ELECTROTOPOLOGICAL STATE STUDIES OF COPPER(II) COMPLEXES WITH α-AMINOACIDATES

Edward Cornwell, Guillermo Larrazábal, Antonio Decinti.*

Departamento de Química Inorgánica y Analítica, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Casilla 233, Santiago, Chile. Fax: (562) 7370567

SUMMARY

Descriptor combinations, consisting of the electrotopological state (E-state) indexes of some skeletal groups, the first-order $^1\chi$ molecular connectivity index and the logarithm of the statistical factor, are employed to describe the second stepwise formation constants of binary and ternary copper(II) complexes with α-aminoacidate ligands. Descriptor sets formed by E-state values of skeletal groups belonging to the chelate rings, $^1\chi$ and the logarithm of the statistical factor lead to the best regression equations. Results suggest that differences in stability over the series of metal chelates depend mainly upon variations in the coordination tendency of the carboxylate ligand groups.

Key Words: Copper(II), aminoacidate ligand, electrotopological state, connectivity index, intramolecular hydrophobic interactions.

INTRODUCTION

Although topological indexes derived from the chemical graph theory have been widely used for the modeling of physicochemical and biological properties of organic compounds, at present, little attention has been paid on their possible applications to coordination chemistry. Quantitative structure-stability analyses of metal complexes with organic ligands through graph theoretical indices could contribute to a better understanding of the factors governing the formation of coordination compounds. Thus, for example, it might be expected that noncovalent interactions between coordinated ligands, such as hydrophobic interactions and steric effects, which are recognized to affect the stability of metal chelates [1,2], could be appropriately described by topological indexes encoding structural information about size, shape or branching. In previous reports we have successfully studied the modeling of stability constants of metal complexes of biological interest [3-6] by means of electrotopological state indexes computed from hydrogen-suppressed graphs of the respective free neutral ligands [7,8]. Moreover, for α-aminoacid ligands [6] we have observed significant correlations between the electrotopological state indices of the potential coordinating groups and the hydrophobicity scale of aminoacid side chains [9]. However, in the above mentioned modeling studies somewhat large sets of independent variables were taken relative to the number of available experimental data [3-6], so that the probability of incidence of chance correlations with $r^2 \geq 0.9$ was sometimes up to 6 % [10]. In this work the modeling of the second stepwise formation constants of binary and ternary copper(II) complexes with α-aminoacidate ligands was attempted by using descriptor sets consisting of the electrotopological state indices (E-states) of some selected skeletals groups [7,8] and the first-order $^1\chi$ molecular connectivity index [11]. Both types of descriptors were computed from hydrogen-suppressed graphs of the metal complexes. However, seeing that these studies deal simultaneously with both binary and ternary complexes, the logarithm of the statistical factor (sf) was also included in the descriptor sets [12]. Further, a fitly restricted number of independent variables was considered, so as to keep the probability of occurrence of chance correlations with $r^2 \geq 0.9$ at levels far lesser than 1% [10].

METHOD

Logarithms of the stepwise formation constants $K_{CuAB}{}^{B} = [CuAB]/[CuA][B]$ at 25°C were taken from the literature [2]. In this expression A and B denote aminoacidate ligands, and A = B or A ≠ B for binary and ternary complexes, respectively. The electrotopological states of the skeletal atoms of the [CuAB] complexes were calculated from the appropriate hydrogen-suppressed graphs by means of the expression

$$S_i = I_i + \Delta I_i$$

where I_i is the intrinsic state of atom i and ΔI_i is the perturbation of this atom due to its interactions with the remaining atoms of the molecule [7,8]. Though the metal ion was considered as a vertex in the hydrogen-suppressed graphs, its intrinsic-state value was always set equal to zero because the E-state descriptors have originally been defined for the s-block and p-block elements only [8]. For the remaining skeletal groups the I_i values were calculated through the expression [7,8]

$$I_i = [(2/N)^2\delta^v + 1]/\delta$$

where N is the principal quantum number, and δ^v and δ are the counts of valence electrons and σ electrons respectively, in the skeleton of the metal complex molecule. In turn, δ^v and δ were computed by the equations:

