Hydrophobicity of Amino Acid Residues in Globular Proteins

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Abstract. *During biosynthesis, a globular protein folds into a tight particle with an interior core that is shielded from the surrounding solvent. The hydrophobic effect is thought to play a key role in mediating this process: nonpolar residues expelled from water engender a molecular interior where they can be buried. Paradoxically, results of earlier quantitative analyses have suggested that the tendency for nonpolar residues to be buried within proteins is weak. However, such analyses merely classify residues as either "exposed" or "buried." In the experiment reported in this article proteins of known structure were used to measure the average area that each residue buries upon folding. This characteristic quantity, the average area buried, is correlated with residue hydrophobicity.*

A hydrophobic substance is readily soluble in nonpolar solvents but only sparingly soluble in water (*1*). The hydrophobic effect is believed to play a major role in organizing the self-assembly of water-soluble, globular proteins (*1–4*). Upon folding, residues with nonpolar side chains that are driven from water will comprise a molecular interior where they can be shielded from solvent access. The effect is analogous to the segregation of oil in water, with the important distinction that residues in proteins are covalently bound to their chain neighbors and cannot partition independently.

To quantitate this effect, many scales of hydrophobicity for the amino acids, their residues, and their analogs have been proposed (*1–5*). Such scales can be classified as solution measurements, empirical calculations, or some combination of the two. Solution scales are based on distribution coefficients between an aqueous phase and a suitably chosen organic phase, while empirical scales are based on partitioning between the solvent accessible surface and the buried interior in proteins of known structure.

Significant differences exist among scales. Residues that are strongly hydrophobic on one scale may appear to be strongly hydrophilic on some other scale. For example, in solution measurements, Nozaki and Tanford (*1*) find tryptophan and tyrosine to be very hydrophobic, while Wolfenden and co-workers (*2*) find these residues to be very hydrophilic. Scales are compared and their differences have been discussed (*6*).

We now derive two new scales that are based on accessibility to solvent for residues within proteins of known structure. These scales measure two quantities that can be distinguished:

1) The area lost when a residue is transferred from a defined standard state to a folded protein. The area a residue buries upon folding is proportional to its hydrophobic contribution to the conformational free energy, ΔG_{conf} (*7*).

2) The fractional accessibility of a residue, defined as its mean accessible area in protein molecules divided by the standard state area. The fractional accessibility is an intrinsic measure of hydrophobicity.

Although related, these quantities are not equivalent. For example, a bulky arginine residue makes a large hydrophobic contribution to ΔG_{conf} because its area loss upon folding is large, approximating that of leucine. Yet, the fractional accessibility of an arginine is comparatively high because the remaining unburied area is also large.

In his influential review (*8*), Kauzmann used model compounds to show that burial of hydrophobic groups is a significant source of stabilization energy in proteins. More than a decade later, analysis of x-ray elucidated proteins disclosed that many hydrophobic groups remain unburied (*3–4, 9*). Summarizing these findings, Richards wrote (*7*):

> Of the accessible areas of native structures, roughly half represents polar atoms and half nonpolar atoms. Thus the 'grease' is by no means all 'buried'. In the folding process there are roughly equivalent decreases in the accessibility of both the polar and nonpolar groups. The relevant forces and the final structure require more careful definition than is implied by the common feeling that inside equals nonpolar and outside equals polar.

Subsequent studies revealed further complexity: the correlation of hydrophobicity with total residue surface area is excellent (*10*), but the corresponding correlation with residue area buried upon folding is poor (*3, 4*).

Thus, it has been widely accepted (*2–4, 11*) that only a weak relation exists between the tendency for residues to be buried within proteins and their hydrophobicity, when measured as the free energy of transfer from water to organic solvent (*1*). However, we now report findings that lead to the opposite conclusion, revealing a strong correlation between hydrophobicity and the surface area residues bury upon folding.

Calculation of solvent-accessible surface areas. The solvent-accessible surface area (*9*) was calculated for 4410 residues taken from monomers of 23 x-ray elucidated proteins (*12*); atomic radii used were those of Richards (*9*). Normalized distribution functions were then compiled, as shown in Fig. 1. Each distribution is, in effect, a histogram showing the percentage of residues of each type that are: fully accessible, 5 percent buried, 10 percent buried, and so on until completely buried.

