

Research article

A simple and illustrative conceptual amino acid hydrophathy scale

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Abstract

A conceptual hydrophathy scale based only on amino acid structure is developed which is compared to three scales from the literature. Called the H/P scale, it is arrived at by finding the ratio of hydrophobic to polar atoms for a given amino acid, where the amino acid takes part in a polypeptide chain. The polar atoms of the main chain amides are included, which sets the H/P scale apart from most other approaches by not discriminating against hydrogen bond interactions in a protein or peptide, which always include the main chain amides, either intramolecularly, or intermolecularly with water molecules. The divergences observed for the H/P scale from those in the literature are explained with simple chemical concepts, which include more favorable packing in gas phase clusters due to hydrogen bonding, less favorable packing for aromatics, and the presence or absence of unsaturation in amino acid side chains. Statistical treatment of the regression analysis uncovers outlier amino acids whose hydrophathy values are difficult to characterize, which are Trp, Pro, Lys, Gly, Cys, and Met. These amino acids are discussed in terms of their chemical structures and functions within proteins, and any hydrophathy values for them should be considered carefully. Hydrophathy scales, including the H/P scale, can be used to find relative ranking for the 14 non-outliers amino acids, with due consideration of the presence or absence of side chain unsaturation. Because it is not based on experimental data, the H/P scale can be regarded as conceptual.

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The H/P scale provides an easy way to arrive at values which rely on intuitive chemical concepts, which are both pedagogically and practically useful.

Introduction

A certain degree of trepidation is justified when a contribution to the area of amino acid hydropathy is contemplated, since it forms one of the pillars of biochemistry, used to help understand protein structure and which parts of membrane proteins are exposed to the lipid bilayer. One paper states there are over 100 hydropathy scales in the literature [1], providing grounds for reticence on the one hand due to the vast volume of material to cover, and motivation on the other to help provide some clarity. The present work will focus on just three scales, one of which is used in text books [2], and is the work of Kyte and Doolittle [3], hereafter referred to as the K&D scale, one is a newer gas phase scale devised by Hoffman, et al. [1], hereafter called the GP scale, and the last is based on HPLC retention times studied by Kovacs, et al. [4], which will be called the LC scale. The hope is these scales will suffice for making the point the paper tries to illustrate without being wholly comprehensive on the topic of hydropathy.

Briefly, hydropathy attempts to turn the concept of polarity into a quantitative value by assigning an index to each amino acid. Those with low or negative values are more polar, while those with positive high values are more non-polar, or more descriptively, hydrophobic. Of course, all amino acids are zwitterions in aqueous solution (and therefore polar), and so polarity is really referring to the side chain; and in fact, it is more accurate and realistic to think about amino acid polarity if it is part of a polypeptide, where its amino and acid parts are tied up as amides. Regarding protein structure, it is widely understood that proteins fold into their final functional forms by a process sometimes called hydrophobic collapse [5], where hydrophobic side chains exchange their aqueous solvation for hydrophobic interactions on the interior of proteins, in a largely entropy driven process. For membrane proteins, whose water insolubility makes their isolation and characterization a challenge [6], significant portions of their exposed polypeptide chains are hydrophobic, making them overall more likely to insert themselves into the hydrophobic interior of the membrane bilayer. Those portions of a protein's sequence which have high hydropathy values are expected to be on the interior of water-soluble proteins, or play an important role in the protein-lipid interaction for membrane proteins.

The physical chemistry of hydrophobic molecules interacting with water can be envisioned largely as a process of desolvation [7]. This picture is critical for understanding the entropy driven processes of phase separation, micelle formation, and protein folding, to name a few. Water molecules form an ordered solvation shell around a hydrophobic molecule (or the

hydrophobic part of a molecule), the order of which causes the system to have low entropy. As the water molecules leave the hydrophobic moiety (desolvate), their disorder and entropy go up, driving the hydrophobic parts to interact with each other, in a process often referred to as the hydrophobic effect.