$$\delta^v = Z^v - h \quad \text{and} \quad \delta = \sigma - h$$

where Z^v is the number of valence electrons, σ is the count of electrons in σ orbitals and h is the number of bonded hydrogen atoms. The nonbonded contributions were evaluated by the expression [7,8]

$$\Delta I_i = S_i(I_i - I_j)/(r_{ij})^2$$

where r_{ij} is the count of atoms in the shorter path between atoms i and j, including both i and j (i.e. the graph distance plus one). According to the above quoted definitions, an S_i value encodes both electronic

and topological information because the intrinsic-state I_i reflects the valence-state electronegativity of atom i whereas the perturbation term ΔI_i embodies the influence on such atom by all the other atoms in the molecular skeleton [8]. S_i values for equivalent skeletal groups were added together. First-order $^1\chi$ molecular connectivity indexes for the metal complexes were calculated by the expression [11]:

$$^1\chi = \Sigma\,(\delta_i\delta_j)^{-0.5}$$

where δ is the number of adjacent skeletal groups, i and j correspond to the pairs of adjacent skeletal groups and the summation is over all bonds between skeletal groups. The statistical factor [12] was calculated from the corresponding definition: sf = (r+s)!/r!s!, where r and s are the stoichiometric subscripts in the general formulation $[CuA_rB_s]$. Thus, log(sf) takes the values 0 and log2 for binary and ternary complexes, respectively. Different sets of descriptors, consisting of the ΣS_i values of two or three selected skeletal groups, the $^1\chi$ index and the logarithm of the statistic factor, were alternately correlated with the logarithms of the stepwise formation constants $K_{CuAB}{}^B$. Multiple regression analyses were performed by using the software Origin 4.0 [13] on a DTK 486 computer.

RESULTS AND DISCUSSION

Some of the calculated topological indexes have been collected in Table I. These selected indexes were found to provide the best descriptions of $\log K_{CuAB}{}^B$. In turn, the best four- and five-descriptor combinations were { ΣS(-O-), $\Sigma S(C_1)$, $^1\chi$, log(sf)} and {ΣS(-O-), $\Sigma S(C_1)$, $^1\chi$, $\Sigma S(-NH_2-)$, log(sf)}, respectively. The corresponding regression equations are:

$\log K_{CuAB}{}^B$ = 0.9254 (±0.2219) $\Sigma S(C_1)$ - 0,6451(±0.3011)ΣS(-O-) + 0.2015(±0.0762) $^1\chi$ ···
···+1.4133(±0.1333) log(sf)+12.1403(±2.4004) (1)
r = 0.963 , s = 0.0767 , F = 48

and

$\log K_{CuAB}{}^B$ = 1.8819(±0.4432) $\Sigma S(C_1)$ - 1.0425(±0.4346) $\Sigma S(-NH_2-)$ - 0,4268 (±0.2777)ΣS(-O-) ···
··· + 0.2063(±0.0665) $^1\chi$ + 1.4514(±0.1173) log(sf) + (2)
13.9085 (±2.2178)
r = 0.974 , s = 0.0669 , F = 52

In these expressions the numbers in parentheses are the standard deviations on the respective regression coefficients. From the statistics for the regression equations, it can be noticed that both correlations are significant. In Table II the values calculated through equations 1 and 2 are compared with the experimental $\log K_{CuAB}{}^B$ data taken from ref. 2. As can be seen, discrepancies between the experimental and computed values, expressed as percentage, fall in the ranges 0.00 - 2.02 and 0.00 - 2.17, for equations 1 and 2, respectively. The upper limits of these ranges are smaller than or, at least, similar to the standard errors currently reported for experimental data of formation constants of Cu(II)-aminoacidate complexes [14]. Equations 1 and 2 reasonably suggest that some skeletal groups belonging to the chelate rings are closely related to the internal factors determining the thermodynamic stability of the metal complexes in aqueous solution [12]. Thus, the E-states of -O- and C_1 skeletal groups can be correlated with some thermodynamic parameters which are well recognized to affect such property. Accordingly, the ΣS(-O-) values give a good linear correlation with the hydrophobicity scale of aminoacid side chains [9]. The corresponding regression equation is