Accessibility must be measured relative to a defined standard state. Two ways of specifying a standard state have been discussed (*13, 14*). The extended standard state for a residue, X, is taken to be the surface area of that residue in the extended tripeptide Gly-X-Gly (see Fig. 2), with dihedral angles $\phi = -140°$, $\psi = 135°$, $\chi_1 = -120°$, and $\chi_{2...N} = 180°$ (*13*). In the present study we use a stochastic standard state, defined as the mean accessibility of an ensemble of tripeptides having dihedral angles taken from the observed distribution in actual proteins (*14*). For example, if there are N

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phenylalanines in the database of proteins, then N tripeptides, Gly-Phe-Gly, are constructed with angles

$$\phi_i, \psi_i, \chi_{i(1)} \text{ where } i = 1, 2, \ldots, N$$

The mean accessibility for phenylalanine and its substituent groups is the ensemble average. Physically, the stochastic standard state reflects the degree to which residues are buried by backbone atoms from covalent neighbors in the ensemble. Both extended and stochastic standard states give similar values; individual residue differences range between 1 and 15 percent.

Surface area and hydrophobicity. Mean accessibilities, $<A_i>$, were calculated for the distributions shown in Fig. 1. Using the mean and standard state accessibilities, we derived several characteristic quantities for each residue. These are listed in Table 1 and include:

1) A^0, the stochastic standard state accessibility—that is, the solvent accessible surface area of a residue in the standard state.

2) $<A>$, the mean solvent-accessible surface area—that is, the average solvent accessible surface area of a residue in folded proteins.

3) $A^0 - <A>$, the mean area buried on transfer from the standard state to the folded protein (proportional to the hydrophobic contribution to ΔG_{conf}).

4) $(A^0 - <A>)/A^0$, the mean fractional area loss, denoted f, where

$$f = 1 - (<A>/A^0)$$

5) ΔG_t^0 the Nozaki-Tanford (*1*) free energy of transfer from water to organic solvent, in kilocalories per mole (scale includes 11 residues only).

The mean fractional area loss, f, is the average area a residue buries upon folding, normalized by its standard state area. The relation between area buried upon folding and standard state area is presented graphically in Fig. 3. The residues can be divided into three groups: (i) hydrophobic, including (Gly), Ala, Cys,

Table 1. Mean (designated $<A>$) and standard state surface areas (A^0) for the amino acid residues.

Residue*	A^0 (Å^2)	$<A>$ (Å^2)	$A^0 - <A>$ (Å^2)	$(A^0 - <A>)/A^0$	ΔG_t^0 (kcal)
Ala (397)	118.1	31.5	86.6	0.74	0.5
Arg (137)	256.0	93.8	162.2	0.64	
Asn (221)	165.5	62.2	103.3	0.63	
Asp (239)	158.7	60.9	97.8	0.62	
Cys (98)	146.1	13.9	132.3	0.91	
Gln (164)	193.2	74.0	119.2	0.62	
Glu (217)	186.2	72.3	113.9	0.62	
Gly (435)	88.1	25.2	62.9	0.72	0.0
His (99)	202.5	46.7	155.8	0.78	0.5
Ile (255)	181.0	23.0	158.0	0.88	
Leu (297)	193.1	29.0	164.1	0.85	1.8
Lys (288)	225.8	110.3	115.5	0.52	
Met (66)	203.4	30.5	172.9	0.85	1.3
Phe (135)	222.8	28.7	194.1	0.88	2.5
Pro (152)	146.8	53.7	92.9	0.64	
Ser (341)	129.8	44.2	85.6	0.66	−0.3
Thr (265)	152.5	46.0	106.5	0.70	0.4
Trp (75)	266.3	41.7	224.6	0.85	3.4
Tyr (181)	236.8	59.1	177.7	0.76	2.3
Val (348)	164.5	23.5	141.0	0.86	1.5

*The values in parentheses are the numbers of residues of each type in the database. All other quantities are described in the text.

