Session on Thermodynamic Aspects of the Interaction between Metal Ions and Ligands of Biological Interest

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Thermodynamic Aspects of Solvophobic Forces in Simple and Mixed Complex Formation of Metal Ions with Biofunctional Ligands

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Solvophobic [1] or hydrophobic [2, 3] interactions are known to occur in biomolecules and to contribute to the formation of distinct structural conformations, which provide the specificity and the reversibility required in most biological processes [4]. These forces occur between two aliphatic or alicyclic groups, between two aromatic groups and between aliphatic and aromatic groups.

As regards metal complexes of low molecular weight, the presence of this interaction has been invoked to explain i) the biological activity of some coordination compounds [5, 6]; ii) the stability enhancement of some ternary complexes [7]; and iii) other distinct features in their reactivity [8] and their thermodynamic properties [9]. The appearance of this so-called 'secondary' bond has usually been inferred from potentiometric titrations, UV-difference spectra and NMR shift measurements.

Recently, we have shown that the calorimetric technique is a very powerful tool to bring to light the solvophobic interactions in some ATP metal complexes [9]. In particular, the effect of these forces resulted in a more favourable enthalpic and in a less favourable entropic contribution for $[M(ATP)(trp)]^{3-}$ with respect to $[M(ATP)(ala)]^{3-}$ species. As for zinc(II) complexes, the difference was more pronounced in comparison with what was found for copper(II). The formation of $[Zn(ATP)(trp)]^{3-}$ was about 10 Kcal mol^{-1} more exothermic and 30 e.u. lower with respect to $[Zn(ATP)(ala)]^{3-}$. Bearing in mind that in the latter complex stacking interaction is not possible, this difference has been assumed as an index of the presence of solvophobic interaction. Such a favourable trend in $\Delta H°$ values has been found for other mixed complexes of zinc(II) with ATP and some biofunctional ligands [10]. Furthermore, on the basis of the thermodynamic properties, the study of the mixed complexes of 2,2'-bipyridyl and mono- or di-alkyl substituted malonate ligands with copper(II) and zinc(II), has shown that the occurring of solvophobic forces is dependent on the geometrical

coordination requirement of metal ions. Finally, the role of these interactions in the thermodynamic stereoselectivity of some dipeptide complexation has also been assessed. For example, the formation of $[Cu(L,L\text{-leu,leuH}_{-1})]$ complex is more enthalpically and less entropically favoured with respect to $[Cu(L,D\text{-leu,leuH}_{-1})]$ species. This behaviour is due to favourable orientation of side chains which gives rise to a solvophobic interaction in the 'pure' with respect to the 'mixed' derivative.

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Thermodynamic Evaluation of Chelate and Cooperativity Effects

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The chelate effect occurs in the binding of a ligand, containing two or more donor atoms, with a metal ion [1] or a macromolecule [2]. The chelate effect causes an increase in the stability of the complexes with respect to those formed with the same number of donor atoms belonging to separate liganding molecules. The evaluation of the chelate effect has been done up to now by calculating the constant $K_{chel} = K_{ML}/\beta_{MA_2}$, where M = metal or macromolecule, A = monodentate ligand, L = bidentate chelating ligand, K_{ML} = formation constant of the chelate ML, β_{MA_2} = cumulative formation constant of the complex MA_2. L (homotropic chelate) has two donor atoms equal to that of A.

By an analysis of the binding polynomial [3] on the Bjerrum plane ($\bar{n}$, $-\log L$), it can be shown how the correct equilibrium constant to evaluate the chelate effect is $K_\epsilon = K_{ML}/\beta_{MA_2}^{1/2}$ for bidentate chelating ligands and $K_\epsilon = K_{ML}/\beta_{MA_n}^{1/n}$ for n-dentate ligands. These adimensional constants are obtained as the ratio of two operational equilibrium constants, namely K_{ML} and $\beta_{MA_n}^{1/n}$, each of which is expressed in homogeneous reciprocal concentration units (conc.$^{-1}$). If the donor atoms of the chelating ligand are different (heterotropic chelate), then the thermodynamic stability can be evaluated by $K_{\epsilon'} = K_{ML}/\beta_{MAB}^{1/2}$, where MAB is a mixed ligand complex, and similar constants hold for higher complexes. Again the ratio is between two operational constants K_{ML} and $\beta_{MAB}^{1/2}$, each expressed in conc^{-1}.