$\Sigma\Delta f_t$=4.0209(±0.190)ΣS(-O-)-34.4877(±1.705) (3)
r = 0.981 , s = 0.2859 , F = 448

where $\Sigma\Delta f_t$ is the sum (HA plus HB) of the group contributions to the free energy transfer of aminoacid side chains from 100% organic solvent to water at 25°C [2,9]. The plot of $\Sigma\Delta f_t$ against ΣS(-O-) is shown in Figure I. These results suggest that ΣS(-O-) encodes some information about the contributions of the intramolecular hydrophobic interactions to the stability of the copper(II) complexes herein considered. However, if this statement were accepted, the regression coefficient for ΣS(-O-) would be occurring with a *wrong* sign in both equations 1 and 2. Namely, these equations indicate that $\log K_{CuAB}{}^B$ should decrease as ΣS(-O-) increases. Instead, intramolecular hydrophobic interactions are known to enhance the stability of binary and ternary metal complexes [1,2]. This inconsistency can be ascribed to the fact that the descriptors here used are mutually interdependent, i.e., they are correlated to each other to some extent [15,16]. In fact, ΣS(-O-) values give a significant positive linear correlation with $^1\chi$ values (r = 0.876). Accordingly, if $\log K_{CuAB}{}^B$ is correlated with the set {$\Sigma S(C_1)$, ΣS(-O-), $\Sigma S(-NH_2-)$, log(sf)}, i.e., if $^1\chi$ is *removed* from equation 2, the regression coefficient of ΣS(-O-) occurs with a positive sign in the resulting regression equation

$\log K_{CuAB}{}^B$ = 1.2935(±0.5028)$\Sigma S(C_1)$ - 1.0020(±0.5453) $\Sigma S(-NH_2-)$ + 0,3643(±0.1384)ΣS(-O-) ···
··· + 1.5606(±0.1404)log(sf) + 7.5203(±1.0368)
r = 0.956 , s = 0.084 , F = 39

In order to discern the true contribution of ΣS(-O-) to $\log K_{CuAB}{}^B$, the descriptors involved in equations 1 and 2 were further subjected to orthogonalization [15,16]. In such process, ΣS(-O-) was taken as the first orthogonal descriptor (W_1). The resulting regression equations are

$\log K_{CuAB}{}^B = 0.5624\Omega_1 + 0.2100\Omega_2 + 0.4497\Omega_3 + 1.4133\Omega_4 + 4.9642$

and

$\log K_{CuAB}{}^B = 0.5624\Omega_1 + 0.2100\Omega_2 + 0.4497\Omega_3 + 1.4133\Omega_4 - 1.0425\Omega_5 + 4.9642$

respectively.

As it can be realized from these equations, $\log K_{CuAB}{}^B$ indeed increases as ΣS(-O-) increases, in accordance with the observed correlation between ΣS(-O-) and the hydrophobicity scale of aminoacid side chains.

Orthogonalization processes taking successively $\Sigma S(C_1)$, $^1\chi$ and $\Sigma S(-NH_2-)$ as first orthogonal descriptors, indicate that $\log K_{CuAB}{}^B$ is directly proportional to each one of these indexes.

The occurrence of a good linear correlation between ΣS(-O-) and $\Sigma\Delta f_t$ is rather surprising considering that it has been shown previously that, for alkyl ethers, the E-state values of bridging oxygen S(-O-) give a good linear correlation with the oxygen partial charges computed by the STO-3G method [7]. Moreover, among the remaining indexes, only $^1\chi$ gives a somewhat significant linear correlation with $\Sigma\Delta f_t$, though being rather poorer than that obtained with ΣS(-O-):

$\Sigma\Delta f_t$ = 0.9148 $^1\chi$ - 4.7276 ; r = 0.815, s = 0.842, F = 36 (compare with equation 3)

The best descriptions of $\Sigma\Delta f_t$ by means of two-index sets were

found to be

$$\Sigma\Delta f_t = 3.7732(\pm0.1538)\Sigma S(\text{-O-}) + 0.9486(\pm0.2384)\Sigma S(C_1) - 31.3276(\pm1.4917) \quad (4)$$

