Investigación

Electropological State Studies of Nickel(II) Complexes with a-Aminoacidates

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Abstract: The electrotopological states of a series of α-aminoacids are calculated. The resulting indices are correlated with the logarithms of the stepwise formation constants K_1 and K_2 of the respective nickel(II)-aminoacidate complexes by using multiple linear regression analysis. Good correlation equations are obtained for both stepwise formation constant series. A reduction in the number of descriptors by combining the electrotopological states of the potential ligands groups with first- order $^1\chi^v$ molecular connectivity indices is also attempted.

Keywords: Electrotopological state, connectivity index, noncovalent interaction, nickel, aminoacidate.

Resumen: Se calcularon los estados electrotopológicos de una serie de aminoácidos. Los índices resultantes se correlacionaron con los logaritmos de las constantes de formación parciales K_1 y K_2 de los respectivos complejos niquel (II)-aminoacidatos, mediante análisis de regresión múltiple. Se obtienen buenas ecuaciones de correlación para ambas series de constantes de formación parcial. Se intentó también una reducción en el número de descriptores, combinando los estados electrotopológicos de los grupos potencialmente ligantes con los índices de conectividad molecular de primer orden $^1\chi^v$.

Palabras clave: Estado electrotopológico, índice de conectividad, interacción no covalente, niquel, aminoacidato.

Introduction

The interactions between α-aminoacids and metal ions have been extensively studied as primary models for metalloproteins and metal-protein reactions [1-3]. An essential step for the quantitative description of these interactions deals with the measurement of thermodynamic stability constants, or stoichiometric stability constants if activity-coefficients are not available [4,5]. A linear relationship between the logarithm of the formation constant (log K_n) and the polarizing effect of the metal ion has been developed through semi-empirical analysis of the structural factors determining the stability of metal complexes [6]. Simplified applications of the above relationship, in which log K_n values of ML or ML_2 metal complexes of a given ligand are correlated with log K_n values of similar complexes of another ligand, have succeeded in predicting unknown stability constants by interpolation or extrapolation [6]. On the other hand, good correlations have been observed between log K_n values and ligand basicities in aqueous solution (pK_a) over series of ML complexes of a same metal ion [7]. However, such correlations are only successful for ligands very close in structure. For ligands having the same donor groups but different structure, e.g. aminoacidates with side chains having different shape, polarity, or types of bonds, pK_a behaves as a rather poor descriptor [7]. In such cases electrotopological information could be useful to account for the structural features and noncovalent interactions which are determinant for the trend of formation constant values observed over a given series of metal complexes. In the present study, electrotopological states [8-10] are calculated for a series of monocarboxylic α-aminoacids in their classical molecular formulations, and the values thus obtained are correlated with the logarithms of the stepwise formation constants K_1 and K_2 of the respective nickel(II)-aminoacidate complexes.

Method

Logarithms of the stepwise formation constants K_1 and K_2 of nickel(II) complexes at 25 °C and ionic strength 0.1 or 0.05 were taken from the literature [11]. The log K_n data given at ionic strength 0.05 were corrected to 0.1 by using the Davies equation [12]. The electrotopological states of the skeleton atoms of each aminoacid were calculated by means of the expression [8,9]:

$$S_i = I_i + DI_i$$

where I_i is the intrinsic state of atom i and DI_i is the perturbation of this atom due to its interactions with the remaining atoms of the molecule. I_i values were calculated through the expression [8,9]:

$$I_i = [\,(2 / N)^2 d^{\,V} + 1\,] / \delta$$

where N is the principal quantum number, and d^V and d are the counts of valence electrons and σ electrons, respectively, in the skeleton of the aminoacid molecule. In turn, d^V and d were computed by the equations: $d^V = Z^V - h$ and $d = s - h$ where Z^V is the number of valence electrons, s 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 [8,9]:

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

where r_{ij} is the count of atoms in the shorter path between atoms i and j, including both y and j (i.e. the graph distance plus one). According to the above definitions, an Si 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 themolecular skeleton [8]. Si values for equivalent skeletal groups were added together. The resulting basis of ΣS_i values was alternately correlated with the logarithms of the stepwise formation constants K_1 and K_2 of the respective nickel(II)-aminoacidate complexes. First-order $^1\chi^v$ molecular connectivity indices [15] for the different aminoacids were also calculated. Multiple regression analyses were performed by using the software Origin 4.0 [13]. Percentages of error were calculated by means of the software Excel 5.0 [14]. Both types of calculations were made on a DTK 486 computer.

