenberg and McLachlan (15). They used an expression of the form of Eq. 1 to compute the free energy of transfer of amino acid side chains from the interior of a protein to an aqueous environment. Their model and the one presented here refer to different physical processes; therefore, they are applicable in different contexts. The free energy parameters used by Eisenberg and McLachlan have been derived from distribution coefficients of amino acids between octanol (or ethanol) and water. Thus, they correspond to the total free energy of transfer of side chains from the interior of the protein to aqueous solution. On the other hand, the present model is designed to supplement the ECEPP (Empirical Conformational Energy Program for Peptides) algorithm (1, 2) that computes the intramolecular energy of the folded protein molecule. The free energy of hydration, to be added to the ECEPP energy, must correspond only to the additional interactions of the atoms of the solute with water. Consequently, it must be derived from observed free energies of transfer from gas to aqueous solution. Additional differences are (*i*) that a variety of simple molecules were used here to fit the g_i coefficients that were then applied to amino acids, whereas Eisenberg and McLachlan parameterized their coefficients on observed data for amino acids; (*ii*) that they assumed that there are no significant changes in the conformation of amino acids during the transfer process, whereas possible shifts of the distribution among various conformations were taken into account in the present work for amino acids (though not for the simple model compounds); and (*iii*) that enthalpies and heat capacities of hydration were also computed here.

A computation based on Eq. 1 is valid if the free energy of hydration is proportional to the accessible surface area. The validity of this assumption has been established for hydro-

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carbons (16–20) and for nonpolar amino acid side chains (13, 21). The linear correlation of the free energy of solvation with the accessible surface area has been used to estimate solubilities of hydrocarbons and monofunctional aliphatic compounds in water (16, 22). The additivity of group contributions has been tested on computations of the heat capacity of nonelectrolytes in aqueous solution (19, 22–24).

METHOD

Accessible surface areas were computed for seven classes of atoms or groups, listed in Table 1—namely, (*i*) aliphatic —CH_3, —CH_2—, and >CH— groups (considered as one class, in order to avoid an increase in the number of parameters), (*ii*) aromatic =CH— groups, (*iii*) hydroxyl —OH groups, (*iv*) amide and amine —NH— and —NH_2 groups, (*v*) carboxyl and carbonyl >C= carbons, (*vi*) carboxyl and carbonyl O= oxygens, and (*vii*) sulfur —S— atoms and thiol —SH groups. Hydrogen atoms cannot be treated as a separate class in the calculations of accessible surface areas because of their small size; hence, they were included with the corresponding groups—i.e., groups containing hydrogen atoms were treated as "united atoms" (4, 25). This assumption has been justified and used in numerous studies (4–6, 16–18, 21, 22, 25). Its application to "polar" hydrogens (attached to N and O atoms) introduced here is a first approximation. The van der Waals radii, R_i, used in the computation are listed in Table 1. The parameters for classes 4, 5, and 6 are used for the atoms of the peptide group (—CO—NH—).

The accessible surface area A_i was computed by the method of Shrake and Rupley (26). The spherical surface around each united atom was represented by 1888 test points distributed approximately regularly on a sphere with radius $R_i + R_w$, where R_w is the effective radius of the solvent molecule used in computing the accessible surface area (12, 26). The value of R_w was determined by initially considering it as an adjustable parameter, instead of equating it to the van der Waals radius of a water molecule. The purpose of this step was to assure that the total free energy of *each group*, ΔG_i°, is expressed as being proportional to A_i with no added constant term—i.e., that $B_i = 0$ for each group i in a linear equation for ΔG_i°:

$$\Delta G_i^\circ = B_i + g_i A_i. \quad [2]$$

If it is required that "buried" atoms should not contribute to the free energy of hydration, in agreement with the basic assumption of the model, it is necessary that $B_i = 0$. The radius R_w was varied between 1.0 and 1.8 Å, and the applicability of Eq. **2** was tested for all compounds used in the fitting (see below). The best least-squares fit of free energies, enthalpies, and heat capacities was obtained for $1.3 \leq R_w \leq 1.4$ Å by using Eq. **5** below. Therefore, R_w was set equal to 1.4 Å for all of the computations. Actually, this value agrees with the usual choice of the van der Waals radius for water in computations of the accessible surface area (12, 13).

