Solvation Descriptors for Zwitterionic α-Aminoacids; Estimation of Water–Solvent Partition Coefficients, Solubilities, and Hydrogen-Bond Acidity and Hydrogen-Bond Basicity

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ABSTRACT: The literature data on solubilities and water–solvent partition coefficients have been used to obtain properties or “Absolv descriptors” for zwitterionic α-aminoacids: glycine, α-alanine (α-aminopropanoic acid), α-amino-2-butanoic acid, norvaline (α-aminopentanoic acid), norleucine (α-aminohexanoic acid), valine (α-amine-3-methylbutanoic acid), leucine (α-amino-4-methylpentanoic acid), and α-phenylalanine. Together with equations that we have previously constructed, these descriptors can be used to estimate further solubilities and partition coefficients in a variety of organic solvents and in water–methanol and water–ethanol mixtures. It is shown that equations for neutral solutes are inadequate for the description of solubilities and partition coefficients for these α-aminoacids, and our equations developed for use with both neutral and ionic solutes must be used. The Absolv descriptors include those for hydrogen-bond acidity, A, and hydrogen-bond basicity, B. We find that both of these descriptors are far smaller in value than those for compounds that contain the corresponding ionic groups. Thus, A for α-alanine is 0.28, but A for the ethylammonium cation is 1.31; B for α-alanine is 0.83, and yet B for the acetate anion is no less than 2.93. The additional descriptors that we developed for equations that involve ions, J⁺ and J⁻, are very significant for the α-aminoacids, although numerically smaller than for ionic species such as EtNH₃⁺ and CH₃CO₂⁻.

INTRODUCTION

The α-aminoacids are one of the most important series of compounds in the chemical and biological sciences, and there has been a very large number of experimental and theoretical studies on this series. Campen et al.† have shown that there are some 517 distinct scales of aminoacid properties. Even so, there are notable omissions in some 517 distinct scales of aminoacid properties. Even so, there are notable omissions in some 517 distinct scales of aminoacid properties. Even so, there are notable omissions in some 517 distinct scales of aminoacid properties. The most common methods2–4 for the estimation of water–solvent partition coefficients only apply to the water–wet octanol system and not to any other water–solvent system. The EPI method for the estimation of solubility5 applies only to solubility in water and not to any other solvent. Most surprisingly, there are no estimations of the hydrogen-bond acidity or of the hydrogen-bond basicity of α-aminoacids. The hydrogen-bond acidity of glycine might be supposed to be close to that of the ethylammonium cation, and the corresponding hydrogen-bond basicity close to that of the acetate anion, but no information on these important hydrogen-bond properties is available.

It is our aim to use known physicochemical properties of zwitterionic α-aminoacids such as water–solvent partitions and solubilities in a range of solvents to obtain “descriptors” of these aminoacids. Together with equations that we have previously obtained, these descriptors can be used to estimate further partition coefficients in various water–solvent systems and further solubilities in various solvents. Crucially, these descriptors include the hydrogen-bond acidity and hydrogen-bond basicity so that it will then be possible to compare values for α-aminoacids with those for other species, both charged and uncharged.

METHODS

Over the past few years, we have developed a system of properties or descriptors of solute molecules, known as Abraham descriptors or as Absolv descriptors,5 and have constructed a data base of these solute properties, now available in the public domain.6 In conjunction with this data base, we have assembled a complementary set of equations for physicochemical and biological properties of solutes, so that a combination of solute descriptors and equation coefficients can be used to predict various physicochemical and biological properties, as set out in a number of reviews.7–11 This work7–11 dealt only with neutral species, but was extended to cover charged solutes, specifically ions such as K⁺ and Cl⁻ and ionic species, defined as protonated base cations and...
Table 1. Coefficients in Equation 3 for Water–Solvent Partitions; $SP = \log P$