$r = 0.990$, $s = 0.2117$, $F = 417$

and

$$\Sigma\Delta f_t = 0.9456(\pm0.0375)\,{}^1\chi + 3.5786(\pm0.2125)\Sigma S(C_1) - 1.4035(\pm0.3286) \quad (5)$$

$r = 0.990$, $s = 0.2174$, $F = 440$

The statistical parameters for these regression equations indicate that both correlations are highly significant. As it can be realized, these descriptions also involve E-states of skeletal groups belonging to the carboxylate ligand group. Moreover, according to equation 5, $\Sigma S(C_1)$ and ${}^1\chi$ should be encoding complementary structural information about $\Sigma\Delta f_t$.

On the other hand, the two-descriptor set containing the E-state values for -O- and C_1 skeletal groups was also found to correlate significantly with the ligand basicities through pK_{a1} and the pH at the isoelectric point, $pI = 1/2(pK_{a1} + pK_{a2})$. Here, thermodynamic values for pK_{a1} and pK_{a2} were considered [14]. The respective regression equations are:

$$pK_{a1}{}^{av} = 1/2[pK_{a1}(H_2A^+) + pK_{a1}(H_2B^+)]$$
$$= 0.3600(\pm0.0231)\Sigma S(C_1) - 0.1089(\pm0.0149)\Sigma S(\text{-O-}) + 3.5755(\pm0.1445) \quad (6)$$

$r = 0.967$, $s = 0:0205$, $F = 122$

$$pI^{av} = \_[pI(HA) + pI(HB)]$$
$$= 0.7437(\pm0.0427)\Sigma S(C_1) - 0.2130(\pm0.0275)\Sigma S(\text{-O-}) + 8.5065(\pm0.2668) \quad (7)$$

$r = 0.973$, $s = 0.0379$, $F = 152$

In both expressions the superscript *av* stands for the average property of the aminoacids HA and HB, as explicitly shown. The statistics for these regression equations indicates that both correlations are fairly significant. In Table 3 the calculated $pK_{a1}{}^{av}$ and pI^{av} values are compared with the corresponding thermodynamic data. In equations 6 and 7 the parameter $\Sigma S(C_1)$ would be reflecting partly the average electron density on the carboxylate ligand groups [7]. Accordingly, from orthogonalization of the descriptors involved in these equations, taking $\Sigma S(C_1)$ as the first orthogonal descriptor, it can be realized that both $pK_{a1}{}^{av}$ and pI^{av} increase as a function of $\Sigma S(C_1)$. This could be related to an increase in the average basicity of the carboxylate ligand groups and, hence, to an increase in $\log K_{CuAB}{}^{B}$ [17].

It should be pointed out that even using $\Sigma S(C_1)$ as a single descriptor of $pK_{a1}{}^{av}$ and pI^{av}, the resulting correlations are still somewhat significant, being characterized by correlation coefficients of 0.853 and 0.872, respectively.

The set of descriptors $\{\Sigma S(\text{-}NH_2\text{-}), \Sigma S(\text{-O-})\}$ was also found to give a rather significant correlation with the pI^{av} values, the corresponding statistical parameters being $r = 0.958$, $s = 0.0473$, $F = 94$. However, as can be noticed, such a correlation is rather poorer than the one obtained by the $\{\Sigma S(C_1), \Sigma S(\text{-O-})\}$ descriptor set (see equation 7). Good linear correlations between $\log K_{CuAB}{}^{B}$ and $(pK_{a1} + pK_{a2})$ have previously been reported for $[Cu(2,2'\text{-bipyridine})(\text{aminoacidate})]^{q+}$ ternary complexes [18]. Such results provide some support to the reliability of the relationships, found in this study, between the above mentioned two-descriptor sets and the thermodynamic $pK_{a1}{}^{av}$ and pI^{av} data.