Results and Discussion

The calculated ΣS_i values for the skeletal groups of the α-aminoacids considered in this study are given in Table 1. Discussion on the significance of the magnitude and sign of the electrotopological-state values has been already given in the literature [8]. The regression equation between the ΣS_i values and the experimental log K_1 values of nickel(II)-amino-acidate complexes turns out to be

$$\log K_1 = 0.2286 (\pm 0.0638) [\text{-CH}_3] + 0.1202 (\pm 0.0497) [\text{-CH}_2\text{-}] + 0.0941 (\pm 0.0857) [\text{>CH-}] + 2.8450 (\pm 1.5021) [\text{>C=}] - 0.5792 (\pm 0.4484) [\text{=O}] + 0.1143 (\pm 0.0388) [\text{-OH}] - 1.4839 (\pm 0.7810) [\text{-NH}_2] - 0.1846 (\pm 0.1278) [\text{>C=(ph)}] + 0.1762 (\pm 0.1153) [\text{>C<}] + 0.0341 (\pm 0.0499) [\text{-S-}] + 19.8143 (\pm 4.0490) \quad \text{[I]}$$

the correlation coefficient and the standard deviation being r = 0.9814 and sd = 0.0597, respectively.

In turn, multiple linear regression analysis between the ΣS_i values and the experimental log K_2 values of nickel(II)-aminoacidate complexes gives the regression equation

$$\log K_2 = 0.1196 (\pm 0.0510) [\text{-CH}_3] + 0.1306 (\pm 0.0397) [\text{-CH}_2\text{-}] - 0.0596 (\pm 0.0685) [\text{>CH-}] + 3.1843 (\pm 1.2008) [\text{>C=}] - 0.4069 (\pm 0.3584) [\text{=O}] + 0.0975 (\pm 0.0310) [\text{-OH}] - 1.4803 (\pm 0.6243) [\text{-NH}_2] - 0.2190 (\pm 0.1022) [\text{>C=(ph)}] - 0.0609 (\pm 0.0922) [\text{>C<}] + 0.2357 (\pm 0.0399) [\text{-S-}] + 17.6862 (\pm 3.2367) \quad \text{[II]}$$

Here, the correlation coefficient and the standard deviation turn out to be r = 0.9864 and sd = 0.0477, respectively. From the above results it may be realized that the electrotopological state indices give reasonably good correlation equations with both log K_1 and log K_2 experimental data. Both multiple regression analyses [I] and [II] were further orthogonalized in order to obtain regression equations with mutually independent coefficients. However, the corresponding results were not included in this paper because they rather contribute to make more difficult the structural interpretation of the electrotopological-state values and their respective coefficients in the regression equations [16]. On the other hand, on substituting the ΣS_i values in both equations [I] and [II] it can be realized that the main contributions to log K_n arise from the potential ligand groups =O and -NH_2. The fact that the coefficients for these groups give negative contributions to log K_n agrees with the expected dependence of their donor properties as a function of the electronegativity. In turn, both the

Table 1. Electrotopological-State values for some α-aminoacids.

