Pergamon

Polyhedron Vol. 16, No. 12, pp. 2145–2146, 1997

0277–5387/97 $17.00+0.00

PII: S0277–5387(96)00550–5

COMMUNICATION

"Salting-in" of neutral complexes of natural amino-acids

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(Received 11 October 1996; accepted 13 November 1996)

Abstract—Uncharged complexes $[M(\alpha)_n]$, where Hα represents a natural amino-acid like glycine or S-alanine, M = Cu, $n = 2$ or M = Co, Cr, Rh, $n = 3$, are well "salted-in" to water by many simple salts (e.g. NH_4NO_3, $AgNO_3$, NaCl, $MgCl_2$) and additives like urea. © 1997 Elsevier Science Ltd. All rights reserved.

Keywords: amino acids; "salting-in"; "salting-out"; solubilizing; cybotaxis; circular dichroism.

"Salting-out" improves many yields in syntheses in water of partly soluble non-electrolytes like cyclohexanone or tris-2,4-pentanedionato chromium(III). Typically, common salt itself is added to aqueous solutions and the uncharged solute separates. Many poly-amino-acids including proteins are similarly salted out, often by adding ammonium sulphate or denatured, often by adding urea. A few proteins, however, such as hemoglobin are "salted-in", being more soluble in brine than in water. These were formerly called globulins. Such effects have recently been used in commenting on solvation of proteins [1] or of transition states in water of organic reactions [2] such as the Diels–Alder.

We now report that many simple uncharged complexes of metal ions with bidentate amino-acids are salted-in to water by many simple salts and by urea. Typically, in the case of copper(II), the solubility of bis-glycinatocopper(II), $[Cu(glyO)_2]$, is enhanced up to 20-fold in 2 M $MgCl_2$ or 4 M $AgNO_3$. Many other simple salts function similarly. From the strong solutions, adducts may crystallize. These new compounds have formulae like $[Cu(glyO)_2]\cdot MgCl_2\cdot 7H_2O$(I) or $[Cu\alpha_2]\cdot 2AgNO_3$(II) (where α denotes the anion of the amino-acid). The formation of (I) involves the equilibrium (1), not previously noticed:

$$[Cu(glyO)_2] + 2Cl^- \rightleftarrows trans\text{-}[Cu(glyO)_2Cl_2]^{2-} \qquad (1)$$

the spectroscopic properties of the bis-chelate in solution are indeed modified by adding any soluble chloride. The new adduct(I) is [3] the monohydrated hexakisaquomagnesium(II) salt of the novel dichloro anion, $[(Mg(OH)_2)_6]\ \{trans[Cu(glyO)_2Cl_2]\}H_2O$.

The structure of (II) shows no clear-cut new simple ion. Rather, it is formed [3] from the superposition upon the intact *trans*-bis-glycinatocopper(II) molecule of a fragment of silver nitrate with a structure similar to that of parent silver nitrate [4].

We view the situation with many other unexpected enhancers of solubility like urea, ammonium sulphate, or cadmium nitrate as effects on local elements of water structure arising from the presence of ionic components of salts. Stewart called this cybotaxis [5].

Typical cases here include the coordinatively saturated tris-amino-acidatometal(III) compounds of kinetically inert cobalt or chromium. Their very insoluble facial isomers are greatly solubilized by salts. They are well salted in by sodium chloride, iodide, nitrate. A few adducts form, such as *fac*-$[Co(glyO)_3]\cdot 2KI$. It is clear from its circular dichroism spectrum that the solute in the case of Λ-*fac*-$[M(S\text{-}alaO)_3]$, is unchanged tris-complex.

These very unusual "salting-in" effects arise from changes in water activity: they are not restricted to compounds of metal ions and natural amino-acids. For example, neutral complexes of α-picolinate with copper(II) and cobalt(III) show similar large enhancement of solubility with salts [3], and Λ-*fac*[Rh (S-alaO)$_3$], extremely insoluble in water, is very sol-

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uble [6] in 5 M $MgCl_2$ solution or in 3 M $AgNO_3$ solution.

Likewise, in the course of a recent study of the solubilization (attributed there to protonation of the solute) of *fac*[Co(α)$_3$] by sulfuric acid, sodium sulphate was found [7] to exert a solubilizing effect on *fac*-[Co(gly-O)$_3$].

This salting-in constitutes a very useful new means of dissolving and working with simple compounds in water. First, by diluting the salted-in solutions with water, the uncharged solutes crystallize. This offers good recrystallization for many previously intractable solids. Secondly, the reactivity of the solutes can now be studied in water. For example, Λ-*fac*-[Cr(glyO)$_3$] is quickly hydrolyzed in 2 M calcium chloride solution. Organic ligand reactivity is also more accessible in these new concentrated solutions (for example, racemization of S-ligands or Knoevenagel addition to glycinate).

The popular concepts of "spectator ions" and of control of ionic strength need close inspection for systems containing non-electrolytes. Many compounds of the present type, such as [Cuα$_2$], are constituents of living matter, where their properties are unlikely to be predictable from the commonly tabulated equilibrium or rate constants. For example, "stable" [Cu(α)$_2$] yields "unstable" $[CuBr_4]^{2-}$ when concentrated sodium bromide is added to its solution in water.

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