Since the second stepwise ionization of aminoacids involves deprotonation of an NH_3^+ group, it could be expected $\Sigma S(\text{-}NH_2\text{-})$ to give a good correlation with $1/2[pK_{a2}(HA) + pK_{a2}(HB)]$. Indeed, this was not observed. Instead, $\Sigma S(\text{-}NH_2\text{-})$ was found to give a significant correlation with $\Sigma S(C_1)$, the corresponding correlation coefficient being $r = 0.945$.

In spite of this interdependence, description of $\log K_{CuAB}{}^{B}$ notedly impairs with respect to equation 2 on replacing $\Sigma S(\text{-}NH_2\text{-})$ by the E-states of other skeletal groups, such as $\Sigma S(\text{-OH})$, ($r = 0.965$, $F = 38$), or $\Sigma S(C_2)$, ($r = 0.964$, $F = 37$).

On the other hand, when binary and ternary complexes are separately considered, $\Sigma S(\text{-}NH_2\text{-})$ values give moderately significant positive correlations with the logarithms of the second stepwise formation constants of both series of metal complexes. The corresponding correlation coefficients are 0.889 and 0.811, for binary and ternary complexes, respectively. As it should be expected, $\Sigma S(C_1)$ values also give significant positive correlations with both series of experimental data, the correlation coefficients being 0.901 and 0.803, for binary and ternary complexes, respectively. Though being of moderate quality, these results allow us to realize the role of log(sf) in equations 1 and 2. Thus, this descriptor would encode structural information which is appropriate to unite the binary and ternary complexes in the above mentioned equations. In fact, if the index log(sf) is removed from the descriptor set leading to equation 2, the statistical parameters of the resulting regression equation turn out to be: $r = 0.621$, $s = 0.2233$, $F = 2.4$, i.e., poorer than those of equation 1. It has to be borne in mind that the latter equation also arises from a correlation between $\log K_{CuAB}{}^{B}$ and a four-descriptor set.

It has been pointed out recently that molecular connectivity index ${}^1\chi$ can be interpreted as the encoding of intermolecular accessibility, i.e., as the contribution of one molecule to bimolecular interactions arising from encounters of bonds among two molecules [19]. In the present study, as previously stated, the index ${}^1\chi$ was found to give a moderately significant correlation with the $\Sigma\Delta f_t$ scale. Thus, in equations 1 and 2 the molecular connectivity index seems to be merely encoding structural information about molecular size and shape, which would be relevant to characterize the contributions of intramolecular hydrophobic interactions to the stability of the copper(II) complexes herein studied.

The fact that the correlation between ${}^1\chi$ and $\Sigma\Delta f_t$ is only of moderate quality can be ascribed to the presence of polar substituents in the side chains of some aminoacidate ligands (-OH groups). In fact, if ${}^1\chi$ values for metal complexes containing aminoacidate ligands with apolar side chains are separately correlated with the hydrophobicity scale, a fairly good regression equation results: $\Sigma\Delta f_t = 1.0003\,{}^1\chi - 4.4523$; $r = 0.996$, $s = 0.1415$, $F = 596$, $n = 7$. Similarly, for copper(II) complexes containing a single hydroxyl substituent, for example A = gly and B = ser, a rather significant correlation between ${}^1\chi$ and $\Sigma\Delta f_t$ is obtained: $r = 0.984$, $s = 0.2753$, $F = 207$, $n = 9$. In turn, for complexes with two hydroxyl substituents, e.g. A = B = ser, correlation of $\Sigma\Delta f_t$ vs ${}^1\chi$ results also to be highly significant: $r = 0.993$, $s = 0.1984$, $F = 152$, $n = 4$.

Some conclusions can be drawn from the structure-property relationships found in the present study, mainly with regard to the leading role of $\Sigma S(\text{-O-})$ and $\Sigma S(C_1)$ in the description of $\log K_{CuAB}{}^{B}$. So, according to equations 3-5, the stability enhancement arising from the intramolecular hydrophobic interaction would operate mainly through the Cu(II)-O(carboxylate) bonds, i.e., through an increase in the strength

of the coordinate bonds bearing a greater degree of ionic character. This proposal would agree with a view of such interactions as solvent structure-enforced ion-pairing type contributions. In turn, the latter would account for the role of $^1\chi$ in equations 1, 2 and 5. Moreover, equations 6 and 7 suggest that the contributions of the ligand basicities, as determining factors for the differences in $\log K_{CuAB}{}^{B}$ over the series of binary and ternary complexes, can be connected mainly with changes in the basicities of the carboxylate groups. Thus, although the amino group should make a greater contribution to the ligand polarizability than carboxylate [20], the latter group might be more sensitive to undergo changes in polarizability under the influence of differential σ-electronic effects arising from structural modifications of the side chain.