Aminoacids	-CH_3	>CH_2	>CH-	=C<	=O	-OH	-NH_2	>C=	>C< (ph)	-S-
Phenylalanine	0.0000	0.3855	–0.7990	–0.0058	10.3780	8.5180	5.3487	9.3418	0.0000	0.0000
2-amino-2-methylpropanoic	2.8800	0.0000	0.0000	–0.9783	9.8953	8.1249	5.0782	0.0000	–1.0830	0.0000
Methionine	1.9251	1.3656	–0.6831	–0.9117	10.0700	8.2742	5.1894	0.0000	0.0000	1.6033
2-amino-3(methylthio)propanoic	1.8222	0.4819	–0.7041	–0.9302	9.9504	8.1743	5.1065	0.0000	0.0000	1.4317
2-aminobutanoic	1.7350	0.4950	–0.6810	–0.9275	9.8051	8.0569	5.0161	0.0000	0.0000	0.0000
Norvaline	1.9056	1.3922	–0.6670	–0.9095	9.9638	8.1880	5.1273	0.0000	0.0000	0.0000
Norleucine	2.0085	2.4869	–0.6626	–0.8988	10.0798	8.2834	5.2028	0.0000	0.0000	0.0000
Alanine	1.4190	0.0000	–0.7310	–0.9630	9.7541	7.8660	4.8360	0.0000	0.0000	0.0000
Isoleucine	3.7562	0.8131	–0.6284	–0.9117	10.1743	8.3583	5.2709	0.0000	0.0000	0.0000
Valine	3.5530	0.0000	–0.6930	–0.9296	10.0150	8.2272	5.1597	0.0000	0.0000	0.0000
Leucine	3.8945	0.5513	–0.3328	–0.9128	10.1093	8.3056	5.2177	0.0000	0.0000	0.0000
Serine	0.0000	–0.5040	–1.1254	–1.1770	9.6451	15.8959	4.7661	0.0000	0.0000	0.0000
Threonine	1.3322	0.0000	–2.1379	–1.1796	9.8556	16.5527	4.9100	0.0000	0.0000	0.0000
Homoserine	0.0000	–0.0525	–0.9172	–1.0695	9.8528	16.2191	4.9673	0.0000	0.0000	0.0000
Glycine	0.0000	–0.2781	0.0000	–0.9670	9.2429	7.5972	4.5117	0.0000	0.0000	0.0000

Table 2. Logarithms of the stepwise stability constants of nickel(II) aminoacidate complexes modeled with electrotopological state indices.

Aminoacid	log K_1			log K_2		
	Exp.	Calc.	Error %	Exp.	Calc.	Error %
Phenylalanine	5.07	5.07	0.00	4.41	4.41	0.00
2-amino-2-methylpropanoic	5.16	5.16	0.00	4.23	4.23	0.00
Methionine	5.19	5.23	0.77	4.65	4.64	0.22
2-amino-3(methylthio)propanoic	5.26	5.22	0.76	4.56	4.57	0.22
2-aminobutanoic	5.29	5.36	1.32	4.37	4.42	1.14
Norvaline	5.35	5.32	0.56	4.42	4.39	0.68
Norleucine	5.35	5.34	0.19	4.42	4.43	0.23
Alanine	5.40	5.40	0.00	4.47	4.47	0.00
Isoleucine	5.40	5.36	0.74	4.30	4.25	1.16
Valine	5.42	5.40	0.37	4.30	4.28	0.47
Leucine	5.45	5.49	0.73	4.26	4.31	1.17
Serine	5.45	5.46	0.18	4.51	4.51	0.00
Threonine	5.46	5.46	0.00	4.55	4.55	0.00
Homoserine	5.46	5.45	0.18	4.55	4.55	0.00
Glycine	5.78	5.76	0.35	4.80	4.78	0.42