It was assumed that not only the free energies of hydration but also the enthalpies and heat capacities of hydration can be expressed as group contributions for each molecule and that the group contributions are proportional to the accessible surface area—i.e., that it is possible to write analogs of Eq. **1** for the enthalpy and constant-pressure heat capacity:

$$\Delta H_h^\circ = \sum_i h_i A_i \quad [3]$$

$$\Delta C_{p,h}^\circ = \sum_i c_i A_i. \quad [4]$$

The coefficients g_i, h_i, and c_i at T = 298 K for classes 1–6 were determined by applying Eqs. **1**, **3**, and **4**, respectively, to each of the 22 small model compounds in Table 2 and adjusting the values of the coefficients by means of a least-squares procedure applied simultaneously to groups in all classes i = 1–6 (excluding class 7, as described below). The coefficients g_i, h_i, and c_i for any class are independent of each other. The optimized values of the coefficients are listed in Table 1.

The experimental data of Tables 2 and 3 were taken from the compilation of published thermodynamic data of solution for small solutes by Cabani *et al.* (24), supplemented by some data by Wolfenden *et al.* (27). All compounds listed in Table 2 were used in the fitting procedure with the exception of those marked by an asterisk. The latter compounds—namely, methane, methanol, and methylamine—are all small. They were not used in the fitting procedure because their observed thermodynamic parameters do not follow the linear trends established by the higher homologs. In particular, they cannot be fitted with $B_i = 0$ in Eq. **2**. Deviations from regular trends are seen in many physical properties of these first members of homologous series (16, 28). These deviations may be due to the breaking down of the assumptions of additivity of group contributions and of the proportionality of thermodynamic quantities to the accessible surface area with a fixed value of R_w for very small molecules (28).

Only free energies of hydration were available for the three thiols included in Table 1. Therefore, only g could be determined for —SH groups. The thiols were used only to determine g_i for class 7, as described in the second footnote to Table 2.

Table 1. van der Waals radii and the computed coefficients for the thermodynamic parameters*

i	Class of chemical group	van der Waals radius R_i,† Å	g kJ/mol·Å²	g kcal/mol·Å²	$-h$ kJ/mol·Å²	$-h$ kcal/mol·Å²	c J/mol·Å²·K	c cal/mol·Å²·K
1	Aliphatic —CH_3, —CH_2—, >CH—	2.00	0.035	0.008	0.107	0.026	1.547	0.370
2	Aromatic =CH—	1.75	−0.034	−0.008	0.157	0.038	1.240	0.296
3	Hydroxyl —OH	1.40	−0.719	−0.172	0.995	0.238	0.034	0.008
4	Amide and amine —NH_2, —NH—	1.55	−0.552	−0.132	0.805	0.192	−0.051	−0.012
5	Carboxyl and carbonyl >C=	1.55	1.785	0.427	−1.728	−0.413	2.563	0.613
6	Carboxyl and carbonyl O=	1.40	−0.160	−0.038	0.135	0.032	−0.954	−0.228
7	Sulfur —S— and thiol —SH	2.00	−0.086	−0.021				

*Evaluated at T = 298 K.

†Based on the interatomic contact distances used in the revised version of the ECEPP algorithm (1, 2) and, for united atoms, on its modification in the UNICEPP (25) algorithm. The radii used here correspond to the interatomic distance when the nonbonded energy is zero. Therefore, they are smaller by a factor of $2^{1/6}$ than the values in refs. 1 and 25. The radii are assumed to be temperature-independent (20).