| solvents            | $c$  | $e$  | $s$  | $a$  | $b$  | $v$  | $j^*$ | $j^*$ |
|---------------------|------|------|------|------|------|------|-------|-------|
| methanol            | 0.276| 0.334| −0.714| 0.243| −3.320| 3.549| −2.609| 3.027 |
| ethanol             | 0.222| 0.471| −1.035| 0.326| −3.596| 3.857| −3.170| 3.085 |
| propan-1-ol         | 0.139| 0.405| −1.029| 0.247| −3.767| 3.986| −3.077| 2.834 |
| butan-1-ol          | 0.165| 0.401| −1.011| 0.056| −3.958| 4.044| −3.605| 2.685 |
| hexan-1-ol          | 0.115| 0.492| −1.164| 0.054| −3.971| 4.131| −3.100| 2.940 |
| propan-2-ol         | 0.099| 0.344| −1.049| 0.406| −3.827| 4.033| −3.896| 2.889 |
| t-butanol           | 0.211| 0.171| −0.947| 0.331| −4.085| 4.109| −4.455| 2.953 |
| diethylformamide    | −0.305| −0.058| 0.343| 0.358| −4.865| 4.486| −3.605| 0.415 |
| dimethylethamide    | −0.271| 0.084| 0.209| 0.915| −5.003| 4.557| −3.152| 2.432 |
| acetonitrile        | 0.413| 0.077| 0.326| −1.566| −4.391| 3.364| −2.234| 0.101 |
| nitromethane        | 0.023| −0.091| 0.793| −1.463| −4.364| 3.460| −0.149|        |
| N-methylpyrrolidone | 0.147| 0.532| 0.275| 0.840| −4.794| 3.674| −1.797| 0.105 |
| dimethylsulfoxide   | −0.194| 0.327| 0.791| 1.260| −4.540| 3.361| −3.387| 0.132 |
| propylene carbonate | 0.004| 0.168| 0.504| −1.283| −4.407| 3.424| −1.989| 0.341 |
| sulfolane           | 0.000| 0.147| 0.601| −0.318| −4.541| 3.290| −1.200| −0.792 |
| propanone           | 0.313| 0.312| −0.121| −0.608| −4.753| 3.942| −2.288| 0.078 |
| tetrahydrofuran     | 0.223| 0.363| −0.384| −0.238| −4.932| 4.450| −2.278| −2.132 |
| NPOE$^{a}$          | 0.121| 0.600| −0.459| −2.246| −3.879| 3.574| −2.314| 0.350 |
| dichloromethane     | 0.319| 0.102| −0.187| −3.058| −4.090| 4.324| −3.984| 0.086 |
| 1,2-dichloroethane  | 0.183| 0.294| −0.134| −2.801| −4.291| 4.180| −3.429| −0.025 |
| nitrobenzene        | −0.152| 0.525| 0.081| −2.332| −4.494| 4.187| −3.373| 0.777 |
| benzonitrile        | 0.097| 0.285| 0.059| −1.605| −4.562| 4.028| −2.729| 0.136 |
| chlorobenzene       | 0.065| 0.381| −0.521| −3.183| −4.700| 4.614| −4.536| −1.486 |

$^a$NPOE is o-nitrophenolylactylether.

deprotonated acid anions,$^{12−21}$ as recently reviewed.$^{22}$ The total method, for neutral and ionic species, has already been applied to a number of systems.$^{23−30}$ Although we had descriptors for a large number of charged species,$^{22}$ we have not investigated the $\alpha$-electrochemically neutral but with an internal charge separation, that is, zwitterions. Our general method for the analysis of neutral solutes makes use of the two linear free energy relationships, eqs 1 and 2.

To apply eqs 1 or 3 to a given $\alpha$-aminoacid, they can be combined with the two linear free energy relationships, eqs 1 and 2, and so only eq 1 is relevant. This equation can be extended to ionic solutes by incorporation of two new terms, as in eq 3. The $j^+j^-$ term refers to cations, and the $j^+j^-$ term refers to anions. Cations have $j^+ = 0$, anions have $j^- = 0$ and neutral compounds have $j^+ = j^- = 0$, so that the equation coefficients $c$, $e$, $s$, $a$, $b$, and $v$ are the same for neutral molecules, ions, and ionic species. Thus, for neutral molecules, eq 3 reverts to eq 1.

$$SP = c + cE + sS + aA + bB + vV$$

$$SP = c + cE + sS + aA + bB + vV + j^+j^- + j^-j^+$$

To apply eq 1 or 3 to a given $\alpha$-aminoacid, values of the dependent variable, SP are needed. The most direct source is a directly determined water–solvent partition coefficient, $P$, as $\log P$, although for many $\alpha$-aminoacids, partition coefficients are restricted to the water–octanol system, $P_{oct/w}$, Partition coefficients can also be obtained indirectly from solubilities, in mol dm$^{-3}$, in water, $C_w$, and a given (usually dry) solvent, $C_s$, through eq 4.

$$\log P = \log C_s - \log C_w$$

Then, if enough values of $\log P$, direct or indirect, are available for a given $\alpha$-aminoacid, they can be combined with the corresponding equations, eq 3, and the unknown descriptors calculated by solving the set of simultaneous equations. The Microsoft “Solver” add-on is particularly useful, and any set of simultaneous equations can be solved to give a “best-fit”
solution. Coefficients in eq 3 for the ionic equations that we have obtained so far are given in Table 1.

**RESULTS**

We first studied the homologous series of α-amino-n-carboxylic acids, because we thought that it is reasonable to expect that the various solute descriptors would vary regularly with the number of carbon atoms in the aminoacids, and that this would help in the assignment of descriptors.

**Glycine.** Values of directly determined water to (wet) octan-1-ol and water to (wet) butan-1-ol are available. We have the coefficients in eq 3 for partition into both of these solvents, see Table 1. There are a large number of recorded solubilities for glycine in water and various dry solvents, as given in Table 2. Solubilities for glycine in water and various dry solvents, as given in Table 2, are available. We used log C_w taken as 0.49; C_w is the molar solubility in water at 298 K. The values of log P obtained through eq 4 are also in Table 2, and it is these values that we use to derive descriptors for glycine.