Table 1 shows the hydropathy values for selected amino acids from the three literature scales. Also shown is the number of non-polar atoms found in the amino acid side chains obtained by simple counting. While such a simple method of arriving at hydrophobicity

Amino acid	K&D	GP	LC	AA non-polar atoms
Tyr	-1.3	0.998	15.4	13
Trp	-0.9	0.933	32.9	16
Ala	1.8	1.003	3.9	4
Met	1.9	1.053	16.3	10
Phe	2.8	1.042	29.9	14
Leu	3.8	1.101	24.2	13
Val	4.2	1.053	14.4	10
Ile	4.5	1.048	22.4	13

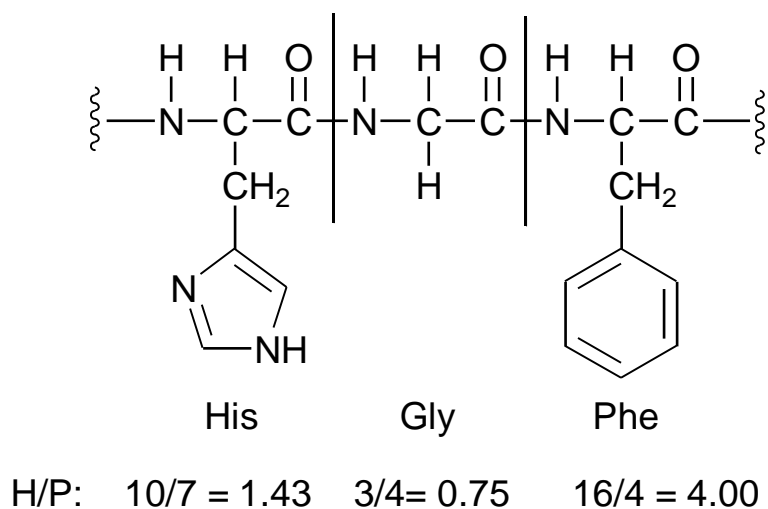
Table 1: Hydropathy values for selected amino acids.

might be suspect, there are areas in chemistry where simple atom counts correlate nicely with physical phenomena, such as boiling point trends [8], chromatographic retention times [9], and viscosity [10]. In the present case, it might appear atom counts are a poor reflection of hydropathy, especially for the aromatic amino acids, where tryptophan, with the largest number of non-polar side chain atoms, has a negative K&D hydropathy value, a relatively low gas phase hydropathy value, and an outsized LC hydropathy value compared to phenylalanine. It is worth noting, however, there appears to be some correlation between hydropathy and atom counts for selected amino acids further down the table, viz., Ala→Met→Leu, suggesting hydropathy can at least partially be predicted by the identity of the atoms in the amino acid.

Neglected so far in the discussion are polar atoms, which can be found in both the main chain as well as the side chains of a polypeptide. Polar atoms include all heteroatoms, as well as carbon atoms and hydrogen atoms which are part of a highly polarized group, such as C=O, O-H, and N-H. Since the goal for many hydropathy related studies is to understand how a protein, a peptide, or a portion of a protein or peptide interacts with a hydrophobic environment such as a membrane interior, it is appropriate in the current context to include the polar main chain atoms in any consideration of hydropathy. The argument could be made

that main chain amides are often involved in hydrogen bonds either in the form of an α -helix or a β -sheet, and therefore should be set aside in hydrophathy calculations. But it can be pointed out that all polar atoms will participate in hydrogen bonds, either with other acceptors or donors intramolecularly within the peptide or protein, or intermolecularly with water, and it is therefore not appropriate to discriminate against main-chain polar atoms in favor of side-chain polar atoms, since it is the total of all hydrophobic and polar interactions that govern hydrophathy. The following provides an easy way to include the main chain polar atoms in a hydrophathy index.

This paper introduces the ratio H/P, which is the total number of hydrophobic atoms divided by the total number of polar atoms found in an amino acid by inspection, noting that the amino acid is part of a polypeptide with bonds to both its amino group and its acid group. The examples shown in Scheme 1 illustrate the concept, and criteria are established below for H and P atom assignments. The derived hydrophathy using the H/P ratio is developed here, where a comparison to the other scales referenced above



Scheme 1

shows the new scale captures elements of all three, and provides a basis for establishing outlier amino acids which by their nature are difficult to classify on hydrophathy scales. The divergences can be explained in many cases using common chemical ideas which further add to a chemical understanding of hydrophathy. In addition, the method can be used to calculate hydrophathy of whole proteins and protein segments, which can be used to highlight overall hydrophathy as well as sequences likely to be on the interior of water soluble proteins.

Methodology

H/P atom assignments

Most atoms in amino acids can be assigned as polar or hydrophobic based on electronegativity differences (ΔX). Using the Pauling scale [11], C=O, N-H and O-H have ΔX values of 0.89, 0.84, and 1.24, respectively, while C-H, C-N, S-H, and C-S have ΔX of 0.35, 0.49, 0.38 and 0.03, respectively. If a cutoff of $\Delta X = 0.8$ is used, values above this amount give polar atoms and values below it give hydrophobic atoms. The C-N group requires some additional qualifications: for histidine, the N-atom bearing the lone pair electrons is considered to be polar on the grounds that it can act as a base ($pK_a \sim 6$), for proline its N-atom is considered to be polar since it participates in a highly polar amide bond, and the C-atom of the guanidine group in arginine is considered to be polar since guanidine also acts as a base ($pK_a \sim 12$). Additionally, the carbon atoms attached to alcohol oxygen atoms in serine, threonine, and tyrosine are considered to be hydrophobic, since it is the polar O-H bond in these amino acids that contribute the most to their chemical properties.