decrease in the contribution of the group $-CH_3$ and the increase in the contribution of the group $-CH_2-$, when passing from equation [I] to equation [II], would be related to a greater influence of the hydrophobic interactions on the stability of the bis-aminoacidate complexes [17]. Experimental values of the logarithms of the stepwise formation constants of the nickel complexes are listed in Table 2 together with the values calculated with the respective regression equations [I] and [II]. Relative errors expressed as percentages are also therein included. As can be seen, there is a good agreement between the experimental and the calculated values for both log K_1 and log K_2, in spite of the rather restricted range of variarion of these parameters through the series of metal complexes. This fact would be of interest from the viewpoint of the chemical significance of the electrotopological state indices since K_1 and K_2 exhibit different dependences upon the side chain features. Thus, the experimental values of K_1 are roughly in the sequence glycine > hydroxylated > branched aliphatic > normal aliphatic > thiomethylated > 2-amino-2-methylpropanoic > phenylalanine. Instead, the experimental values of K_2 are roughly in the series glycine > thiomethylated > hydroxylated > normal aliphatic ≈ phenylalanine > branched aliphatic > 2-amino-2-methylpropanoic. The changes in position of the aromatic, thiomethylated and normal aliphatic aminoacids when passing from the sequence of K_1 values to that of K_2 values would be partly ascribed to additional stabilizing effects arising from the occurrence of intramolecular hydrophobic interactions in the bis-aminoacidate complexes [17]. Hence, as previously suggested, it could be assumed that electrotopological state indices are also reflecting the contributions of the hydrophobic interactions to the stability of 1:2 complexes. In fact, a rather acceptable correlation is observed between the electrotopological state indices of the potential coordinating groups of the aminoacids and the hydrophobicity scale [18]. Thus, considering the sequence: phenylalanine, norleucine, leucine, valine, methionine, alanine, threonine and serine, regression analysis for the correlation between $S(NH_2)$ and Δf_t (the group contribution to the free energy of transfer [18] gives the regression equation

$$S(-NH_2) = 0.1908\ [\Delta f_t] + 4.8332$$

The correlation coefficient and the standard deviation for the above correlation are r = 0.9316 and sd = 0.0828, respectively. In turn, regression analysis for the correlation between S(=O) and Δf_t gives the equation

$$S(=O) = 0.2030\ [\Delta f_t] + 9.7270$$

for which r = 0.9067 and sd = 0.1051. Since $S(-NH_2)$ and S(=O) refer specifically to the potential ligand groups, these results suggest that the perturbation terms ΔI_i, which account for the nonbonded contributions to S_i, are also embodying some information concerning the hydrophobicities of the side chains of the aminoacids.

On the other hand, the possibility that good results obtained with the electrotopological state model (Table 2) were mainly due to the relatively great number of descriptors considered in the respective regression analyses should not be overlooked [16]. In fact, when singly considered, the electrotopological state indices of the potential coordinating groups ($-NH_2$ and =O) behave as bad descriptors for both log K_1 and log K_2. However, multiple linear regression analysis for the correlation between the log K_1 or log K_2 values and the set of descriptors $S(-NH_2)$, S(=O) and $^1\chi^V$ gives significant results, especially in the case of log K_2:

$$\log K_1 = -0.0238\ [^1\chi^V] + 0.0141\ [-NH_2] - 0.4163\ [=O] + 9.4857 \quad [III]$$

r = 0.7373 and sd = 0.1267

Table 3. Logarithms of the stepwise stability constants of nickel(II) aminoacidate complexes modeled with S[-NH_2], S[=O] and first-order $^1\chi^v$ molecular connectivity indices.

Aminoacidate	log K_1				log K_2		
	$^1\chi^v$	Exp.	Calc.	Error	Exp. %	Calc.	Error %
Phenylalanine	3.72222	5.07	5.24	3.37	4.23	4.26	0.74
2-amino-2-methylpropanoic	1.96641	5.16	5.44	5.39	4.26	4.34	1.97
Methionine	4.04355	5.19	5.37	3.41	4.30	4.30	0.03
2-amino-3(methylthio)propanoic	3.54355	5.26	5.42	2.95	4.30	4.29	0.27
2-aminobutanoic	2.16509	5.29	5.47	3.49	4.37	4.39	0.55
Norvaline	3.16509	5.35	5.36	0.24	4.41	4.34	1.52
Norleucine	2.66509	5.35	5.41	1.12	4.42	4.40	0.43
Alanine	1.62709	5.40	5.49	1.73	4.42	4.37	1.03
Isoleucine	3.07578	5.40	5.32	1.40	4.47	4.48	0.21
Valine	2.53777	5.42	5.39	0.57	4.51	4.61	2.22
Leucine	3.02094	5.45	5.54	1.61	4.55	4.53	0.38
Serine	1.77422	5.45	5.35	1.82	4.55	4.48	1.60
Threonine	2.21862	5.46	5.45	0.14	4.56	4.62	1.41
Homoserine	2.27422	5.46	5.45	0.11	4.65	4.64	0.17
Glycine	1.18953	5.78	5.70	1.34	4.80	4.73	1.50

