



PS5.14 — TU

ISABELLA L. KARLE

Laboratory for the Structure of Matter

Naval Research Laboratory

Washington, D.C. 20375-5000

U.S.A.

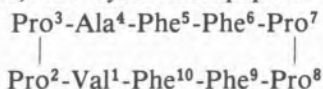
MODES OF COMPLEXATION OF CYCLIC PEPTIDES WITH LIGHT METAL IONS

The structures and conformations of a number of free cyclic peptides and the same peptides complexed with Li^+ , Na^+ , K^+ or Mg^{2+} ions have been established by X-ray diffraction analyses of single crystals. The different modes of complexation that have been found are: 1) an infinite sandwich in which the metal ion and the cyclic peptide alternate [1]; 2) a discrete sandwich in which the metal ion is between two cyclic peptide molecules [2-4]; 3) incomplete encapsulation of the metal ion by one peptide molecule [5,6]; 4) complete encapsulation by one peptide molecule [7,8]; and 5) the metal ion partially *exo* to the polar cavity formed by the peptide [9]. Modes 1-4) appear to be a function of the size of the cyclic peptide, beginning with a pentapeptide for 1) and progressing to a dodecapeptide for 4). Mode 5) can occur when the size of the metal ion is mismatched with the size of the cyclic peptide.

The complexation of cyclic oligopeptides with metal ions requires the formation of ligands between the metal ion and carbonyl oxygens. If the peptide is too small, even acting in pairs, then the incomplete coordination sphere about the metal ion is completed by ligands to the oxygens of water molecules [1] or to O or N atoms of solvent molecules [5,6] such as CH_3CN , $\text{C}_2\text{H}_5\text{OH}$, $(\text{CH}_3)_2\text{CO}$ or to counterions [1] such as SCN^- . The Mg^{2+} ion has shown an almost exclusive preference for octahedral coordination [1,2], with all O- Mg^{2+} -X angles (X=O or N) very near to 90° . The Li^+ and Na^+ ions adjust their coordination to the local geometry, as for example, in the complexes with antamanide and antamanide analogs, the Li^+ and

Na^+ ions have pentacoordination with ligands to four carbonyl O atoms in a square array and the fifth ligand to a polar atom of a solvent molecule at the apex of the coordination pyramid [5,6]. In every case, the ligands to O or N atoms radiate from the metal ion in all directions and a polar envelope about the metal ion is provided that separates it from the lipophilic regions of the peptide.

The free cyclic peptide is not in a conformation ready to accept and encapsulate a metal ion. Severe conformational changes occur upon complexation. To demonstrate that complexation is responsible for the conformational changes rather than other changes in the crystal environment such as packing, intermolecular interactions, and/or solvent inclusion, a number of crystal structure analyses were performed on the uncomplexed peptides, or closely related analogs of the peptide. To illustrate, the cyclic decapeptide antamanide



and the biologically active analog [$\text{Phe}^4, \text{Val}^6$] antamanide were crystallized from solutions containing water and common organic solvents such as $\text{C}_2\text{H}_5\text{OH}$, CH_3CN , acetone, DMFA, *etc.*, and from completely nonpolar solvents such as *n*-hexane. The resulting crystals had different packing arrangements of the peptides, different solvent inclusions (both polar and nonpolar) and several different side chains on the peptides. Nevertheless, the folding of the backbone and the twisting of the side chains are almost identical in all the crystals [10-12]. Similarly, the conformations of the cyclic pentapeptides (Gly-Pro-Gly-D-Ala-Pro) and (D-Phe-Pro-Gly-D-Ala-Pro) are superimposable despite a different side chain and different packing in the respective crystals [13,14]. Similarly, uncomplexed valinomycin crystallized from different solvents and occurring in different crystalline packing arrangements has a unique elongated conformation [15-17].

The process of forming complexes with Li^+ , Na^+ and Mg^{2+} with each of the cyclic peptides involves major changes such as the rotation of one or more peptide units by as much as 180° . On complexation in antamanide, not only does the flattened elongated cyclic backbone become folded, but sequences 4,5,6 and 9,10,1 turn inside out so that

the *exo* carbonyl groups turn into the cavity to form ligands with the metal ion [5,6,10-12]. In addition, *cis/trans* isomerism of amide bonds may occur [2,18], intramolecular hydrogen bonds are broken [1,2,18], and elongated peptide ring backbones become folded. Examples will be presented.