In addition to solubilities in pure solvents, there are also available solubilities in aqueous methanol and aqueous ethanol, for which we have the coefficients in the ionic equation, eq 3, see Table 3. We combined the various solubilities to obtain log P values from methanol to water—methanol mixtures and from water to water—ethanol mixtures, using our selected log P values for partition to 100% methanol and 100% ethanol, for consistency. The log P values that we obtained are in Table 4.

There were a number of solvents, 2-methoxyethanol, dioxane, and 1,2-dimethoxyethane, for which we had coefficients only for neutral species. However, we were still left with log P values for 35 solvents or solvent mixtures. The log P values for water to propanone and water to butan-1-ol (and hence the corresponding solubilities) were quite out of line, and so we were left with 33 values. We obtained a value of E = 0.476 for the neutral species NH₂CH₂CO₂H from a refractive index calculated by the ChemSketch program. Judging from our results on base cations and acid anions, we can take E for the zwitterionic species as that for the neutral species. Similarly, we take V = 0.5646 for the neutral species as that for the zwitterion. Then, we have five descriptors, S, A, B, J, and Jᵇ to obtain from 33 simultaneous equations. The descriptors in Table 5 yield a standard deviation SD = 0.241 log units between observed and calculated log P values. The number of data points used is N. In view of the large discrepancies in the solubilities of glycine, the SD value is as small as could reasonably be expected. The calculated log P values for the water—methanol and water—ethanol mixtures are in Table 4, and the calculated log P values for the organic solvents are in Table 2. We also used exactly the same 33 equations to obtain descriptors through the neutral eq 1, that is with Jᵇ and Jᵇ taken as zero. The SD now rises considerably to 0.348 log units, see Table 5.

**α-Alanine (α-Aminopropanoic Acid).** For α-alanine, there is also a substantial data available. As for glycine, water to (wet) octan-1-ol and water to (wet) butan-1-ol partition coefficients are known. The solubilities of L-α-alanine and DL-α-alanine in water are almost the same, with log C_w = 0.260, 34–37,39,41–48. Solubilities are also known in organic solvents, 34–36,38,39,41–48 water—methanol mixtures, 33,36 and water—ethanol mixtures. We used log C_w = 0.260 to convert solubilities into values of log P through eq 4, see Tables 6 and 7. We obtained E = 0.460 and V = 0.7055 as for glycine and then had five descriptors to obtain from 30 simultaneous equations. The best-fit descriptors are in Table 5. Together with the corresponding equations for log P, these yield the calculated log P values in Tables 6 and 7. The descriptors in Table 5 give SD = 0.206 log units between observed and calculated log P values. If the neutral equation, eq 1 is used, the SD is considerably increased to 0.345 log units, see Table 5.

**α-Aminobutanoic Acid.** There is less data for α-aminobutanoic acid, but log P values into wet octan-1-ol.
Table 3. Coefficients in Equation 3 for Water–Methanol and Water–Ethanol Partitions, \( SP = \log P \); Composition of Mixtures Given as Volume %

| Solvents | Coefficients |
|----------|--------------|
| Methanol | 0.276, 0.334, -0.714, 0.243, -3.320, 3.549, -2.609, 3.027 |
| 95%      | 0.270, 0.278, -0.520, 0.230, -3.368, 3.365, -2.661, 2.909 |
| 90%      | 0.258, 0.250, -0.452, 0.229, -3.206, 3.175, -2.629, 2.707 |
| 80%      | 0.172, 0.197, -0.319, 0.241, -2.912, 2.842, -2.540, 2.421 |
| 70%      | 0.098, 0.192, -0.260, 0.266, -2.585, 2.474, -2.267, 2.164 |
| 60%      | 0.053, 0.207, -0.238, 0.272, -2.157, 2.073, -1.978, 1.872 |
| 50%      | 0.023, 0.223, -0.222, 0.264, -1.747, 1.662, -1.588, 1.569 |
| 40%      | 0.020, 0.222, -0.205, 0.218, -1.329, 1.259, -1.329, 1.259 |
| 30%      | 0.016, 0.187, -0.172, 0.165, -0.953, 0.898, -0.823, 0.930 |
| 20%      | 0.022, 0.142, -0.138, 0.088, -0.574, 0.559, -0.465, 0.599 |
| 10%      | 0.012, 0.072, -0.081, 0.026, -0.249, 0.266, -0.185, 0.287 |
| Ethanol  | 0.222, 0.471, -1.035, 0.326, -3.596, 3.857, -3.170, 3.085 |
| 96%      | 0.238, 0.353, -0.833, 0.297, -3.533, 3.724, -3.020, 2.970 |
| 95%      | 0.239, 0.328, -0.795, 0.297, -3.514, 3.697, -2.985, 2.943 |
| 90%      | 0.243, 0.213, -0.575, 0.262, -3.450, 3.545, -2.794, 2.837 |
| 80%      | 0.172, 0.175, -0.465, 0.260, -3.212, 3.323, -2.466, 2.722 |
| 70%      | 0.063, 0.085, -0.368, 0.311, -2.936, 3.102, -2.203, 2.550 |
| 60%      | -0.040, 0.138, -0.335, 0.293, -2.675, 2.812, -1.858, 2.394 |
| 50%      | -0.142, 0.124, -0.252, 0.251, -2.275, 2.415, -1.569, 2.051 |
| 40%      | -0.221, 0.131, -0.159, 0.171, -1.809, 1.918, -1.271, 1.676 |
| 30%      | -0.269, 0.107, -0.098, 0.133, -1.316, 1.414, -0.941, 1.290 |
| 20%      | -0.252, 0.042, -0.040, 0.096, -0.823, 0.916, -0.677, 0.851 |
| 10%      | -0.173, -0.023, -0.001, 0.065, -0.372, 0.454, -0.412, 0.401 |