Finally, when binary and ternary complexes are simultaneously considered, inclusion of log(sf) in the descriptor sets appears to be essential to achieve an appropriate modeling of $\log K_{CuAB}{}^{B}$.

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CAPTIONS TO TABLES

Table 1: Electrotopological state values for some selected skeletal groups[a] and first-order connectivity indexes for binary and ternary copper(II) complexes with a-aminoacidate ligands.[b]

	[CuAB] A	B	ΣS(-O-)	ΣS(C_t)	ΣS(C_2)	ΣS(-NH_2-)	ΣS(-OH)	$^1\chi$
1	Ser	Ser	8.578	-1.368	-1.592	2.270	17.286	6.453
2	Thr	Thr	8.816	-1.377	-1.674	2.320	18.363	7.198
3	Ala	Ala	8.815	-0.789	-0.642	2.841	0	5.377
4	Val	Val	9.358	-0.714	-0.622	3.042	0	7.198
5	Gly	Gly	8.449	-0.793	0.368	2.736	0	4.536
6	Thr	Ser	8.697	-1.373	-1.633	2.295	17.825	6.826
7	Leu	Leu	9.500	-0.669	-0.573	3.112	0	8.165
8	Phe	Ser	9.167	-1.083	-1.221	2.786	8.746	8.010
9	Ser	Gly	8.514	-1.081	-0.604	2.503	8.570	5.494
10	Ala	Gly	8.626	-0.791	-0.132	2.876	0	4.956
11	Ser	Ala	8.697	-1.079	-1.117	2.555	8.635	5.915
12	Thr	Ala	8.815	-1.083	-1.158	2.581	9.122	6.288
13	Thr	Gly	8.633	-1.085	-0.642	2.528	9.056	5.867
14	Phe	Thr	9.358	-1.088	-1.262	2.650	9.357	8.383
15	Tyr	Thr	9.239	-1.181	-1.384	2.595	18.562	8.793
16	Phe	Ala	9.286	-0.793	-0.746	2.947	0	7.472
17	Tyr	Ala	9.238	-0.887	-0.867	2.855	9.175	7.883
18	Tyr	Gly	9.055	-0.889	-0.342	2.803	9.145	7.462
19	Phe	Gly	9.102	-0.796	-0.222	2.894	0	7.051
20	Tyr	Val	9.510	-0.849	-0.858	2.956	9.227	8.793

[a] (-O-), coordinating oxygen; (C_t), carboxylate carbon; (C_2), α-carbon; (-NH_2) coordinating amino group; (-OH), hydroxyl substituent on aminoacidate side chain.
[b] Gly, glycinate; Ala, alaninate; Ser, serinate; Thr, threoninate; Val, valinate; Leu, leucinate; Phe, phenylalaninate; Tyr, tyrosinate.

Table 2: Comparison between the experimental $\log K_{CuAB}{}^{B}$ data and the values calculated with Equations 1 and 2.