REFERENCES

- [1] I.L. KARLE, *Int. J. Pept. Protein Res.*, **23**, 32-38 (1984).
- [2] I.L. KARLE, J. KARLE, *Proc. Natl. Acad. Sci. USA*, **78**, 681-685 (1981).
- [3] G. KARTHA, K.I. VARUGHESE, S. AIMOTO, *Proc. Natl. Acad. Sci. USA*, **79**, 4519-4523 (1982).
- [4] Y.H. CHIU, L.D. BROWN, W.N. LIPSCOMB, *J. Am. Chem. Soc.*, **99**, 4799-4802 (1977).
- [5] I.L. KARLE, *J. Am. Chem. Soc.*, **96**, 4000-4006 (1974).
- [6] I.L. KARLE, *Biochemistry*, **13**, 2155-2162 (1974).
- [7] M. PINKERTON, L.K. STEINRAUF, P. DAWKINS, *Biochem. Biophys. Res. Commun.*, **35**, 512-518 (1969).
- [8] K. NEUPERT-LAVES, M. DOBLER, *Helv. Chim. Acta*, **58**, 432-442 (1975).
- [9] L.K. STEINRAUF, J.A. HAMILTON, M.N. SABESAN, *J. Am. Chem. Soc.*, **104**, 4085-4091 (1982).
- [10] I.L. KARLE, E.N. DUESLER, *Proc. Natl. Acad. Sci. USA*, **74**, 2602-2606 (1977).
- [11] I.L. KARLE, *J. Am. Chem. Soc.*, **91**, 5152-5157 (1977).
- [12] I.L. KARLE, TH. WIELAND, H. FAULSTICH, H.C.J. OTTENHEYM, *Proc. Natl. Acad. Sci. USA*, **76**, 1532-1536 (1979).
- [13] I.L. KARLE, *J. Am. Chem. Soc.*, **100**, 1286-1289 (1978).
- [14] I.L. KARLE, in A. EBERLE, R. GEIGER, TH. WIELAND (eds.), «Perspectives in Peptide Chemistry», S. Karger, Basel, 1981, pp. 261-271.
- [15] W.L. DUAX, H. HAUPTMAN, C.M. WEEKS, D.A. NORTON, *Science*, **176**, 911 (1972).
- [16] I.L. KARLE, *J. Am. Chem. Soc.*, **97**, 4379-4386 (1975).
- [17] G.D. SMITH, W.L. DUAX, D.A. LANGS, G.T. DE TITTA, J.W. EDMONDS, D.C. ROHRER, C.M. WEEKS, *J. Am. Chem. Soc.*, **97**, 7242-7247 (1975).
- [18] M. CZUGLER, K. SASVÁRI, M. HOLLÓSI, *J. Am. Chem. Soc.*, **104**, 4465-4469 (1982).



PS5.15 — TH

PETER M. MAY
KEVIN MURRAY
DANIEL PEAPER

Department of Applied Chemistry
UWIST
Cardiff
U.K.

THE EFFECT OF SODIUM ION INTERFERENCE ON BIOINORGANIC FORMATION CONSTANTS DETERMINED BY GLASS ELECTRODE POTENTIOMETRY

Recently, a library of computer programs for the determination of metal-ligand formation constants, called ESTA (Equilibrium Simulation for Titration Analysis), has been developed [1]. These programs permit various corrections which are important in the measurement of thermodynamic parameters required by those modelling metal-ion interactions in biological fluids (e.g. blood plasma, intestinal juice and saliva [2]). Changes in ionic activities, liquid junction potentials and ion-selectivity of the electrodes used for potentiometric titrations can be calculated [3].

Such corrections become necessary when the background ionic strength of a titration is not high enough to remain reasonably constant. This is often the case in work of biological relevance, where ionic strengths less than 200 mmol dm⁻³ are commonplace. Moreover, the formation constants of many bioinorganic systems are such that pH measurements need to be made in relatively alkaline solutions where sodium ion interference with the glass electrode response is most pronounced. The object of the present work was to quantify the effect of this interference and to assess the seriousness of neglecting it in a typical study of a metal-ligand interaction with bioinorganic interest.

In the first stage, potential differences arising from the presence of sodium ions in the titration