Table 2. Comparison of computed thermodynamic parameters at 298 K with experimental values for compounds used in determining the coefficients

Compound	ΔG°_h, kJ/mol		$-\Delta H^\circ_h$, kJ/mol		$\Delta C^\circ_{p,h}$, J/mol·K	
	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.
Methane*	8.37	5.07	13.79	15.60	207.5	224.7
Ethane	7.66	6.21	19.76	19.12	250.9	275.4
Propane	8.18	7.25	22.50	22.32	294.8	321.5
Butane	8.70	8.29	25.97	25.52	373.0	367.6
Pentane	9.76	9.33	24.70	28.72	451.8	413.6
Hexane	10.40	10.37	31.60	31.91	491.9	459.7
Benzene	−3.62	−7.40	31.77	34.61	279.3	273.2
Methylbenzene	−3.77	−2.76	36.26	36.08	326.4	344.7
Ethylbenzene	−3.33	−1.24	40.24	38.30	375.6	386.3
n-Propylbenzene	−2.23	−0.21	43.90	41.46	453.7	431.9
Methanol*	−21.40	−24.04	44.52	51.24	114.3	179.9
Ethanol	−20.98	−21.09	52.40	52.62	194.9	234.1
l-Propanol	−20.19	−20.05	57.45	55.82	265.8	280.1
l-Butanol	−19.73	−19.01	61.58	59.02	327.0	326.2
l-Pentanol	−18.72	−17.97	64.75	62.22	390.9	372.3
l-Hexanol	−18.26	−16.96	66.20	65.32	448.2	417.0
Methylamine*	−19.09	−23.80		52.05	104.9	144.1
Ethylamine*	−18.84	−20.42	54.02	52.75		201.2
l-Propylamine	−18.37	−19.38	55.75	55.95	231.2	247.2
l-Butylamine	−17.97	−18.34	59.04	59.15	303.5	293.3
l-Pentylamine	−17.14	−17.30	62.12	62.35	374.2	339.3
l-Hexylamine	−16.87	−16.29	65.76	65.46	439.1	384.1
Acetic acid	−28.05	−29.15	52.80	54.59	98.5	119.6
Propanoic acid	−27.09	−28.81	56.50	58.57	160.2	171.2
Butanoic acid	−26.59	−27.79	59.50	61.72	221.2	216.5
Methanethiol†	−5.19	−4.72				
Ethanethiol†	−5.42	−2.81				
Benzenethiol†	−10.67	−13.58				

*Not used for determining the coefficients for reasons discussed in the text.

†These compounds were used only to determine *g* for class 7. They were not included in the determination of the coefficients for classes 1 and 2. The coefficients for classes 1 and 2 were obtained from the other compounds, but they were taken over as the values determined for the other compounds and used as constants when the data for the three thiols were fitted in order to determine the coefficient *g* for class 7 only.

RESULTS

The computed thermodynamic parameters of hydration for the compounds used in deriving the coefficients are listed in columns 3, 5, and 7 of Table 2 for comparison with the experimental parameters (columns 2, 4, and 6).

The root-mean-square deviation of the computed and observed thermodynamic parameters was calculated by means of Eq. **5**:

$$\langle \delta^2 \rangle^{1/2} = \left[\frac{1}{m} \sum_{k=1}^{m} (D_{obs} - D_{calc})^2 \right]^{1/2}, \quad [5]$$

where $D = \Delta G^\circ_h$, ΔH°_h, or $\Delta C^\circ_{p,h}$, and m is the number of compounds used in the testing. The data for compounds marked with an asterisk and dagger in Table 2 were not used in Eq. **5**; thus, $m = 22$. For the heat capacity, $m = 21$. The value of this deviation is 1.34 kJ/mol, 1.75 kJ/mol, and 24.1 J/mol·K for ΔG°_h, ΔH°_h, and $\Delta C^\circ_{p,h}$, respectively. These values are satisfactory, especially for the enthalpy and heat capacity, in view of the assumptions of simple proportionality to area and additivity of group contributions. Generally, the largest individual deviations occur for the aromatic compounds and for the lowest members of homologous series.