Table 4. Values of \( \log P \) for Glycine from Water to Water–Methanol and Water–Ethanol Mixtures

| Solvents | \( \log P \) Values |
|----------|------------------|
| Methanol | 96, -2.925, -2.750 |
| 95%      | -2.177, -1.999, 95, -2.856, -2.670 |
| 90%      | -1.973, -1.902, 90, -2.538, -2.218 |
| 80%      | -1.631, -1.723, 80, -2.009, -1.865 |
| 70%      | -1.404, -1.525, 70, -1.594, -1.612 |
| 60%      | -1.150, -1.355, 60, -1.259, -1.437 |
| 50%      | -0.987, -1.130, 50, -0.980, -1.233 |
| 40%      | -0.710, -0.862, 40, -0.739, -0.997 |
| 30%      | -0.461, -0.645, 30, -0.522, -0.757 |
| 20%      | -0.300, -0.400, 20, -0.324, -0.551 |
| 10%      | -0.125, -0.185, 10, -0.148, -0.322 |

Table 5. Solute Descriptors Obtained from Equation 3

| Descriptors | Coefficients |
|-------------|--------------|
| Glycine     | 0.476, 2.12, 0.27, 0.72, 0.5646, 0.5854, 0.2483, 0.241 |
| Alpha alanine | 0.460, 2.58, 0.28, 0.83, 0.7055, 0.6226, 0.4186, 0.206 |
| Alpha aminobutyric acid | 0.455, 2.63, 0.28, 0.94, 0.8464, 0.5170, 0.3871, 0.180 |
| Norvaline | 0.454, 2.20, 0.33, 0.92, 0.9873, 0.5106, 0.2001, 0.138 |
| Norleucine | 0.449, 2.10, 0.32, 0.96, 1.1282, 0.5227, 0.2356, 0.155 |
| Valine     | 0.439, 2.38, 0.32, 0.95, 0.9873, 0.5804, 0.2897, 0.204 |
| Leucine    | 0.438, 2.61, 0.32, 0.96, 1.1282, 0.3397, 0.1336, 0.074 |
| Alpha phenylalanine | 1.150, 2.48, 0.77, 1.70, 1.3133, 0.1907, 0.5312, 0.144 |
| Glycine    | 0.476, 1.92, 0.19, 1.05, 0.5646, 0.000, 0.32, 0.348 |
| Alpha alanine | 0.460, 2.14, 0.30, 1.09, 0.7055, 0.000, 0.29, 0.345 |
| Alpha aminobutyric acid | 0.455, 2.18, 0.49, 1.14, 0.8464, 0.000, 0.16, 0.331 |
| Norvaline  | 0.454, 2.05, 0.34, 1.20, 0.9873, 0.000, 0.27, 0.214 |
| Alpha phenylalanine | 1.150, 1.58, 1.00, 1.65, 1.3133, 0.000, 0.30, 0.330 |

\(^{a}\)Alpha aminobutyric acid. \(^{b}\)Alpha aminopentanoic acid. \(^{c}\)Alpha aminohexanoic acid. \(^{d}\)Value of A fixed.
Table 6. Solubilities of α-Alanine in Organic Solvents, as log $ C $, and Water–Solvent Partition Coefficients, as log $ P $, at 298 K

