Thermodynamic Approach in Coordinative Interactions in Solution (Including Computer Assisted Methods)

The Formation of Metal Complexes; the Known and the Unknown

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In relation to the formation of metal complexes there are certain aspects which have been understood for some time while there are others, which may be equally important, about which little is known. To illustrate this point, when a ligand and a metal ion are brought together, it is not always possible to predict whether they will form a complex or not; if a complex is formed it is likewise impossible to be certain of the exact nature of the complex since it might, for example, be protonated, or contain hydroxo species or be polynuclear.

On the other hand, one can say with absolute certainty that complexes are formed in successive steps and that their step-wise formation in solution is always the result of a substitution reaction in which a ligand molecule replaces a solvent molecule which is bound to the metal ion. It is therefore not surprising that the type of solvent used can influence the formation of the metal complexes and that, in certain cases, by changing the ionic nature of the solvent, one can appreciably alter the stability of the resulting complexes.

Following on from this, the stability of a complex can be increased considerably by an increase in the number of donor atoms per ligand molecule, giving rise to the possibility of polydentate complexes. Provided the number and type of donor atos remain constant, an increase in stability results from an increase in the number of chelate rings present in the complex. This is traditionally referred to as the *Chelate Effect* and has been known for many years. More recently, a good deal of attention has been directed towards the cyclisation of linear polydentate ligands to form cyclic compounds. The marked increase in stability of these cyclic metal complexes over their linear counterparts has been called the *Macrocyclic Effect.*

A quantitative statement of the stability of a metal complex is to be found in its stability constant, which, as is well known, can be broken down into both an enthalpy and an entropy term. While these two terms may appear to be completely independent, it appears, for comparable reactions, that the one compensates the other; thus as the contribution from the enthalpy decreases that of the entropy increases and *vice versa*. This effect has been acknowledged to be of particular importance in the field of biological chemistry.

The introduction of computerized methods of calculation has been the foremost responsible factor in the rapid progress which has been made during the last few years in the experimental determination of stability constants. It has consequently been possible to develop models which simulate *in vivo* systems containing a large number of complexes of various types, using the calculated values of the stability constants. In a similar way, the introduction of commercial calorimeters which are extremely sensitive has made it much easier to collect enthalpy data which are sufficiently accurate on which to base theories and hypotheses. However, there are still many aspects of complex formation with which chemists find it hard to come to terms. The most widespread of these relates to the seemingly simple process of a complex dissolving. Many ignore, or perhaps choose to ignore, that it is only very infrequently that a complex will dissolve without undergoing a radical and fundamental change in its constitution. The other relates to the determination of stability constants. Here, too many graduates in chemistry believe, because they are in a position to measure stability constants without bothering too closely with the accuracy, that by repeating their measurement at different temperatures they can arrive at a reliable value for the enthalpy change of the reaction. As a topical example of this potential folly, it is interesting to speculate that the values of ΔH^0 obtained by this method for the formation of complexes with molecular oxygen can almost certainly be treated with a considerable pinch of salt, and that it would be most unwise to draw too many conclusions or to base too many hypotheses on them.

The significance of the solvent can be seen for the 1:1 complexes of zinc with cyclam in water and acetonitrile, where ΔH^0 values of 61.9 kJ mol^{-1} and 113.0 kJ mol^{-1} have been reported respectively in these two solvents. When such values differ by 100%, it is not difficult to understand that some complexes, which prove impossible to prepare from aqueous solution, can nonetheless be prepared using other solvents.

Finally, in relation to the *Macrocyclic Effect,* I want to show you how careful we chemists need to be. One of the first, and very popular hypotheses, which was formulated about the origin of the stability of macrocyclic complexes was based on a ΔH° value obtained from the temperature dependence of the appropriate stability constant. It was concluded that the origin of this enhanced stability derived from the smaller solvent-interaction of macrocyclic as opposed to non-cyclic ligands. To-day, this attractive hypothesis is recognized as only one of the possible contributions to this extra stability and this change has essentially been brought about by the direct calorimetric determination of the enthalpies of formation of macrocyclic metal complexes, revealing gross discrepancies from the ΔH° values obtained by indirect route, of which a criticism has already been levelled.

Thermodynamics of Complex Formation with Multidentate Ligands

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Complex formation in solution is generally described by a reaction of type I. This formulation does not correspond to what actually takes place, namely

$$M^{z+} + L^{n-} \rightarrow ML^{(z-n)+} \qquad \text{I}$$

process II, because of the omission of the solvent as

$$M(H_2O)_q^{z+} + L(H_2O)_m^{n-} \rightarrow ML(H_2O)_p^{(z-n)+} + (q + m - p)\,H_2O \qquad \text{II}$$

reacting partner. Indeed the entropy of complex formation is generally positive and large, depending strongly on the dentateness of the ligand, and not negative as it would be expected for reaction I, because of the decrease of the number of species in solution. The influence of the solvent seems also to be reflected in the value of the enthalpy of complex formation: for complexes with multidentate charged O-ligands it is generally not very different from zero. This is because the endothermic effect for the dehydration of the reacting species is almost compensated by the exothermic effect of the ligand coordination. On the contrary, for neutral ligands, the enthalpy is remarkably negative as result of (*1*) the lower hydration of the ligand, (*2*) the covalency of the bonding, and (*3*) no charge neutralisation occurs.

In multidentate ligands the donor atoms connected together by chains which, on complex formation, give rise to chelate rings. These are considered responsible for the higher stability of complexes with multidentate ligands with respect those of monodentate ligands, if in the complexes the same number of donor atoms are involved. The interpretation of this effect, the *Chelate Effect,* has been the subject of active discussion over the last thirty years and it is still a matter of opinion. In this connection, one should consider not only for five-, six- and seven-membered chelate rings a positive *Chelate Effect* is observed. If there are more than six atoms between the donor atoms or chelating units, their neutral influence decreases and eventually reduces to that of a statistical effect.

The values of the enthalpy and of the entropy for complex formation with the same ligand and a series of related metal ions, such as the alkaline earth, the 3d divalent metal or the 4f trivalent lanthanide ions can be correlated with stereochemical and electronic effects at the central ion such as the dentateness of the ligand, the coordination number of the metal ion and ligand field effects.

The formation of mixed (ternary) complexes will be also considered in some detail. These have recently received more attention, especially because of their increased stability with respect to that expected by statistical consideration and in relation of their importance in biological systems.

The Macrocyclic Effect in Tetraaza-Macrocyclic Ligands

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The origin of the Macrocyclic Effect [1] in complexes of *cyclam* as compared with those of its open-chain analogue *2,3,2-tet* is discussed. It is not readily apparent that the presence of four secondary (2°) nitrogens in *cyclam,* as opposed to two primary (1°) and two 2° in *2,3,2-tet* should make much difference, since the pK_a's of 2° amines are not much different from those of 1°. Proton basicity in water is a misleading guide to base-strength. For example, $\log K_n$-(RNH_2) with Ag(I) increases strongly as R changes