Table 3. Comparison of thermodynamic quantities computed by the accessible surface area method with experimental values at 298 K

Compound	ΔG°_h, kJ/mol		$-\Delta H^\circ_h$, kJ/mol		$\Delta C^\circ_{p,h}$, J/mol·K	
	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.
Heptane	10.96	11.24	33.79	34.58		498.1
Octane	12.10	12.25	39.75	37.72		543.4
2-Methylpropane	9.70	8.25	22.49	25.38	144.4	365.5
2,2-Dimethylpropane	10.46	8.71	27.84	26.81	514.6	386.1
Napththalene	−10.01	−9.55	46.86	44.64	343.4	352.4
Anthracene	−17.70	−11.69	58.58	54.68	200.7	431.6
1,3-Dimethylbenzene	−3.50	1.90	41.51	37.52	410.4	416.1
1,4-Dimethylbenzene	−3.37	1.89	40.96	37.52	335.1	416.0
2-Propanol	−19.90	−19.85	58.21	55.60	272.3	280.7
2-Butanol	−19.1	−16.38	62.72	55.73	335.8	329.6
Phenol	−27.68	−37.56	56.94	73.01	211.9	237.1
3-Methylphenol		−32.91	58.66	74.41		308.1
4-Methylphenol	−25.67	−32.91	61.63	74.46	259.5	308.5
Acetic acid methyl ester	−13.87	−7.40	42.50	35.92	205.1	241.8
Acetic acid ethyl ester	−12.95	−4.21	45.60	36.88	283.0	295.2
N,N'-Dimethylformamide		39.62	62.89	−16.04	136.2	270.4
Acetamide	−40.63	−28.04				
Propionamide	−39.41	−21.78				
4-Methylimidazole	−42.92	−25.64				
Propylguanidine	−45.73	−56.91				
3-Methylindole	−24.75	−17.10				

As a test, the thermodynamic parameters of hydration were computed for 21 compounds that had not been used in the determination of the coefficients of Table 1. The observed and computed parameters are listed in Table 3. The root-mean-square deviations of ΔG°_h, ΔH°_h, and $\Delta C^\circ_{p,h}$ are 8.35 kJ/mol (for $m = 19$), 7.78 kJ/mol (for $m = 16$), and 85.9 J/mol·K (for $m = 13$), respectively.

The free energy and enthalpy at $T = 298$ K have been computed for the *N*-acetyl-*N'*-methylamides of all 20 naturally occurring amino acids (Table 4). The energy of each compound in the absence of hydration is given by Eq. **6**

$$E_t = -RT \ln \left(\sum_j e^{-\Delta E_j / RT} \right), \quad [6]$$

where the summation is carried out over all j low-energy conformations of each amino acid derivative as computed by Vásquez *et al.* (29),§ and ΔE_j is the computed intramolecular conformational energy (29). In the presence of hydration,

$$G_t = -RT \ln \left(\sum_j e^{-\Delta G_j / RT} \right), \quad [7]$$

where

$$\Delta G_j = \Delta E_j + \Delta G_{h,j}. \quad [8]$$

In Eq. **7** the summation is carried out over the same set of conformations as in Eq. **6** (i.e., without minimizing the free energy of the hydrated conformations). Thus, ΔE_j is the same as that used in Eq. **6**, and $\Delta G_{h,j}$ is computed for each

§For serine, revised values were used (K. D. Gibson, S. Chin, G.N., E. Clementi, and H.A.S., unpublished data).

Table 4. Computed free energy (ΔG_h°) and enthalpy (ΔH_h°) of hydration at 298 K for the *N*-acetyl-*N'*-methylamides of the 20 naturally occurring amino acids