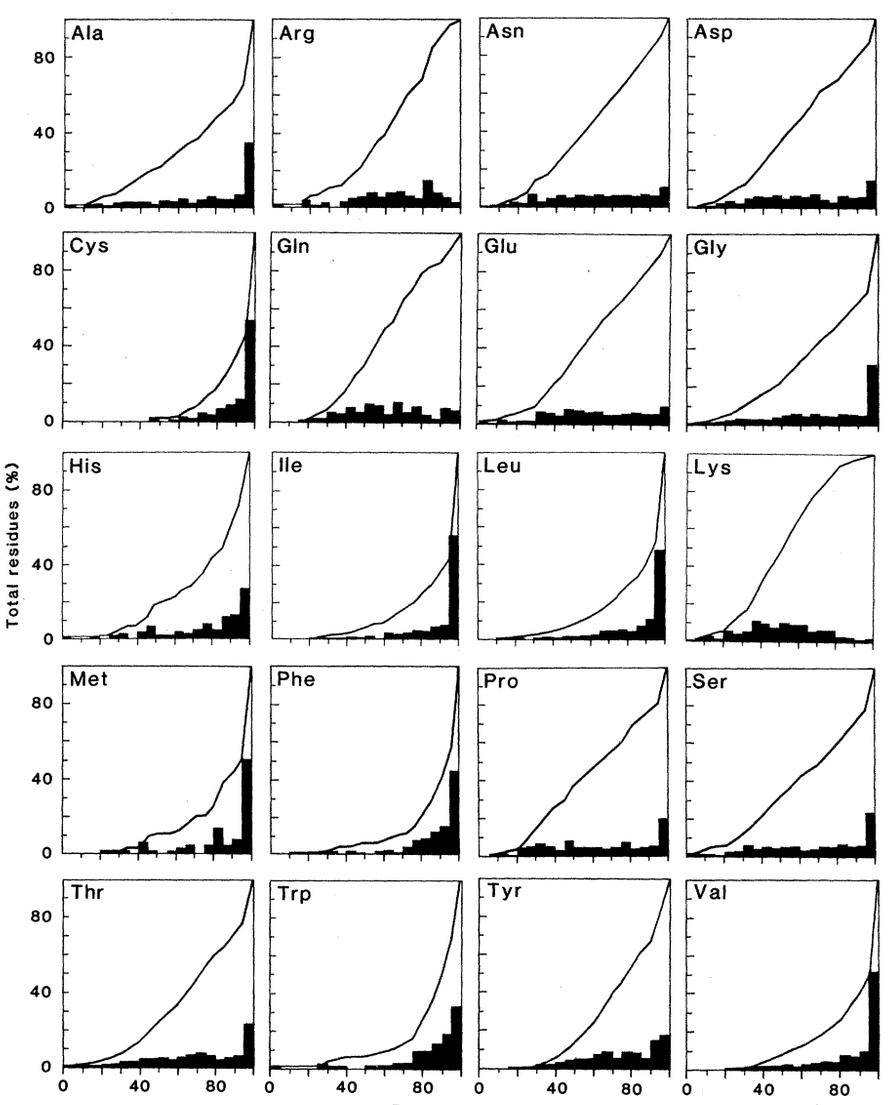


Fig. 1. Normalized distribution functions of accessibility to solvent for the 20 residues, calculated from proteins of known structure (*12*). Each function is, in effect, a histogram showing the percentage of residues of that type that are: fully accessible, 5 percent buried, 10 percent buried, . . . , completely buried. An integrated curve is superimposed on the histograms; the curve is a plot of percentage of residues that are 0 to 5 percent buried, 0 to 10 percent buried, . . . , 0 to 95 percent buried, 0 to 100 percent buried. (By definition, the integrated curve must range from 0 to 100 percent of total number of residues as the proportion of buried residues is varied from 0 to 100 percent.)

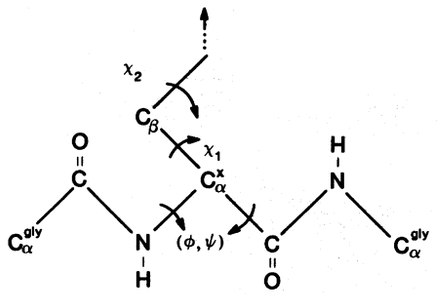
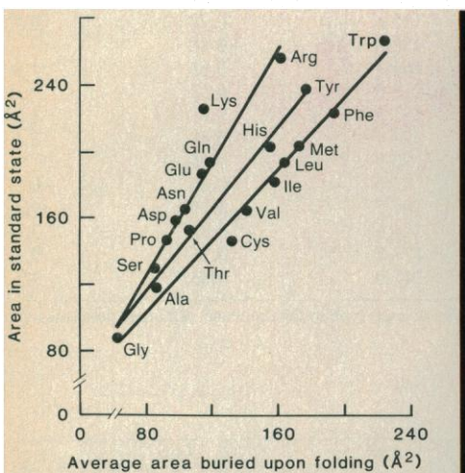


Fig. 2. Degrees of freedom in the tripeptide unit Gly-X-Gly. ϕ and ψ are backbone dihedral angles, and χ_1, χ_2, . . . are side-chain dihedral angles.