The H/P hydrophathy scale

Table 2 displays the H/P values found for the 20 common amino acids. The H/P values vary from a low of 0.56 to a high of 4.00 with no negative values. This last attribute is shared with the GP scale; the negative values in the K&D scale were arbitrarily created in

Amino acid	H/P	Amino Acid	H/P
Asn	0.56	Cys	1.75
Asp	0.63	Lys	2.00
Gly	0.75	Tyr	2.5
Ser	0.83	Trp	3.00
Gln	0.89	Val	3.00
Arg	0.92	Met	3.25
Glu	1.0	Pro	3.67
Thr	1.33	Ile	3.75
His	1.43	Leu	3.75
Ala	1.50	Phe	4.00

Table 2: H/P values calculated by inspection of amino acid structures.

order to have the values vary between the extremes of -4.5 and +4.5 [3], and any scale can be manipulated with appropriate scaling factors in order to make graphical comparisons more convenient.

Statistical treatment

The hydropathy scales from the three listed literature sources are compared to the H/P scale using linear regression analysis. Good agreement with the model is found for the GP and the LC scale, with clear outliers, while for the K&D scale two separate trends are found with somewhat poorer agreement with the models, and one clear outlier. Points are judged to be outliers if they fall outside the range defined by twice the standard error of estimate [12], or $2S_Y$, using the model appropriate for the scale used for comparison. Graphical representations of the outliers can be found in *Figures S1-S3*. The outliers from each comparison are collected in *Table 3*.

Scale	Outliers
GP	Q,H,N,A,F,W,P
K&D	K
LC	W,K,P

Table 3: Outlier amino acids when the H/P scale is compared to other scales using linear regression analysis.

Results and Discussion

First comparison: GP scale

A graphical comparison between the new H/P parameter and the GP literature values is found in *Figure 1*. It can be seen that 12 out of 20 GP values are judged to be well enough correlated to the H/P values to create the model, with the outliers using the criteria described in the Statistical treatment section. It is notable that the outliers with low hydropathy values fall above the predicted line, while the outliers with high hydropathy values fall below the predicted line. A possible explanation for this observation is that the GP values are found using an electrospray mass spectrometric technique, in which amino acids form clusters whose sizes are measured and whose abundances reflect the ability of the amino acid to form intermolecular attractions, which in turn is related to hydropathy. During the electrospray process, the very polar and hydrogen bond forming amide-containing amino acids Asn and Gln could be more likely to aggregate, giving the higher GP values. This argument can also be applied to His. The aromatic amino acids Trp and Phe (as opposed to amino acids with

aliphatic side chains) could be prevented from aggregation, and thus give lower GP values, due to poor packing in the aggregate, perhaps as a result of the tendency of aromatics to pack in an edge-to-face manner [13]. As for the other outliers, Ala and Pro, the rationalizations are based on different chemical properties: Ala could suffer from a tendency to over-aggregate as a result of superior packing due to the symmetry of the methyl group, while cyclic Pro might be prevented from aggregating normally owing to the fact that it has one less polar N-H group.

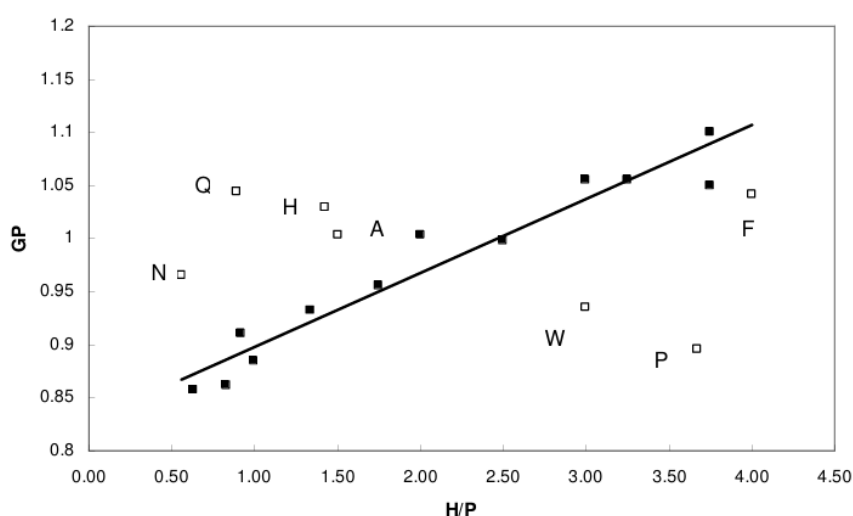


Figure 1: Correlation between GP hydrophathy values and H/P hydrophathy values. The labeled open boxes are for values rejected according to the Statistical treatment section. Least squares line $R^2 = 0.939$.