$$\log K_2 = 0.2547\ [^1\chi^V] - 1.2123\ [\text{-NH}_2] - 0.0778\ [\text{=O}] + 10.6862 \quad [IV]$$
$$r = 0.9377 \text{ and } sd = 0.0609$$

In Table 3 the values of the logarithms of the stepwise formation constants of the nickel complexes calculated by means of regression equations [III] and [IV] are compared with the respective experimental data. Relative errors expressed as percentages are also therein included. The above results suggest that it would be interesting to search for alternative approaches involving a reduction in the number of electrotopological descriptors. Such search could be started, for instance, by including the metal ion as skeletal group in the molecular graphs, to afterwards try the electrotopological states of the donor atoms and the term of perturbation of the graph field over the metal ion as the only descriptors. In this way there would be available two separate sets of descriptors, one for log K_1 and another for log K_2, which would better represent the structural characteristics of the respective metal complexes. This possibility will be considered in future studies.

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References

1. Freeman, H. C., in: *Inorganic Biochemistry*; Chapter 4, Eichhorn, G. L., Ed., Elsevier Scientific Publishing Company: Amsterdam, 1975, 121.
2. Baidya, N.; Ndreu, D.; Olmstead, M. M.; Mascharak, P.K. *Inorg.Chem.* **1991**, *30*, 2448-2451.
3. El-Shahawi, M. S. *Transition Met. Chem.* **1993**, *18*, 385-390.
4. Lomozik, L.; Wojciechowska, A.; Jaskolski M. *Monatsh. Chem.* **1982**, *114*, 1185-1189.
5. Blais, M.-J.; Kayali, A.; Berthon, G. *Inorg. Chim. Acta* **1981**, *56*, 5-14.
6. Yatsimirskii, K. B.; Vasil'ev, V. P. *Instability Constants of Complex Compounds*, Chapter 4, Pergamon Press, New York, 1960, 70-74.
7. Angelici, R. J., in: *Inorganic Biochemistry*; Chapter 2, Eichhorn G. L., Ed.; Ersevier Scientific Publishing Company, Amsterdam, 1975, 76-78.
8. Hall, L. H.; Mohney, B.; Kier, L. B. *J. Chem. Inf. Comput. Sci.* **1991**, *31*, 76-82.
9. Hall, L. H.; Kier, L. B. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 1039-1045.
10. Hall, L. H.; Kier, L. B.; Brown, B. B. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 1074-1080.
11. Martell, E; Smith, R.M. *Critical Stability Constants*, Vol. 1, Ed. Plenum Press: New York, 1974.
12. Davies, C.W., *Ion Association*, Chapter 3, Butterworths: London, 1962, 41.
13. Microcal Origin 4.00, Copyright 1991-1995. Microcal Software, Inc. One Rundhouse Plaza. Northampton, MA 01060. USA.
14. Microsoft Excel 5.0. Copyright 1885-1994. Microsoft Corporation.
15. Sabljic, A.; Horvatic, D. *J. Chem. Inf. Comput. Sci.* **1993**, *33*, 292-295.
16. Randic, M. *J. Chem. Inf. Comput. Sci.* **1997**, *37*, 672-687.
17. Tabata, M.; Tanaka, M. *Inorg. Chem.* **1988**, *27*, 3190-3192.
18. Nozaki Y.; Tanford, C. *J. Biol. Chem.* **1971**, *246*, 2211-2217.