	Total*				Side-chain contribution†			
	ΔG_h°		ΔH_h°		ΔG_h^s		ΔH_h^s	
Residue	kJ/mol	kcal/mol‡	kJ/mol	kcal/mol	kJ/mol	kcal/mol	kJ/mol	kcal/mol
Ala	−2.61	−0.62	−42.16	−10.08	2.50	0.60	−1.56	−0.37
Asp	−33.38	−7.98	−78.41	−18.75	−28.28	−6.76	−37.81	−9.04
Cys	−10.23	−2.45	§		−5.12	−1.22	§	
Glu	−34.09	−8.15	−82.57	−19.74	−28.98	−6.93	−41.97	−10.03
Phe	−8.79	−2.10	−58.78	−14.05	−3.69	−0.88	−18.18	−4.35
Gly	−5.11	−1.22	−40.60	−9.71	0.00	0.00	0.00	0.00
His	−28.38	−6.78	−82.06	−19.62	−23.27	−5.56	−41.45	−9.91
Ile	1.25	0.30	−49.22	−11.77	6.36	1.52	−8.62	−2.06
Lys	−25.68	−6.14	−84.60	−20.23	−20.58	−4.92	−44.00	−10.52
Leu	0.80	0.19	−49.64	−11.87	5.91	1.41	−9.04	−2.16
Met	−4.70	−1.12	§		0.40	0.10	§	
Asn	−32.86	−7.86	−78.73	−18.82	−27.75	−6.63	−38.13	−9.12
Pro	−2.91	−0.70	−43.22	−10.33	2.19	0.52	−2.62	−0.63
Gln	−33.08	−7.91	−81.88	−19.57	−27.97	−6.69	−41.27	−9.87
Arg	−58.60	−14.01	−128.59	−30.74	−53.50	−12.79	−87.98	−21.03
Ser	−26.63	−6.37	−72.15	−17.25	−21.52	−5.15	−31.55	−7.54
Thr	−19.35	−4.63	−66.52	−15.90	−14.25	−3.41	−25.92	−6.20
Val	−0.25	−0.06	−47.50	−11.36	4.85	1.16	−6.90	−1.65
Trp	−22.66	−5.42	−80.23	−19.18	−17.55	−4.20	−39.63	−9.47
Tyr	−38.36	−9.17	−96.53	−23.08	−33.25	−7.95	−55.92	−13.37

*Computed from Eq. **9**.
†Computed from Eq. **10**.
‡1 kcal/mol = 4.1868 kJ/mol.
§Not computed because no value is available for the parameter *h* for sulfur atoms.

conformation *j* from Eq. **1**. The total free energy of hydration is

$$\Delta G_h^\circ = G_t - E_t. \quad [9]$$

The contributions of each side chain to the thermodynamic parameters of hydration (Table 4) are obtained by subtracting the value of glycine from that of the other residue Xaa (30):

$$\Delta G_h^s = \Delta G_h^\circ(\text{Xaa}) - \Delta G_h^\circ(\text{Gly}). \quad [10]$$

Corresponding expressions apply to the enthalpy. The values of ΔG_h^s give an indication of the hydrophobicity or hydrophilicity of each residue.

The computed (ϕ, ψ) maps for *N*-methyl-*N'*-methyl-L-alaninamide in the absence (29) and in the presence of water are compared in Fig. 1. The overall appearance of the maps is similar, as noted earlier (6). The largest difference between them appears in the region of the C_7^{eq} conformation, around (ϕ, ψ) ≈ (−80°, 80°). In the absence of water, this region has the lowest energy on the map, because of the presence of an intramolecular hydrogen bond in the C_7^{eq} conformation but not in the others. The interaction of water molecules with the —NH— and —CO— groups in the other conformations lowers the energy of these conformations relative to that of the C_7^{eq} conformation, so that the latter is no longer as strongly favored.

The contribution of hydration to the difference in free energy between the native and *one* extended conformation has been computed for three proteins of different sizes (Table 5). The intramolecular energy E_{in} has been obtained by using ECEPP (2), and the free energy of hydration, by the present method. The increase in intramolecular energy upon unfolding is partially compensated by the more favorable free energy of hydration in the extended conformation. Nevertheless, the total difference in free energy ΔG_{tot} is positive—