| solvent            | log $ C $ | refs | obs | taken | calc |
|--------------------|-----------|------|-----|-------|------|
| methanol           | −1.921    | 34   | −2.181 | −2.30 | −1.95 |
| methanol           | −3.119    | 37   | 3.379 |       |      |
| methanol           | −2.045    | 36   | −2.305 |       |      |
| ethanol            | −2.700    | 36   | −2.960 | −2.96 | −3.06 |
| ethanol            | −2.301    | 36   | −2.561 |       |      |
| ethanol            | −2.694    | 39   | −2.954 |       |      |
| propan-1-ol        | −2.700    | 34   | −2.960 | −3.56 | −3.31 |
| propan-1-ol        | −2.588    | 39   | −2.848 |       |      |
| propan-1-ol        | −3.297    | 47   | −3.557 |       |      |
| propan-2-ol        | −2.400    | 39   | −2.660 | −3.86 | −3.88 |
| propan-2-ol        | −2.523    | 36   | −2.783 |       |      |
| propan-2-ol        | −2.458    | 39   | −2.718 |       |      |
| propan-2-ol        | −3.607    | 44   | −3.867 |       |      |
| tert-butanol       | −2.401    | 34   | −2.660 | −2.94 | −4.09 |
| tert-butanol       | −2.680    | 35   | −2.940 |       |      |
| ethylene glycol    | −0.824    | 44   | −1.076 | −1.08 | −1.19 |
| ethylene glycol    | −0.816    | 42   | −1.084 |       |      |
| ethylene glycol    | −0.814    | 41   | −1.074 |       |      |
| DMSO               | −1.339    | 41   | −1.599 | −1.12 | −1.10 |
| DMSO               | −0.859    | 48   | −1.119 |       |      |
| dioxane            | −3.873    | 43   | −4.133 |       |      |
| acetonitrile       | −1.443    | 42   | −1.693 | −1.69 | −1.77 |
| dimethylformamide  | −1.319    | 44   | −1.579 | −1.58 | −2.29 |
| 2-methoxyethanol   | −0.678    | 45   | −0.938 | −0.94 |       |
| 1,2-dimethoxyethane| −0.833    | 46   | −1.093 | −1.09 |       |
| octan-1-ol, wet    | 2         | 2.96  | −2.96  | −3.35 |       |
| butan-1-ol, wet    | 32        | −1.60 | −1.60  | −1.65 |       |

“Not used in the calculations.”

Table 8. Solubilities of DL-α-Aminobutanoic Acid in Water and Organic Solvents, as log $ C $, and Water–Solvent Partition Coefficients, as log $ P $, at 298 K

| solvent                  | log $ C $ | refs | obs | taken | calc |
|--------------------------|-----------|------|-----|-------|------|
| ethanol                  | −2.507    | 37   | −2.84 | −2.84 | −2.73 |
| ethylene glycol          | −0.584    | 42   | −0.92 | −0.93 | −1.06 |
| ethylene glycol          | −0.604    | 44   | −0.94 |       |      |
| ethylene glycol          | −0.606    | 41   | −0.94 |       |      |
| DMSO                     | −1.171    | 41   | −1.50 | −1.50 | −1.74 |
| acetonitrile             | −1.284    | 42   | −1.62 | −1.62 | −1.53 |
| dimethylformamide        | −1.372    | 44   | −1.71 | −1.71 | −1.81 |
| 2-methoxyethanol         | −0.664    | 45   | −1.00 | −1.00 |       |
| ethanol                  | 96%       | 37   | −2.48 |       |       |
| 95%                      | 37        | −2.37 |       |       |
| 90%                      | 37        | −1.99 |       |       |
| 80%                      | 37        | −1.43 |       |       |
| 70%                      | 37        | −1.07 |       |       |
| 60%                      | 37        | −0.84 |       |       |
| 50%                      | 37        | −0.66 |       |       |
| 40%                      | 37        | −0.50 |       |       |
| 30%                      | 37        | −0.36 |       |       |
| 20%                      | 37        | −0.22 |       |       |
| 10%                      | 37        | −0.09 |       |       |
| octan-1-ol, wet          | 2         | −2.53 |       |       |
| butan-1-ol, wet          | 32        | −1.34 |       |       |

“Not used in the calculations.”

Norvaline (α-Aminopentanoic Acid). Values of log $ P $ from water to wet butan-1-ol and wet octan-1-ol are known for norvaline, and solubilities are available for DL-norvaline in water–ethanol mixtures and in a few organic solvents, as set out in Table 10. We took $ E = 0.449 $ and $ V = 1.1282 $, calculated as before. Then, using log $ C_w = 1.062 $, we obtained the given log $ P $ (obs) values. The log $ P $ value for propanone was considerably out of line, but the remaining log $ P $ values yielded 17 simultaneous equations from which we could calculate the descriptors shown in Table 5. The set of equations and calculated solute descriptors yield observed and calculated values of $ P $ with $ SD = 0.153 $ log units.