Second comparison: K&D scale

The second comparison to the literature can be seen in *Figure 2* with scaled K&D values. While the K&D values appear to fit the theoretical lines less well than in the case of the GP comparison, the scatter is below the standard error of estimate for both models as shown in *Figure S2*. The data fall cleanly into two groups, which have been separated out in *Table 4*.

Group 1	Group 2
“□” $y = 0.5537x + 1.4672$	“■” $y = 0.6317x + 0.213$
Gly, Ser, Thr	Asn, Asp, Gln
Ala, Cys, Val	Arg, Glu, His
Ile, Leu	Tyr, Trp, Met, Pro, Phe

Table 4: Amino acid groups with models indicated which make up the data in *Figure 2*.

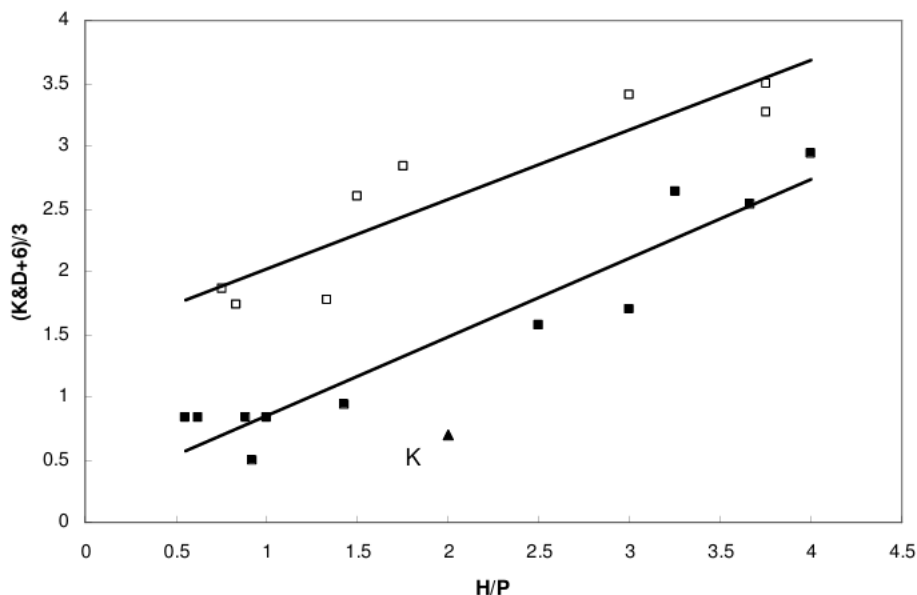


Figure 2: Correlation between scaled K&D hydrophathy values and H/P hydrophathy values. Open boxes: model $y = 0.5537x + 1.4672$, $R^2 = 0.839$. Closed boxes: model $y = 0.6317x + 0.213$, $R^2 = 0.916$. One outlier (solid triangle) is marked as lysine (K).

The first group in *Table 4* comprises polar side chains whose polarity is due to the OH group, hydrophobic aliphatic side chains, and Gly and Cys. These can be contrasted to the second group, whose polar side chains are either acids, amides, imidazole or guanidine, hydrophobic side chains comprised of aromatic groups, and Met and Pro. These observations can be rationalized as follows. For the most part, the K&D hydrophathy values rely on measurements of water-vapor transfer free energies for model compounds meant to mimic amino acid side chains. For the polar groups, this leads to more negative (favorable) transfer energies and higher hydrophathy values for alcohols compared to amides, acids, imidazole and guanidine. For hydrophobic groups, this leads to more favorable transfer energies and higher hydrophathy values for aliphatics over aromatics. These energetic considerations help explain the two groups depicted in *Figure 2*, where the Group 1 amino acids have saturated side chains, and the Group 2 amino acids have unsaturated side chains, with the obvious exceptions being Met and Pro.