With the same arguments it can be shown that the cooperativity effect, *i.e.* the mutual repulsion or attraction between ligands, can be evaluated by $K_\gamma = \beta_{MA_2}^{1/2}/K_{MA}$ and by $K_{\gamma'} = \beta_{MAB}^{1/2}/(K_{MA} \cdot K_{MB})^{1/2}$ for homotropic and heterotropic cooperativity, respectively.

The chelate effect comprehends in itself the cooperativity effect and this can be taken into account in the constants $K_\eta = K_\epsilon \cdot K_\gamma$ and $K_{\eta'} = K_{\epsilon'} \cdot K_{\gamma'}$. The constants K_ϵ, K_γ, $K_{\epsilon'}$, and $K_{\gamma'}$ must be corrected for statistical effects. All these constants are expressed in the same units as the activity coefficients. From these constants, the corresponding changes in chemical potentials, $\Delta\mu° = -RT \ln K$ can be calculated. These values expressed in kJ mol^{-1} allow the evaluation on the same scale of chelate and cooperativity effects, together with changes in the activity coefficients.

The correctness of the choice of scale is shown by examining the chelate effect values obtained for copper(II) complexes of dicarboxylic acids at 25 °C [4]. Cu(II)/succinate 1/1 chelate would have been unstable according to $K_{chel.} = 0.32$ mol dm^{-3}, whereas it comes out to be stable according to $K_\eta = 11.4$ mol^{-1} dm^3 ($\Delta\mu_\eta° = -6.03$ kJ mol^{-1}), in agreement with the experimental evidence [5].

The net chelate effect, $\Delta\mu_\eta°$, is linearly related both to the number of donor atoms and to the number of chelate rings.

The enthalpy and entropy contributions to the chelate effect can also be calculated and critically analysed.

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Thermodynamics of Axial Ligand Addition and Spectroscopic Trends of a Series of Symmetrical and Unsymmetrical Derivatives of Tetraphenylporphinatozinc(II) and -iron(III)

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The electronic spectra and equilibrium constants for addition of 3-picoline to a series of symmetrically and unsymmetrically phenyl-substituted ZnTPP derivatives have been measured. It is found that the α band energy varies slightly nonlinearly, yet systematically, with the sum of the Hammett sigma constants of the substituents within the series $(p\text{-Cl})_x(p\text{-NEt}_2)_y$-TPPZn(II) and related complexes, while the smaller variation in the β band appears to be linear. The log of the intensity ratio of the α and β bands, $\log A_\beta/A_\alpha$, however, varies linearly with the band energies of both the α and β bands for both 4- and 5-coordinate complexes of unsymmetrical ZnTPP derivatives. Likewise, log K_{eq} for 3-picoline addition to this series of ZnTPPs varies linearly with the sum of the Hammett sigma constants for all complexes investigated, irrespective of the symmetry of placement of phenyl substituents. Thus the electronic effects of unsymmetrically placed substituents are averaged by the metal Zn to yield a Lewis acid strength toward 3-picoline which is dependent only on the sum of the electronic effects and not on the identity of the substituents or the symmetry of their distribution.

In contrast to the results for Zn(II), the same series of TPPFe(III) complexes do not exhibit spectroscopic trends independent of the symmetry of placement of the substituents in either the high-spin chloroiron(III) or low-spin bis-N-methylimidazoleiron(III) forms. Likewise, log β_2 for N-methylimidazole addition does not vary linearly with the sum of the Hammett sigma constants for unsymmetrically substituted TPPFe(III) derivatives. Rather, unsymmetrically substituted TPPFe(III) derivatives deviate from the linear relationship shown by the symmetrical complexes [1] in either a negative direction (log β_2 smaller than expected, based on $\Sigma\sigma$), as is found for p-Cl, p-NEt$_2$ mixed substituent complexes, or in a positive direction (log β_2 larger than expected on the basis of $\Sigma\sigma$), as is found for p-NO$_2$, p-H or m-NO$_2$, m-CH$_3$, or m- or p-NHCOCH$_3$, H mixed substituent combinations.

The reason for the difference in thermodynamic and electronic spectral behavior of the unsymmetrically phenyl substituted TPP derivatives of Zn(II) and Fe(III) must be due to the difference in electron configuration of the two metals (d^{10} *vs.* d^5), and