Valine (α-Amino-3-methylbutanoic Acid). log $ P $ values for partition to wet octan-1-ol (−2.26) and to wet butan-1-ol (−1.14) are known, and solubilities are available in water, organic solvents, and water–ethanol mixtures, and water–ethanol mixtures. The solubilities of L-valine and DL-valine differ somewhat. In water, values of log $ C $ are −0.122, and −0.243. However, log $ P $ values to water–ethanol mixtures as calculated from solubilities of L-valine and DL-valine in water and water–ethanol mixtures are essentially the same for both isomers, as expected. In Table 11 are given values of log $ P $ as obtained from solubilities of L-valine in water and organic solvents or from solubilities of DL-valine in water and organic solvents. The total of log $ P $ values is in Table 11. We took $ E = 0.439 $ and $ V = 0.9873 $, as before, and used 27 simultaneous equations to obtain the descriptors given in Table 5; the value of $ A = 0.32 $ was fixed by comparison to other aminoacids. For the observed and calculated values of log $ P $ in Table 11, $ SD = 0.204 $ log units.
Leucine (α-Amino-4-methylpentanoic Acid). Dey and Lahiri\textsuperscript{36} report solubilities of 1-leucine in water, water–methanol, water–ethanol, and water-propan-2-ol mixtures. The derived log $P$ values for water to pure solvents are in Table 12. Cohn et al.\textsuperscript{35} also determined solubilities of L-leucine in water–ethanol mixtures, but the value of log $P$ from water to ethanol is $-2.13$, as compared to that of $-1.54$ by Dey and Lahiri.\textsuperscript{36} Pal et al.\textsuperscript{35} listed similar data in water-tert–butanol mixtures, and the log $P$ value from water to tert-butanol itself is in Table 12. Also given\textsuperscript{35,36} are log $P$ values from water to wet octan-1-ol and wet butan-1-ol. Gekko\textsuperscript{34} has determined solubilities in water–methanol mixtures, and his values in water and pure methanol lead to a log $P$ value of $-1.05$, as compared to the value of $-1.48$ from Dey and Lahiri.\textsuperscript{36}

The derived log $P$ values in Table 12 for partition from water to methanol and ethanol are very inconsistent. In addition, those for partition into propan-2-ol and tert-butanol are far out of line by comparison with those for the other α-amino acids. The only way that we could assign descriptors to leucine was on the basis of the already obtained descriptors for the other α-amino acids listed in Table 5. The suggested descriptors for leucine are in Table 5 and lead to the calculated log $P$ values in Table 12. Clearly, more data on leucine are needed.

### Table 9. Solubilities of Norvaline in Water and Organic Solvents, as log $C$, and Water–Solvent Partition Coefficients, as log $P$, at 298 K

| solvents    | isomer | log $C$ | refs | log $P$ |
|-------------|--------|---------|------|---------|
| water       |        | -0.166  | 44   |         |
| water       |        | -0.169  | 45   |         |
| ethylene glycol |      | -0.811  | 42   | -0.643  |
| DMSO        |        | -1.334  | 41   | -1.166  |
| acetone     |        | -1.348  | 42   | -1.180  |
| dimethylformamide |   | -1.520  | 44   | -1.352  |
| 2-methoxyethanol |   | -0.836  | 45   | -0.668  |
| 1,2-dimethoxyethane | | -1.014  | 46   | -0.846  |
| methanol    |        | -1.153  | 52   |         |
| ethanol     |        | -1.155  | 51   | -2.359  |
| 96% ethanol |        | -1.07   | 51   | -2.135  |
| 95% ethanol |        | -1.07   | 51   | -2.069  |
| 80% ethanol |        | -1.07   | 51   | -1.265  |
| 70% ethanol |        | -1.07   | 51   | -0.979  |
| 60% ethanol |        | -1.07   | 51   | -0.801  |
| 50% ethanol |        | -1.07   | 51   | -0.656  |
| 40% ethanol |        | -1.07   | 51   | -0.525  |
| 30% ethanol |        | -1.07   | 51   | -0.396  |
| 20% ethanol |        | -1.07   | 51   | -0.268  |
| 10% ethanol |        | -1.07   | 51   | -0.138  |
| methanol    |        | -1.07   | 51   | -1.447  |
| 96% methanol|        | -1.07   | 51   | -1.327  |
| 90% methanol|        | -1.07   | 51   | -1.196  |
| 80% methanol|        | -1.07   | 51   | -0.972  |
| 70% methanol|        | -1.07   | 51   | -0.808  |
| 60% methanol|        | -1.07   | 51   | -0.684  |
| 50% methanol|        | -1.07   | 51   | -0.580  |
| 40% methanol|        | -1.07   | 51   | -0.479  |
| 30% methanol|        | -1.07   | 51   | -0.374  |
| 20% methanol|        | -1.07   | 51   | -0.261  |
| 10% methanol|        | -1.07   | 51   | -0.139  |
| octan-1-ol, wet | 2  | -2.11   | 2    | -2.43   |
| butan-1-ol, wet | 32 | -0.98   | 32   | -1.09   |