Lysine is the outlier in *Figure 2* and lysine is unusual structurally owing to the long tetramethylene group intervening between the amine and the amino acid. This long alkyl chain gives rise to its relatively high H/P value. Lysine has been found near the transmembrane segments of membrane proteins, where the aliphatic tetramethylene group is buried in the lipid bilayer and the charged amino group is closer the polar interface, giving

rise to a phenomenon called lysine snorkeling [14]. Thus, lysine hydrophobicity is on the low side on the K&D scale, more similar to arginine, but its H/P value is more in line with its favorable lipid interaction properties.

The amino acids for which no very clear chemical explanation exists to rationalize their presence in either Group 1 or Group 2 are Gly, Cys, Met and Pro. Observations from protein crystal structures show both Gly and Pro are often found in turn regions [15], suggesting the ability to make tight turns may be more important biologically than hydrophobicity, making their hydrophobicity more difficult to classify. Structurally, cysteine can form disulfide bonds which help stabilize proteins from denaturation. Disulfides are usually found on the interior of proteins, which again could lead to ambiguous hydrophobicity since in some settings, such as at the active site of cysteine proteases, the SH group is highly polar [16]. The hydrophobic thioether in Met is grouped with aromatics in *Figure 2*, which is consistent with work showing the polarizable sulfur atom can interact with aromatic side chains analogous to π -stacking [17]. Thus, even though the side chain of methionine is saturated, the polarizable sulfur atom can give it characteristics more like an aromatic side chain.

Third comparison: LC scale

The comparison to the LC values can be found in *Figure 3*. In this case, the correlation is good with only three outliers, which is perhaps a reflection of the whole-peptide approach taken in this work [4], where test peptides were used with only one amino acid changed to test its hydrophobicity. The HPLC technique utilized places lysine closer to arginine in hydrophobicity, where the partitioning between the mobile and stationary phases may be similar to the water-vapor transfer energies used for the K&D scale. Thus the HPLC technique does not uncover lysine's hydrophobicity but is more influenced by the charged ammonium group. The LC scale for proline predicts a moderate-to-low hydrophobicity, which underestimates its hydrophobicity compared to the K&D scale perhaps due to poor access of the five membered ring to the stationary phase. This is in contrast to

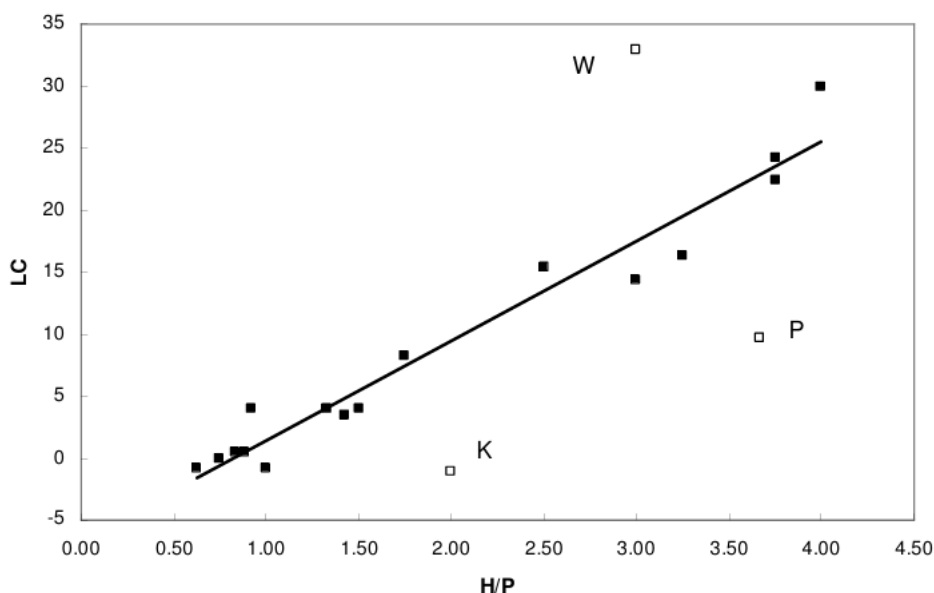


Figure 3: Correlation between LC hydrophathy values and H/P hydrophathy values. The labeled open boxes are for values rejected according to the Statistical treatment section. Least squares line $R^2 = 0.956$.

tryptophan, whose side chain, even with its polar N-H group, interacts strongly with the stationary phase giving a very high LC hydrophathy. Tryptophan is found in much higher abundance in transmembrane proteins compared to soluble proteins, where its unique properties are utilized near the hydrophobic/polar interface [18].

Summary of outlier amino acids

The following summarizes the amino acids which are either outliers or do not have a clear chemical reason to be in Group 1 or Group 2 in *Table 4*.

