CHROM. 5432

Ligand chromatography as a novel method for the investigation of mixed complexes: stereoselective effects in α-amino acid copper(II) complexes

Investigation of the formation of the mixed complexes in a solution containing two or more structurally (or sterically) different ligands often encounters a number of complications. The kinetically inert (stable) cobalt(II), chromium(III) and platinum group metal mixed complexes have been studied in some detail, but in the case of the kinetically labile (unstable) Cu(II), Zn(II), Ni(II) and Co(II) complexes the investigation of their formation becomes rather difficult since it is quite impossible to determine the equilibrium composition of the solution by means of the quantitative isolation of its components. The crystallization process immediately shifts the equilibrium towards the side of the less soluble product. Some indirect physical methods could possibly give some information on the composition of the system at equilibrium, but physical characteristics of the individual complexes are not always available for the successful application of these methods.

However, when one of the ligands is bonded covalently to an insoluble polymeric support and a chromatographic procedure is applied to such a heterogeneous system, it becomes possible to obtain data directly on the relative thermodynamic stability of all the mixed complexes formed by that fixed ligand. When a ligand mixture is chromatographed in the presence of a complexing metal ion the order of the emergence of the ligands from the chromatographic column falls into line with the increasing thermodynamic stability of their mixed complexes with that stationary ligand.

In the present work this principle is employed for investigating the stereoselective effects in some square planar copper(II) complexes. (Under the term "stereoselectivity" we mean the difference in the interaction of two molecules or structures, which are optical antipodes, with some third asymmetric structure or, in other words, the difference in the formation and properties of molecular diastereoisomers.)

Nowadays it is commonly accepted that, unlike the octahedral tris-complexes[1,2], the formation of the square planar copper(II) bis-complexes of α-amino acids (aa) occurs without stereoselective effects, *i.e.* that the properties of the [Cu(L-aa)$_2$], [Cu(D-aa)$_2$] and [Cu(L-aa) (D-aa)] in solution are nearly equal.

Conformational studies[3] show that the five-membered chelate 1,2-diamine ring is not planar and the stabilities of the enantiomeric [Cu(+pn)$_2$]$^{2+}$ and [Cu(—pn)$_2$]$^{2+}$ complexes are greater than that of the mixed meso-complex [Cu(+pn) (—pn)]$^{2+}$. The α-amino acid chelate ring has an almost planar structure and interacts very slightly with the second ring of the complex[4,5]. Thus the superiority of [Cu(L-aa)$_2$] and [Cu(D-aa)$_2$] over [Cu(L-aa) (D-aa)] should be less marked.

Actually in recent studies the stabilities of the copper(II) bis-complexes of bifunctional amino acids such as alanine, valine, phenylalanine, proline[1,6,7], and trifunctional amino acids such as asparagine, aspartic acid, glutamine, and glutamic acid[8] have been found to be independent of the amino acid steric configuration. In addition, the difference between the formation constants observed for the mixed copper complexes of L-proline with L- and D-valine (log β_{11} = 16.86 ± 0.09 and 17.00 ± 0.20, respectively)[9] do not exceed the error of the experiment.

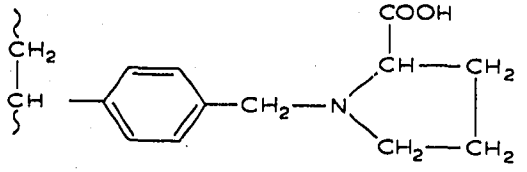
The α-amino acid chelate ring can, however, have a slight distortion from

planarity[10] which may be as high as 30° in the crystal state[11]. Furthermore, the crystalline copper complexes with racemic neutral amino acids always display the meso-(D)(L) structure[11].

Employing the principle of ligand-exchange chromatography we have attempted to obtain more accurate data on the absence or presence of weak stereoselective effects in the copper(II)–amino acid complexes.

Experimental

An asymmetric sorbent having a structural unit of



with the L-proline groupings acting as stationary ligands was used for the chromatography. This was prepared from a chloromethylated styrene–0.8 % divinylbenzene copolymer[12] by treatment with L-proline in the presence of NaI as a catalyst for the reaction with the chloromethyl groups[13]. This sorbent produces stable complexes with copper(II) ions, its copper exchange capacity of 1.9 mequiv./g being in good agreement with the amino acid group content.

A chromatographic column (diameter 9 mm, length 475 mm) was packed with the asymmetric sorbent (11 g) saturated with the copper ions. A second small column containing the same sorbent (2 g) but free from the metal ions was fitted after the main column.

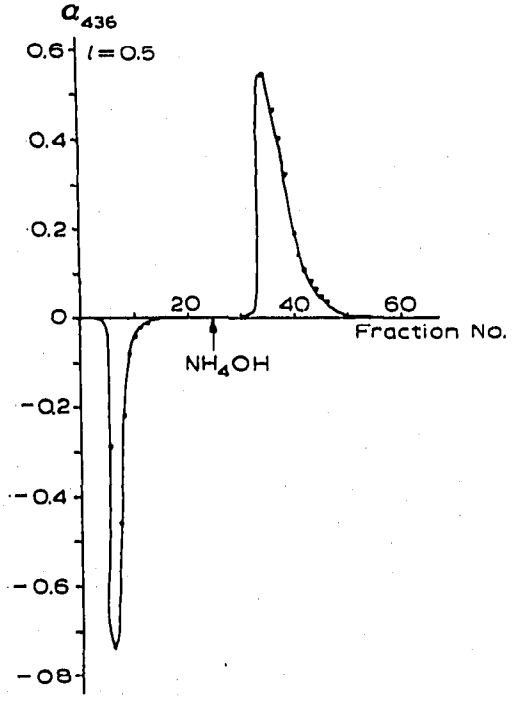


Fig. 1. Chromatography of 0.5 g D,L-proline (optical rotation of the eluent).