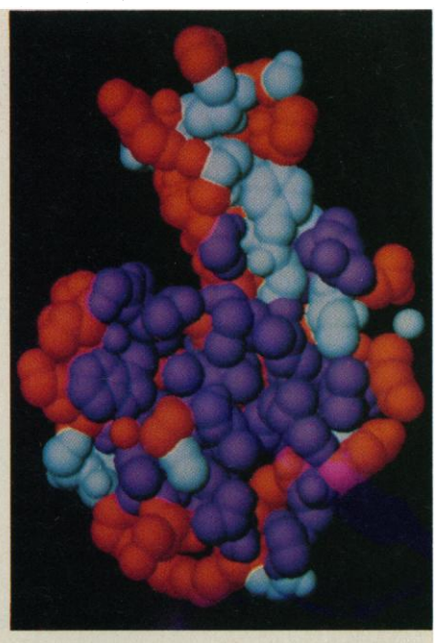


Fig. 3. (Left) Plot of average area buried upon folding, $A^0 - \langle A \rangle$, against the standard state area, A^0, for all 20 residues. The mean fractional area loss, f, defined as the average area buried divided by the standard state area, is an intrinsic measure of residue hydrophobicity. The straight lines of best-fit are given in Eqs. 1, 2, and 3. (Right) A computer-generated space-filling model of the protein hen egg lysozyme, showing the largest cross section through the molecule (*19*). The color coding scheme, based on the data in the left panel, divides the residues into three groups: hydrophobic (purple), moderately polar (blue), and very polar (orange red). With the sequences encoded in this way, it can be seen that hydrophobic residues tend to cluster in the interior, while very polar residues are dispersed to the exterior.

Val, Ile, Leu, Met, Phe, and Trp; (ii) moderately polar, including (Gly), Ser, Thr, His, and Tyr; and (iii) very polar, including (Gly), Pro, Asp, Asn, Glu, Gln, and Arg.

For each of the above groups, the observed linear relationship extrapolates back through glycine, the logical first member of any group. Equations for the straight lines of best-fit (and standard errors) for each group are

Hydrophobic

$$A^0 = 1.0(\pm 0.05) \cdot (A^0 - \langle A \rangle) + 17.3(\pm 7.9) \quad (1)$$

Moderately polar

$$A^0 = 1.2(\pm 0.07) \cdot (A^0 - \langle A \rangle) + 18.6(\pm 9.3) \quad (2)$$

Very polar

$$A^0 = 1.7(\pm 0.08) \cdot (A^0 - \langle A \rangle) - 9.6(\pm 8.4) \quad (3)$$

The form of Eqs. 1 to 3 is:

$$A^0 = m \cdot (\text{average area buried}) + b$$

The reciprocal slope, $1/m$, reflects the incremental area buried, on average, for each increment of standard state area. Equations 1 to 3 are interpreted to mean that beyond a threshold quantity, b, hydrophobic residues are fully buried ($m = 1$), moderately polar residues are 83 percent buried ($m = 1.2$), and very polar residues are 59 percent buried ($m = 1.7$).

Another interpretation of Fig. 3 is also consistent with the data. If groups 1 to 3 are extrapolated back through zero, instead of through Gly, the slopes are similar and the standard errors are comparable. In this case, Gly is included in group 2 only. The resultant equations have no residual threshold and are interpreted to mean that, on average, hydrophobic residues are still fully buried, moderately polar residues are 76 percent buried, and very polar residues are 63 percent buried.

In Fig. 3, left, proline appears to be more polar than anticipated, a probable consequence of its frequent occurrence in reverse turns which are usually situated at the protein surface (*6*). Lysine is an outlier, appearing more polar than any other residue. In our more detailed analysis lysine backbone and beta carbon (C_β) atoms were observed to behave normally, while C_γ, C_δ, and C_ϵ appear to have anomalous values of f. Such behav-