*Not used.*

### Table 10. Solubilities of DL-Norleucine in Water and Organic Solvents, as log $C$, and Water–Solvent Partition Coefficients, as log $P$, at 298 K

| solvents    | isomer | log $C$ | refs | log $P$ |
|-------------|--------|---------|------|---------|
| water       |        | -1.062  | 38   |         |
| formamide   |        | -1.762  | 38   | -0.70   |
| propanone   |        | -4.101  | 38   | -3.04\textsuperscript{a} |
| methanol    |        | -2.068  | 38   | -1.01   |
| butan-1-ol  |        | -3.474  | 38   | -2.41   |
| ethanol     |        | -2.982  | 38   | -1.92   |
| 96%         |        | -2.663  | 38   | -1.60   |
| 95%         |        | -2.593  | 38   | -1.53   |
| 90%         |        | -1.888  | 38   | -0.83   |
| 80%         |        | -1.671  | 38   | -0.61   |
| 70%         |        | -1.563  | 38   | -0.50   |
| 60%         |        | -1.504  | 38   | -0.44   |
| 50%         |        | -1.450  | 38   | -0.39   |
| 40%         |        | -1.378  | 38   | -0.32   |
| 30%         |        | -1.279  | 38   | -0.22   |
| 20%         |        | -1.165  | 38   | -0.10   |
| 10%         |        | -1.162  | 38   | -0.10   |
| octan-1-ol, wet | 2  | -1.54   | 2    | -1.92   |
| butan-1-ol, wet | 32 | -0.51   | 32   | -0.76   |

*Not used.*
Phenylalanine. Solubilities have been determined for both L-phenylalanine and DL-phenylalanine. In water, at 298 K, values of log \( C_w \) are −0.762 for L-phenylalanine \(^{33−36,54,55} \) and −1.065 for DL-phenylalanine.\(^{56−59} \) We use the values of log \( C_w \) = −0.762 and −1.065 to convert solubilities of L-phenylalanine \(^{33,54} \) and DL-phenylalanine \(^{40} \) in solvents to the corresponding log \( P \) values; details are in Table 13. Gomaa\(^{40} \) has determined solubilities of phenylalanine in several solvents. There is no indication of which isomer was used, but we have simply calculated log \( P \) values from the given solubilities in solvents and in water, see Table 13. There should be no difference in the log \( P \) values for L-phenylalanine and DL-phenylalanine for transfer to a given solvent. Also included in Table 13 are recent determinations of solubilities and hence log \( P \) values in dimethylsulfoxide,\(^{61} \) methanol,\(^{62} \) and ethanol.\(^{63} \) Where necessary, we have averaged the various values. Also, given\(^{7} \) are experimental values of log \( P \) for partition into wet octan-1-ol and wet butan-1-ol.

We calculated \( E = 1.15 \) in the same way as for glycine, and we took \( V = 1.3133 \) the same as the corresponding neutral species. We have data for 30 solvents, including aprotic solvents, and derive the descriptors in Table 5 with an SD of 0.144 log units as between observed (taken) and calculated log \( P \) values. If the analysis is carried out with the neutral equations, SD rises to 0.330 log units.

## DISCUSSION

There are a number of other zwitterionic \( \alpha \)-amino acids to those in Table 5 for which solubility data are available. The latter invariably refer only to hydroxyl solvents and water–solvent mixtures. In these cases, the set of simultaneous equations for a given amino acid can still be solved, but there then exists numerous solutions that have nearly the same statistical quality, so that no definite set of descriptors can be obtained. Unless data in a number of aprotic solvents such as dimethylsulfoxide, dimethylformamide, acetonitrile, and also propylene carbonate are available, it is difficult to use our method of simultaneous equations to determine descriptors. Exceptions are norleucine, valine, and leucine that are structurally so close to other \( \alpha \)-amino acids, Table 5, that it is possible to estimate some of their descriptors.

One complication is that many \( \alpha \)-amino acids exist as optical isomers (especially as the L- or DL-forms). Although the L- and D-isomers will have the same solubilities, the DL-form may have different solubilities to the L- and D-forms. Then, application of eq 4 requires that log \( C_w \) and log \( C_w \) refer to the same isomer. Of course any value of log \( P \) obtained through eq 4 or directly determined will be the same for an L- or DL-isomer.

An objective of this work was to establish if the properties of \( \alpha \)-amino acids could reasonably be estimated using our simple equation for neutral species, eq 1, or whether the more complicated “ionic” equation, eq 3 should be used. For the five \( \alpha \)-amino acids in Table 5 for which we have reliable descriptors, the average SD as between observed and calculated values of log \( P \) is 0.182 log units, which suggests that we can predict...
Table 14. Solute Descriptors for Aminoacids and Other Species