When an aqueous solution of a racemic neutral α-amino acid is passed through the columns its optical isomers leave the system separately; this can be readily established by measuring the optical rotation of the eluate. The L-isomers of alanine, valine, isovaline, leucine, isoleucine, β-phenyl-α-alanine, proline and some other amino acids move much faster along the column than their D-antipodes thus affording their complete separation. In the case of the said amino acids the L-isomers are eluted with water, whereas the D-antipodes may only be desorbed from the column by 0.5–1.0 *N* ammonia solutions.

Fig. 1 shows the optical rotation of the eluate in a typical experiment in which 5 ml of a 10 % aqueous racemic proline solution was introduced into the main column and the system was washed with water and then with 1 *N* ammonia solution at a rate of 7.5 ml/h. Evaporation of the portions No. 5–18 and 32–50 gave 0.25 g each of L- and D-proline with $[\alpha]_D^{20}$ 80.5 (c 1, water).

Discussion

An asymmetric complexing ion exchanger, obtained by the reaction of a chloromethylated crosslinked polystyrene with the amino group of L-proline, displays in the presence of copper ions a much higher affinity to the D-amino acids than to the L-antipodes. This means that the mixed copper complexes of ligands of the N-benzyl-L-proline type are more stable with the D-amino acids than the corresponding complexes with the L-antipodes. The stereoselectivity observed in this system must be of a thermodynamic rather than of a kinetic origin.

This conclusion is supported by direct investigation of the mixed N-benzyl-L-proline copper complexes by potentiometric titration[14] and circular dichroism measurements[15].

It should be noted that the system described is not a single example. Stereoselective effects were clearly observed in several other systems containing other amino acids as the stationary ligand. This makes us believe that stereoselectivity is a quite common phenomenon in the case of square planar copper complexes with bifunctional α-amino acids.

It would not be unexpected that ligand-exchange chromatography could be a much more sensitive method for studying labile mixed complexes, than the other common methods because of its ability to summate a large number of very small effects. The fact that the results so far obtained by common methods are in good agreement with the results found by the ligand-exchange chromatography method, allows one to conclude that the latter provides us with true information about the situation in labile mixed complexes and that this situation is not changed or significantly affected by the polymer support present in the system.

Institute of Organo-Element Compounds, Academy of Sciences, Moscow (U.S.S.R.)

V. A. DAVANKOV
S. V. ROGOZHIN

1 J. H. DUNLOP AND R. D. GILLARD, *Adv. Inorg. Chem. Radiochem.*, 9 (1966) 185.
2 R. D. GILLARD AND N. C. PAYNE, *J. Chem. Soc., A*, (1969) 1197.
3 E. J. COREY AND J. C. BAILAR, *J. Amer. Chem. Soc.*, 81 (1959) 2620.
4 K. M. WELLMAN, T. G. MECCA, W. MUNGALL AND C. R. HARE, *J. Amer. Chem. Soc.*, 89 (1967) 3646.
5 K. M. WELLMAN AND B. K. WONG, *Chem. Commun.*, (1969) 1213.

6 R. D. GILLARD, H. M. IRVING, R. M. PARKINS, N. C. PAYNE AND L. D. PETTIT, *Chem. Commun.*, (1965) 81; *J. Chem. Soc., A*, (1966) 1159.
7 VL. SIMEON AND O. A. WEBER, *Croat. Chem. Acta*, 38 (1966) 161.
8 J. H. RITSMA, G. A. WEIGERS AND F. JELLINEK, *Rec. Trav. Chim. Pays Bas*, 84 (1965) 1577.
9 M. M. PETIT-RAMEL AND M. S. PARIS, *Bull. Soc. Chim. Fr.*, (1968) 2791.
10 K. M. WELLMAN, W. MUNGALL, T. G. MECCA AND C. R. HARE, *J. Amer. Chem. Soc.*, 89 (1967) 3647.
11 H. C. FREEMAN, *Adv. Protein Chem.*, 22 (1967) 257.
12 S. V. ROGOZHIN, V. A. DAVANKOV, V. V. KORSHAK, V. VESA AND L. A. BELCHICH, *Izv. Akad. Nauk SSSR, Ser. Khim.*, N3 (1971) 502.
13 V. A. DAVANKOV, S. V. ROGOZHIN, V. V. KORSHAK AND M. P. TSURUPA, *Izv. Akad. Nauk SSSR, Ser. Khim.*, N7 (1967) 1612.
14 V. A. DAVANKOV, S. V. ROGOZHIN AND A. A. KURGANOV, *Izv. Akad. Nauk SSSR, Ser. Khim.*, N1 (1971) 204.
15 V. A. DAVANKOV AND P. R. MITCHELL, *J. Chem. Soc.*, in press.

Received April 27th, 1971