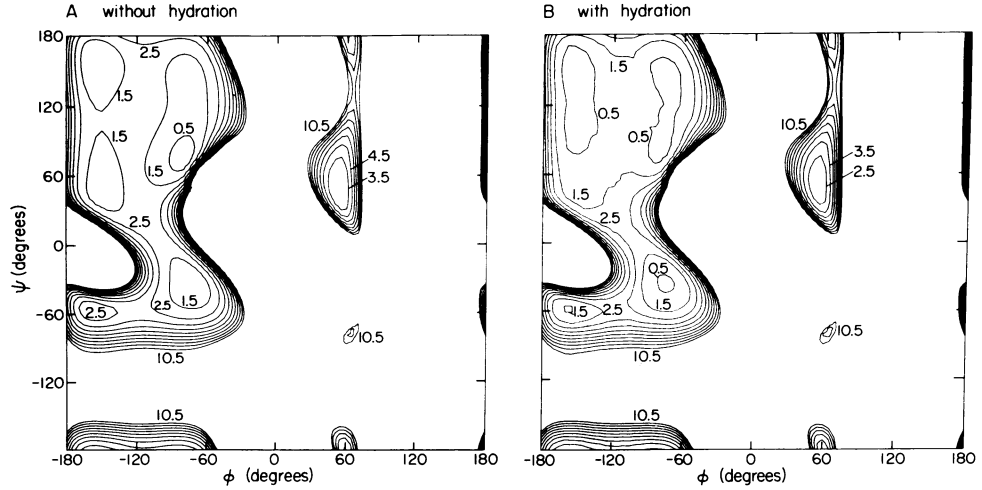

FIG. 1. Conformational energy (or free energy) contour maps of *N*-acetyl-*N'*-methylalaninamide as a function of ϕ and ψ in the absence (*A*) and presence (*B*) of hydration. Free energies were calculated at 5° intervals of ϕ and ψ, for fixed values of $\omega_0 = \omega_1 = 180°$ and $\chi^1 = 60°$. Contours are drawn at 1 kcal/mol intervals and are labeled in kcal/mol above the lowest computed point in each contour map.

Table 5. Comparison of the computed intramolecular energy (E_{in}), the free energy of hydration (ΔG_h), and the total free energy* (ΔG_{tot}) of the native conformation and *one* extended conformation† of three proteins at 298 K (kcal/mol)

	Bovine pancreatic trypsin inhibitor			Ribonuclease A			Elastase		
	E_{in}	ΔG_h	ΔG_{tot}	E_{in}	ΔG_h	ΔG_{tot}	E_{in}	ΔG_h	ΔG_{tot}
Native	−467	−149	−616	−954	−233	−1187	−1767	−428	−2195
Extended	−213	−242	−455	−303	−535	−838	−459	−869	−1328
Difference	254	−93	161	651	−302	349	1308	−441	867
No. of residues	58			124			240		

*$\Delta G_{tot} = E_{in} + \Delta G_h$.

†Computed for a conformation with (ϕ, ψ, ω) = (−155°, 160°, 180°) and the side chain fixed in its lowest energy conformation for the given backbone conformation in every residue (29), except that ϕ = 75° was used for all prolines. For Val-116 of ribonuclease A, (ϕ, ψ) = (−154°, 140°) was used.

i.e., the native conformation is more stable than a *single* extended conformation. The values of ΔG_{tot} are roughly proportional to the chain length, with a contribution of around 3 kcal/mol per residue. It must be emphasized that the ΔG_{tot} computed here describes the free energy change on going from the native to a single extended conformation. Therefore, it does not correspond to the overall free energy of unfolding of a protein. The latter contains large entropic contributions arising from the presence of an ensemble of conformations in the statistically coiled unfolded state and from the increased flexibility in each of these conformations. Therefore, the overall free energy of unfolding is considerably more favorable than the ΔG_{tot} listed in Table 5.

The coefficients in Table 1 have been computed for T_0 = 298 K. Utilizing them, it is possible to compute the thermodynamic parameters at any other temperature by using Eqs. **11–13**:

$$\Delta G_h^\circ(T) = (T/T_0)\,\Delta G_h^\circ(T_0) + \Delta H_h^\circ(T_0)\,(1 - T/T_0) - \Delta C_{p,h}^\circ[T\ln(T/T_0) + T_0 - T], \quad [11]$$

$$\Delta H_h^\circ(T) = \Delta H_h^\circ(T_0) + \Delta C_{p,h}^\circ(T - T_0), \quad [12]$$

$$\Delta S_h^\circ(T) = [\Delta H_h^\circ(T) - \Delta G_h^\circ(T)]/T. \quad [13]$$

CONCLUSIONS

The derivation of the coefficients of the thermodynamic functions from a variety of model compounds has shown that the use of accessible surface areas, together with the assumption of additivity of contributions from various functional groups, is a good approximation for the estimation of the free energy, enthalpy, and heat capacity of hydration. The parameters derived here will be useful in conformational energy studies of peptides.