Asparagine, Glutamine, Histidine: The polar side chains of these amino acids with hydrogen bond forming properties helps account for their gas phase clustering behavior. Owing to the fact that solvent is absent in the measurements, these properties might be overrepresented, and therefore they may be classified as provisional outliers.

Alanine: The high symmetry of the methyl group is used to account for excess clustering for this amino acid, where again the absence of solvent could make clustering more favored. Alanine is also classified as a provisional outlier.

Phenylalanine: With the highest H/P value, this amino acid is hypothesized to cluster less in the gas phase due to poor side chain packing. Its presence in Group 2 in the K&D comparison makes it align well with the model, which is theorized to be appropriate for unsaturated side chains. Phenylalanine is a provisional outlier.

Tryptophan: Poor packing is used to account for less gas phase clustering for this amino acid, but its obvious high affinity for the stationary phase in the LC comparison makes tryptophan unusual. Its uneven distribution in membrane proteins has been noted, and its overall low abundance suggests it has outsized biological importance. With hydrophobicity difficult to assign, tryptophan is a clear outlier.

Proline: Lack of one N-H bond in its chemical structure compared to the other 19 common amino acids is used to account for proline's poor gas phase clustering. Its presence in Group 2 in the K&D comparison is less easily rationalized, but does suggest this amino acid has unusual properties, reinforced by the low affinity for the LC stationary phase. Proline plays an important role in turns, as noted, and it has been highlighted for its presence in collagen and for its importance in signaling [19]. Proline is a clear outlier.

Lysine: This amino acid displays gas phase behavior which aligns well with its H/P value, in contrast to the other two scales, which both may under-represent its hydrophobicity. Its lipid interaction properties have been noted, making lysine a clear outlier.

Glycine: A lack of a proper side chain makes hydrophobicity difficult to characterize for this amino acid. It is in Group 1 in the K&D comparison, even though the term saturated here has no meaning. As noted by Kyte and Doolittle [3], glycine "does not have strong feelings about water" but its role in polypeptide turns has been noted. Glycine is a clear outlier.

Cystine: With unique thiol reactivity, it is unsurprising this amino acid is difficult to classify. While it is not strictly an outlier, its presence in Group 1 in the K&D comparison (unlike methionine) suggests it behaves more like amino acids with saturated side chains. The H/P scale, like the others discussed here, does not reveal this amino acid's reactivity. With its ability to make disulfides, which has been noted, cysteine is regarded as an outlier.

Methionine: This amino acid's presence in Group 2 in the K&D comparison is rationalized by the polar thio ether having the ability to interact strongly with aromatic rings, in a process analogous to π -stacking, as noted above. The nominally hydrophobic side chain otherwise correlates well with the other scales, but this unusual amino acid should be classified as an outlier.

This listing of amino acids classifies only Trp, Pro, Lys, Gly, Cys, and Met as true outliers, based on the notion that the gas phase experiment, while valid from a strictly chemical point of view, does not necessarily reflect the behavior of amino acids in an aqueous environment. Therefore, the outliers in the GP comparison, with the exception of Trp and Pro, are considered provisional outliers. With only six true outliers, this leaves 14 amino acids whose hydrophathy can be considered to be well characterized. In using any scale, the investigator should be cognizant of the differences found here for Group 1 and Group 2 amino acids shown in *Figure 2*, where for example the K&D scale might over-represent hydrophathy for saturated side chains (or under represent hydrophathy for aromatics). In instances where the hydrophathy of a true outlier amino acid as described here is required, the investigator should consider hydrophathy carefully.

Main chain polar atoms and H/P scale shortcomings

It has been pointed out that a peptide or protein will interact with its aqueous environment utilizing all its atoms, whether they reside on side chains or on the main chain of a polypeptide. Traditionally, hydrophathy scales have focused on the side chains of amino acids, because naturally this is where the variation occurs from amino acid to amino acid. The LC scale discussed here by its nature takes into account the properties of the main chain, since peptides are analyzed in this experiment. The H/P scale takes into account the main chain atoms as well, and upon reflection, it is only possible to have an H/P ratio for purely hydrophobic side chains if the polar atoms of the main chain are included, viz., phenylalanine. It may be that inclusion of polar main chain atoms underestimates hydrophobicity in these cases, and a scale based on counting only side chain atoms, and computing a different value, such as H minus P, might be appropriate. A brief examination of this idea (data not shown) indicates a very poor correlation to the LC data, suggesting the inclusion of polar side chain atoms is appropriate in cases where the hydrophathy of the whole biomacromolecule, or portions of it, is of interest.