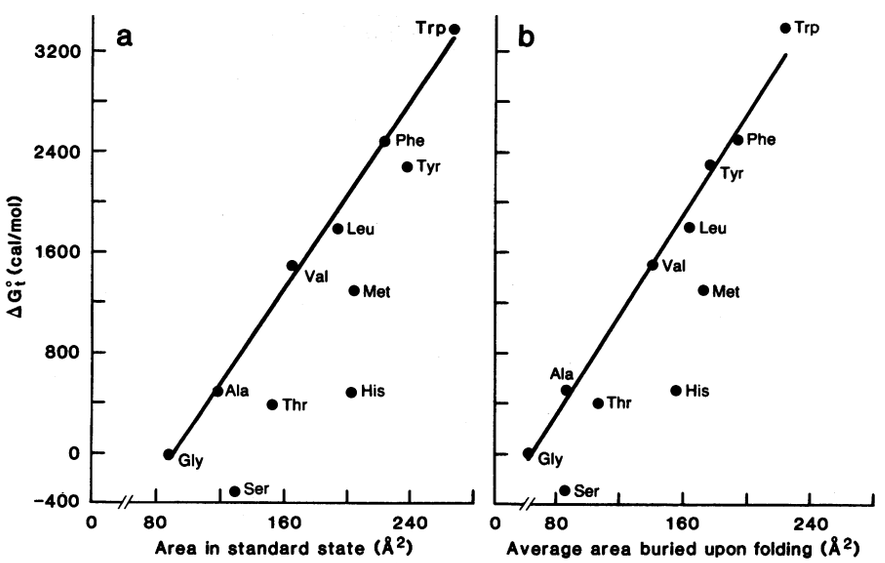


Fig. 4 (a) Plot of stochastic standard state area, A^0, versus the Nozaki-Tanford free energy of transfer from water to organic solvent, ΔG_t^0 (*1*). The line, given by Eq. 4, was best-fit to Gly and members of the hydrophobic series: Ala, Val, Leu, Phe, and Trp. (b) Plot of the average area buried upon folding, $A^0 - \langle A \rangle$, as a function of the Nozaki-Tanford free energy of transfer, ΔG_t^0 (*1*). The line, given by Eq. 5, was best-fit to Gly and members of the hydrophobic series. The area residues bury upon transfer from the stochastic standard state to the mean folded state is linearly related to the Nozaki-Tanford values.

ior may be an artifact of the way disordered lysyl side chains are assigned to the crystal structure data.

A linear relationship between a standard state area and the free energy of transfer from water to organic solvent (*1*), ΔG_t^0, was demonstrated by Chothia (*10*) more than a decade ago. Figure 4a is such a plot for the 11 residues determined by Nozaki and Tanford (*1*). The straight line of best fit for members of the hydrophobic series (Gly, Ala, Val, Leu, Phe, and Trp) is:

$$\Delta G_t^0 = 18.9(\pm 0.7) \cdot A^0 - 1706(\pm 122) \quad (4)$$

Assuming additivity, Nozaki and Tanford calculated ΔG_t^0 for residue side chains as ΔG_t^0 (whole residue) − ΔG_t^0 (glycine). Accordingly, Eq. 4 intercepts the line $\Delta G_t^0 = 0$ at 88.1 Å^2, the value of A^0(Gly).

With the stochastic standard states used here, Trp also behaves as a hydrophobic residue. Ser, Thr, and Tyr, with one polar group, constitute a second line; and His, with two polar groups, is an outlier. In these experiments, Met behaves as though it contains a polar group, as observed in the earlier study (*10*).

The mean area buried upon folding, $A^0 - \langle A \rangle$, also scales linearly with ΔG_t^0 as shown in Fig. 4b. The straight line of best-fit for residues of the hydrophobic series—Gly, Ala, Val, Leu, Phe, and Trp—is:

$$\Delta G_t^0 = 20.1(\pm 1.1) \cdot (A^0 - \langle A \rangle) - 1307(\pm 168) \quad (5)$$

Corresponding to the Nozaki and Tanford assumption of additivity (*1*) discussed for Fig. 4a, Eq. 5 intercepts the line $\Delta G_t^0 = 0$ at 62.9 Å^2, the value of A^0(Gly) − $\langle A$(Gly)$\rangle$.

The lines of best-fit for hydrophobic residues in Fig. 4, a and b, are approximately parallel, but with intercepts shifted by 25 Å^2. Thus, upon subtraction of a constant, points corresponding to hydrophobic residues from Fig. 4a, including Met, can be superimposed upon themselves almost exactly in Fig. 4b because their average accessible areas, $\langle A_i \rangle$, are almost the same.