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1. Momany, F. A., McGuire, R. F., Burgess, A. W. & Scheraga, H. A. (1975) *J. Phys. Chem.* **79,** 2361–2381.
2. Némethy, G., Pottle, M. S. & Scheraga, H. A. (1983) *J. Phys. Chem.* **87,** 1883–1887.
3. Némethy, G., Peer, W. J. & Scheraga, H. A. (1981) *Annu. Rev. Biophys. Bioeng.* **10,** 459–497.
4. Gibson, K. D. & Scheraga, H. A. (1967) *Proc. Natl. Acad. Sci. USA* **58,** 420–427.
5. Hopfinger, A. J. (1971) *Macromolecules* **4,** 731–737.
6. Hodes, Z. I., Némethy, G. & Scheraga, H. A. (1979) *Biopolymers* **18,** 1565–1610.
7. Scheraga, H. A. (1979) *Acc. Chem. Res.* **12,** 7–14.
8. Paterson, Y., Némethy, G. & Scheraga, H. A. (1981) *Ann. N.Y. Acad. Sci.* **367,** 132–149.
9. Paterson, Y., Némethy, G. & Scheraga, H. A. (1982) *J. Solution Chem.* **11,** 831–856.
10. Kang, Y. K., Némethy, G. & Scheraga, H. A. (1987) *J. Phys. Chem.*, in press.
11. Gibson, K. D. & Scheraga, H. A. (1987) *J. Phys. Chem.*, in press.
12. Lee, B. & Richards, F. M. (1971) *J. Mol. Biol.* **55,** 379–400.
13. Richards, F. M. (1977) *Annu. Rev. Biophys. Bioeng.* **6,** 151–176.
14. Rose, G. D., Geselowitz, A. R., Lesser, G. J., Lee, R. H. & Zehfus, M. H. (1985) *Science* **229,** 834–838.
15. Eisenberg, D. & McLachlan, A. D. (1986) *Nature (London)* **319,** 199–203.
16. Hermann, R. B. (1972) *J. Phys. Chem.* **76,** 2754–2759.
17. Harris, M. J., Higuchi, T. & Rytting, J. H. (1973) *J. Phys. Chem.* **77,** 2694–2703.
18. Reynolds, J. A., Gilbert, D. B. & Tanford, C. (1974) *Proc. Natl. Acad. Sci. USA* **71,** 2925–2927.
19. Gill, S. J., Dec, S. F., Olofsson, G. & Wadsö, I. (1985) *J. Phys. Chem.* **89,** 3758–3761.
20. Gill, S. J. & Wadsö, I. (1976) *Proc. Natl. Acad. Sci. USA* **73,** 2955–2958.
21. Chothia, C. (1974) *Nature (London)* **248,** 338–339.
22. Amidon, G. L., Yalkowsky, S. H., Anik, S. T. & Valvani, S. C. (1975) *J. Phys. Chem.* **79,** 2239–2246.
23. Nichols, N., Skold, R., Spink, C., Suurkuusk, J. & Wadsö, I. (1976) *J. Chem. Thermodyn.* **8,** 1081–1093.
24. Cabani, S., Gianni, P., Mollica, V. & Lepori, L. (1981) *J. Solution Chem.* **10,** 563–595.
25. Dunfield, L. G., Burgess, A. W. & Scheraga, H. A. (1978) *J. Phys. Chem.* **82,** 2609–2616.
26. Shrake, A. & Rupley, J. A. (1973) *J. Mol. Biol.* **79,** 351–371.
27. Wolfenden, R., Andersson, L., Cullis, P. M. & Southgate, C. C. B. (1981) *Biochemistry* **20,** 849–855.
28. Némethy, G. & Scheraga, H. A. (1962) *J. Chem. Phys.* **36,** 3401–3417.
29. Vásquez, M., Némethy, G. & Scheraga, H. A. (1983) *Macromolecules* **16,** 1043–1049.
30. Nozaki, Y. & Tanford, C. (1971) *J. Biol. Chem.* **246,** 2211–2217.