Extension of H/P calculations to whole proteins or peptides is easily accomplished by simply counting all the atoms in a peptide or protein, which of course will include main chain atoms. Intriguing observations along these lines suggest water soluble proteins have very similar H/P ratios, which can be distinguished from the H/P ratios of membrane proteins. It is also possible to find H/P ratios of regions of peptides and proteins, which can help identify hydrophobic regions likely to be on the interiors of proteins or imbedded in membranes [20]. A full elaboration of the use of the H/P ratio in these ways is beyond the scope of the present work.

It is observed here that in the GP comparison, side chains with polar amides show positive deviations from the model and aromatic side chains show negative deviations from the model. In the K&D comparison, separating saturated and unsaturated side chains is required in order to find better fits to the two models found. These observations point to a weakness of the H/P calculations where simple H and P assignments cannot reflect the presence of double bonds. Double bonds can contribute significantly to polarity. For example, in the case of methanol and formaldehyde, the dipole moments are 1.70 D and 2.33 D [8], respectively. For aromatic systems, delocalization of electrons is used to explain excess polarizability compared to saturated systems, as illustrated, for example, in the index of refraction for benzene (1.5011) versus cyclohexane (1.4266) [8]. In principle, a modified H/P scale could be devised where H-type atoms found to be in aromatic settings are given fractionally larger values, or polar atoms in extreme situations like C=O or H-O could be given fractionally smaller values, but this would detract from the simplicity of the scale. It is also pointed out that the relative ranking of the non-outlier amino acids could be adjusted to better match the K&D scale, but then the correlation to the other scales would suffer.

Another weakness of the H/P scale is its inability to take into account amino acids whose side chains are charged at physiological pH. These include anions (Asp, Glu) and cations (Lys, Arg), as well as histidine, which can act as a base, as already noted. The actual degree of ionization for amino acids depends their pKa's which can be influenced by their local environments in a protein [2]. This weakness might suggest these amino acids should be outliers, but it can be seen only lysine has been uncovered as a true outlier in the present discussion. As with the problem discussed regarding unsaturation, a modified H/P designation could be contemplated to account for side chain ionization. However, it is perhaps remarkable that Asp, Glu, Arg, and His are not outliers, and suggests the H/P ratio captures their hydrophathy adequately, without the need for taking into account their ionization state. Moreover, any such adjustment would be protein-specific, and negate any advantage of the simplicity of this atom counting method.

Conclusion

The new conceptual H/P hydrophathy scale is developed which is based on the number of polar and hydrophobic atoms found in an amino acid which ranges from 0.56 to 4.00. It differs from most other scales by including the polar atoms found in the main chain of polypeptides, which is justified on the grounds that all polar atoms will participate in hydrogen bonding, either intramolecularly, or intermolecularly with water molecules, and that polypeptide hydrophathy considerations should not be biased against main chain interactions. The H/P scale is compared to three scales from the literature using regression analysis. Outliers are determined by examining residuals which exceed twice the standard

error of estimate. The outliers can be rationalized in one case by the differing ability of side chains to pack into gas phase aggregates, where hydrogen bonding gives rise to excess packing, and edge to face orientation of aromatics gives rise to poor packing. In another case, amino acid side chains fall into two groups: those with saturated side chains and those with unsaturated side chains. The former is found to have higher than expected hydrophobicity and the latter to have lower than expected hydrophobicity, and illustrates how a simple atom counting method cannot account satisfactorily for unsaturated molecules. In the final case, where the H/P scale fits the model most accurately, outliers are found to have unusual chromatographic retention times. In all cases, outliers form a set of amino acids with hydrophobicity that is difficult to characterize, the amino acids being Trp, Pro, Lys, Gly, Cys, and Met. The specific qualities of these amino acids and their functions in proteins are discussed. The H/P scale can provide an easy way to visually inspect an amino acid and characterize its hydrophobicity, which is both pedagogically and intuitively appealing.