[CuAB] A	B	$\log K_{CuAB}{}^{B}$ exp	Equation 1 $\log K_{CuAB}{}^{B}$ calc	residue exp - calc	error %	Equation 2 $\log K_{CuAB}{}^{B}$ calc	residue exp - calc	error %
Ser	Ser	6.64	6.64	0.00	0.00	6.64	0.00	0.00
Thr	Thr	6.74	6.63	0.11	1.63	6.62	0.12	1.78
Ala	Ala	6.81	6.81	0.00	0.00	6.81	0.00	0.00
Val	Val	6.86	6.89	-0.03	0.44	6.88	-0.02	0.29
Gly	Gly	6.89	6.87	0.02	0.29	6.89	0.00	0.00
Thr	Ser	6.92	7.06	-0.14	2.02	7.07	-0.15	2.17
Leu	Leu	6.94	7.04	-0.10	1.44	7.04	-0.10	1.44
Phe	Ser	7.14	7.26	-0.12	1.68	7.14	0.00	0.00
Ser	Gly	7.17	7.18	-0.01	0.14	7.20	-0.03	0.42
Ala	Gly	7.18	7.27	-0.09	1.25	7.20	-0.02	0.28
Ser	Ala	7.19	7.15	0.04	0.56	7.16	0.03	0.42
Thr	Ala	7.20	7.14	0.06	0.83	7.15	0.05	0.69
Thr	Gly	7.21	7.17	0.04	0.55	7.19	0.02	0.28
Phe	Thr	7.23	7.21	0.02	0.28	7.27	-0.04	0.55
Tyr	Thr	7.25	7.28	-0.03	0.41	7.29	-0.04	0.55
Phe	Ala	7.38	7.35	0.03	0.41	7.36	0.02	0.27
Tyr	Ala	7.42	7.37	0.05	0.67	7.38	0.04	0.54
Tyr	Gly	7.43	7.41	0.02	0.27	7.42	0.01	0.13
Phe	Gly	7.44	7.38	0.06	0.81	7.40	0.04	0.54
Tyr	Val	7.50	7.42	0.08	1.07	7.42	0.08	1.07

Table 3: Comparison between the thermodynamic pK_{a1}^{av} and pI^{av} data and the values calculated with Equations 6 and 7, respectively.

[CuAB]		Equation 6				Equation 7			
		pK_{a1}^{av}		residue	error	pI^{av}		residue	error
A	B	obs	calc	obs-calc	%	obs	calc	obs-calc	%
Ser	Ser	2.187	2.149	0.038	1.74	5.698	5.662	0.036	0.63
Thr	Thr	2.088	2.120	-0.032	1.53	5.594	5.605	-0.011	0.20
Ala	Ala	2.347	2.332	0.015	0.64	6.108	6.042	0.066	1.08
Val	Val	2.286	2.299	-0.013	0.57	6.002	5.982	0.020	0.33
Gly	Gly	2.350	2.370	-0.020	0.85	6.064	6.117	-0.053	0.87
Thr	Ser	2.138	2.134	0.004	0.19	5.646	5.633	0.013	0.23
Leu	Leu	2.329	2.300	0.029	1.25	6.038	5.986	0.052	0.86
Phe	Ser	2.194	2.187	0.007	0.32	5.727	5.749	-0.022	0.38
Ser	Gly	2.269	2.259	0.010	0.44	5.881	5.889	-0.008	0.14
Ala	Gly	2.349	2.351	-0.002	0.09	6.086	6.081	0.005	0.08
Ser	Ala	2.268	2.240	0.028	1.23	5.903	5.852	0.051	0.86
Thr	Ala	2.218	2.226	-0.008	0.36	5.851	5.824	0.027	0.46
Thr	Gly	2.219	2.245	-0.026	1.17	5.829	5.861	-0.032	0.55
Phe	Thr	2.144	2.165	-0.021	0.98	5.675	5.704	-0.029	0.51
Tyr	Thr	2.139	2.144	-0.005	0.23	5.642	5.660	-0.018	0.32
Phe	Ala	2.274	2.279	-0.005	0.22	5.932	5.939	-0.007	0.12
Tyr	Ala	2.269	2.250	0.019	0.84	5.899	5.879	0.020	0.34
Tyr	Gly	2.270	2.269	0.001	0.04	5.877	5.917	-0.040	0.68
Phe	Gly	2.275	2.298	-0.023	1.01	5.910	5.976	-0.066	1.12
Tyr	Val	2.238	2.234	0.004	0.18	5.846	5.850	-0.004	0.07

CAPTIONS TO FIGURES

Fig. 1: Correlation between ΣS(-O-) and the hydrophobicity scale for aminoacid side chains, $\Sigma\Delta f_t$ (kcal mol^{-1}). Numbers refer to compounds in Table 1.