| Solute | E    | S    | A    | B    | V   | J'   | J''  |
|--------|------|------|------|------|-----|------|------|
| glycine   | 0.476 | 2.12  | 0.27  | 0.72  | 0.5646 | 0.5854 | 0.2483 |
| α-alanine | 0.460 | 2.58  | 0.28  | 0.83  | 0.7055 | 0.6226 | 0.4186 |
| α-aminoisobutyric acid | 0.455 | 2.63  | 0.28  | 0.94  | 0.8464 | 0.5170 | 0.3871 |
| norvaline | 0.454 | 2.20  | 0.33  | 0.92  | 0.9873 | 0.5106 | 0.2001 |
| norleucine | 0.449 | 2.10  | 0.32  | 0.96  | 1.1282 | 0.5227 | 0.2356 |
| valine    | 0.439 | 2.38  | 0.32  | 0.95  | 0.9873 | 0.5804 | 0.2897 |
| leucine   | 0.438 | 2.61  | 0.32  | 0.96  | 1.1282 | 0.3397 | 0.1336 |
| α-phenylalanine | 1.150 | 2.48  | 0.77  | 1.70  | 1.3133 | 0.1907 | 0.5312 |
| betaine   | 0.315 | 1.57  | 0.00  | 2.00  | 0.9873 | −0.3240 | 0.8760 |
| ethylammonium cation | 0.086 | 2.50  | 1.31  | 0.00  | 0.5117 | 0.7680 | 0.0000 |
| acetate anion | 0.415 | 2.19  | 0.00  | 2.93  | 0.4433 | 0.0000 | 2.0750 |
| ethylamine | 0.236 | 0.35  | 0.16  | 0.61  | 0.4902 | 0.0000 | 0.0000 |
| acetic acid | 0.265 | 0.64  | 0.62  | 0.44  | 0.4648 | 0.0000 | 0.0000 |

Further values of log P to about 0.20 log units. Once a given value of log P has been estimated through a combination of descriptors and equation coefficients, the corresponding value of log Cw can be obtained from log Cao, eq 4. If the neutral equation eq 1 is used, the average SD for the five α-aminoacids rises to 0.314 log units. However, we expect that the SD from an equation with five descriptors will be larger than the SD from an equation with seven descriptors. We, therefore, carried out a multiple linear regression of the 33 log P values for glycine against the five solvent descriptors E, S, A, B, and V and found that the Fisher F-statistic was 172.2. For a regression against the seven solvent descriptors E, S, A, B, V, J', and J'', we found that F = 206.0, so that even when taking into account the extra two descriptors, the equation with J' and J'' is preferred. We conclude that use of eq 3 with the J' and J'' descriptors is necessary for the analysis of partition and solubility of α-aminoacids by our method.

In the solution of a set of simultaneous equations for a given solute, the solute descriptors are all determined in the same analysis, so that the individual errors in the descriptors are not obtained. However, the overall errors in the analyses, Table S, are larger than the errors we usually find with neutral compounds for which we have estimated descriptor errors to be around 0.02 units. We suggest that descriptor errors for the α-aminoacids could be 0.03–0.04 units. The obtained descriptors for α-aminoacids, Table S, are of some interest, especially in that the α-aminoacids appear to have remarkably small values of the hydrogen-bond descriptors A and B. It is useful to compare some of the α-aminoacid descriptors with those for other charged species, as shown in Table 14, with α-alanine as an example. There are some very notable differences between the α-alanine descriptors and those for charged species that might be suitable models. Both α-alanine and the ethylammonium cation contain the C-NH3⁺ group, and yet A is only 0.28 for α-alanine as against 1.31 for the cation. α-Alanine, betaine, and the acetate ion all contain the C-CO3²⁻ group, and yet B values are 0.83, 2.00, and 2.93, respectively. The hydrogen-bond acidity and hydrogen-bond basicity of α-alanine are far less than expected by comparison to these particular charged species. Alagona et al. have used the Monte Carlo simulation to show that glycine has an intramolecular hydrogen bond and a quantum mechanics, molecular mechanics simulation by Tünón et al. yields a similar result. The existence of an intramolecular hydrogen bond would at least partially explain the relatively small values of A and B for the α-aminoacids. It is interesting that betaine, which would not be expected to have an intramolecular bond, has a much larger value of B than have the α-aminoacids. Tsai et al. have suggested that zwitterionic α-aminoacids are far less hydrophilic than expected from the presence of two charged groups; the small values of A and B would certainly lead to this result. α-Phenylalanine has substantially larger values of A and B than the other aminoacids in Table 14. Possibly, the presence of the phenyl group interrupts the intramolecular bond that reduces the values of A and B in the other α-aminoacids. This interruption results in a B-value just short of that in betaine, which can have no intramolecular bond.

As we have shown, above, the ionic descriptors J' and J'' are very significant for the α-aminoacids, although they are numerically smaller than those for the ionic species EtNH3⁺ and MeCO3⁻. This parallels the situation with the descriptors A and B and suggests again that the charged groups in the α-aminoacids cannot be compared directly with those in typical anionic and cationic species.

A feature of the log P values for the α-aminoacids is that the observed log P is more negative than calculated in mixtures with a high proportion of alcohols and the observed log P is more positive than calculated in mixtures with a high proportion of water. It is worth pointing out that these differences are quite small. For the glycine/methanol/water system, the errors between observed and calculated log P are −0.18 log units (95% methanol) and + 0.06 log units (10% methanol), see Table 4. For methanol itself, observed values of log P range from −2.43 to −2.86, a difference of 0.43 log units, and for ethanol itself, observed values range from −2.56 to −3.90, a difference of no less than 1.34 log units (Table 2). In view of the errors in observed values, we just note the (rather small) variation of log P with alcohol/water content.

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**Notes**
The authors declare no competing financial interest.
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