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Supplementary Information

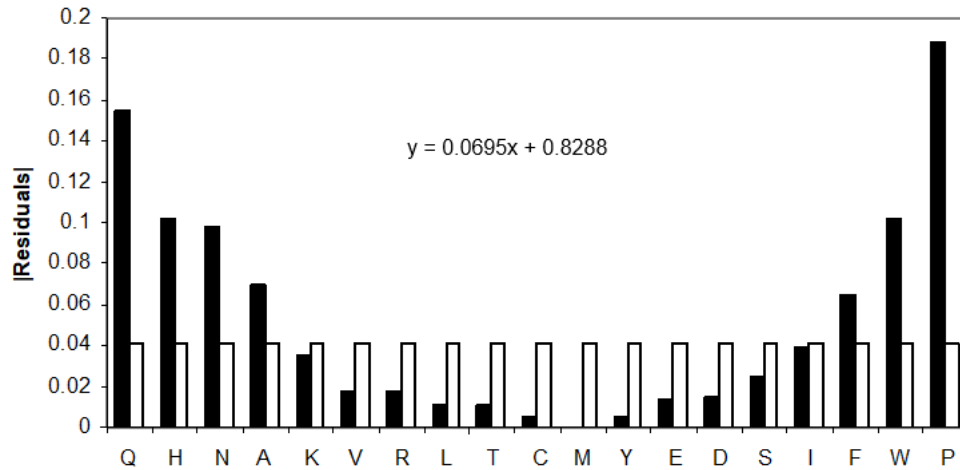


Figure S1: Residual absolute values (black bars) for amino acids after linear regression analysis using the model shown of the GP scale vs. the H/P scale. White bars show the magnitude of twice the standard error of estimate, 2S_Y

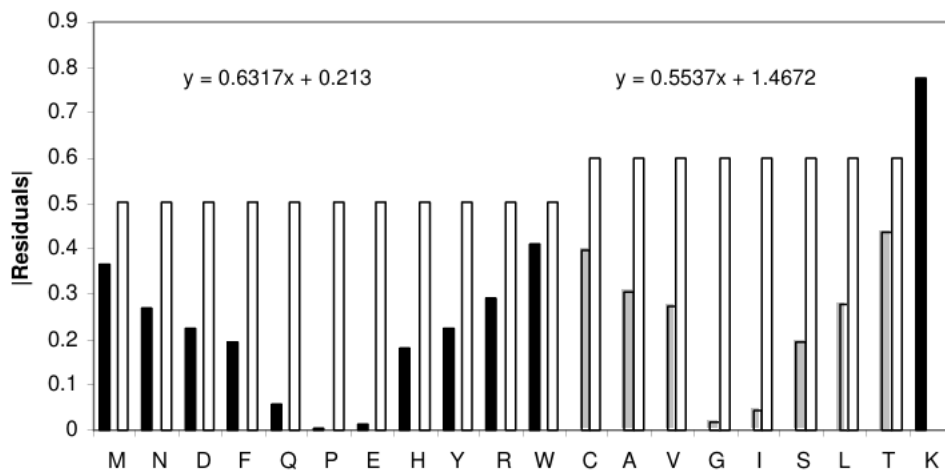


Figure S2: Residual absolute values (black bars, hash marks) for amino acids after linear regression analysis using the models shown of the K&D scale vs. the H/P scale. White bars show the magnitude of twice the standard error of estimate, 2S_Y.

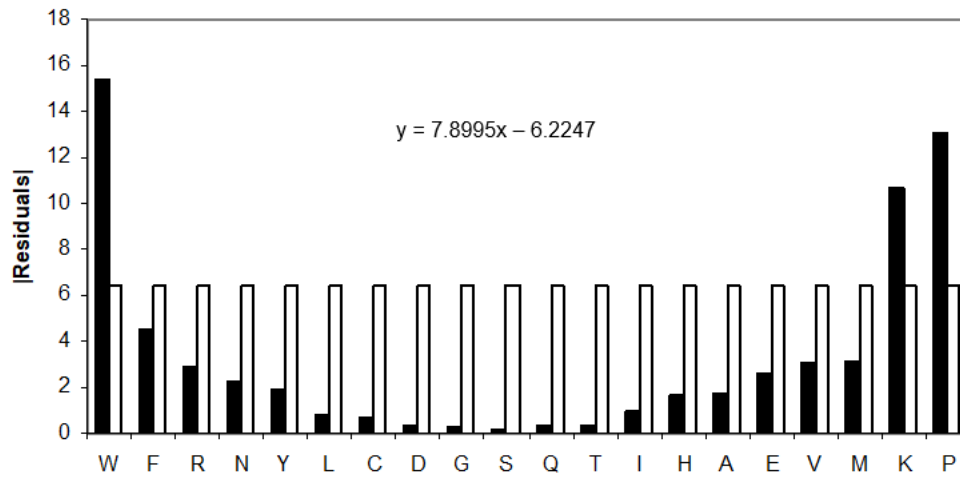


Figure S3: Residual absolute values (black bars) for amino acids after linear regression analysis using the model shown of the LC scale vs. the H/P scale. White bars show the magnitude of twice the standard error of estimate, 2S_y.