A similar but larger shift relates residues of the moderately polar series—Ser, Thr, Tyr, and His—in Fig. 4, a and b. A larger shift is to be expected in this case because polar residues are less efficiently buried than hydrophobic residues (see Fig. 3) and must contribute proportionately more area to sustain a given value of ΔG_t^0. Equation 5, as well as companion equations for the moderately polar and very polar residues, can be obtained by substituting Eqs. 1 to 3 into Eq. 4.

One outcome of the difference in offset between hydrophobic and polar residues is that Tyr appears to be displaced from the polar to the hydrophobic series upon going from Fig. 4a to Fig. 4b, but the effect is fortuitous; Ser, Thr, and Tyr remain colinear in Fig. 4, a and b. The Trp side chain has a polar component because the indole group can be a hydrogen bond donor. For this reason, $\langle A$(Trp)$\rangle$ is about 10 Å^2 larger than that of other hydrophobic residues, and Trp is shifted slightly more than these other groups upon going from Fig. 4a to Fig. 4b.

These results can be summarized as follows.

1) The area that residues bury upon going from the stochastic standard state to the mean folded state is strongly related to the Nozaki-Tanford hydrophobicity (*1*), ΔG_t^0.

2) The residues can be divided into three groups based upon the derivative of their mean fractional area loss (Fig. 3).

Comparison of scales. Early studies raised the possibility that amino acid residues might partition within macromolecules much as they do in model organic solvents (*8, 15*). Such a relationship, however, turned out to be inconsistent with later work (*2–4, 7*). Nonetheless, Fig. 4b demonstrates a simple linear relationship between the area a residue buries upon folding and its hydrophobicity, as measured by the free energy of transfer from water to organic solvent, ΔG_t^0 (*1*). These discrepancies beg explanation.

Wolfenden and co-workers (*2*) measured the free energy of transfer of side-chain analogs between water and the dilute vapor phase, ΔG_h^0. They showed that ΔG_h^0 is correlated with the empirical tendency of residues to be buried within proteins. Conversely, Chothia (*3*) and Janin (*4*), in empirical analyses, and Wolfenden *et al.* (*2*) noted a lack of correlation between the degree to which residues are buried and the Nozaki-Tanford ΔG_t^0.

Such findings are surprising. Polar groups can satisfy hydrogen bonding requirements in aliphatic alcohols and dioxan (*15*), and within proteins (*3, 7, 13*), but not in the dilute vapor phase. Thus, while ethanol may not be an ideal model for the protein interior, it would seem to be a more suitable choice than dilute vapor.

Rose *et al.* (*6*) have questioned these empirical studies on the grounds that the criterion for whether a residue is buried is based upon a threshold that is both nominal and stringent. In particular, classifying residues as exposed if they are less than 95 percent buried (*3*) or have more than 20 Å^2 of accessible surface (*4*) disregards all but the information in the final vertical bar of the histograms in Fig. 1. Because these criteria for burial are very stringent, residues, especially amphiphilic residues, are biased toward the accessible state in empirical studies. Similarly, amphiphilic residues favor the aqueous phase in water to vapor transfer experiments because there is no compensation for broken hydrogen bonds. These conjoint tendencies result in a misleading correlation. A similar criticism has been raised by Guy (*16*) on the grounds that large side chains can span the interface between the molecular interior and exterior, defying simple binary classification as either buried or accessible.

Recently, Miyazawa and Jernigan (*17*) calculated interresidue contact energies from proteins of known structure; the calculations were based on the premise that contact pair formation constitutes a virtual chemical reaction. Their values for the average energy change upon contact formation, e_{ir}, and our values and theirs for the characteristic fractional area loss, f, are well correlated; the product-moment coefficient of correlation is 0.96 for the 20 residues. In their work, as in ours, lysine appears unusually exposed.

The foregoing analysis urges revision of earlier empirical assessments of the relation between the area a residue buries upon folding and ΔG_t^0. A strong linear relationship between these two quantities is demonstrated in Fig. 4b. Furthermore, the unitary slope of Eq. 1 argues that hydrophobic residues are essentially buried, on average, with the exception of a small residual area that is approximately constant. The moderately polar residues, identified by Eq. 2, and the very polar residues, identified by Eq. 3, also appear to bury a characteristic fraction of their available surface upon going from the stochastic standard state to the folded state. In addition to reconciling apparent discrepancies between amino acid behavior in solution and in proteins, the scales in Table 1 may find practical application in algorithms to predict structure (*18*).

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