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Tailoring molecular assemblies for metal ion binding

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Abstract. An investigation of a subtle, but potentially important, effect in metal coordination chemistry concerned with the spontaneous formation of host-guest assemblies between organic moieties which are themselves potential metal-ion ligands is reported. The use of a ligand 'package' of this type for metal complexation (where the package exists in solution in equilibrium with its corresponding metal complex) is potentially a contributing factor to enhanced complex stability.
Initially, nmr titration studies were carried out on host-guest systems formed between carboxylic acids and both open chain and macrocyclic amine-containing ligands. The stoichiometries of the resulting adducts formed in deuterated methanol or chloroform were determined and in some instances it has proved possible to determine the corresponding step-wise binding constants.

Solvent extraction experiments (water/chloroform) involving 1,4,8,11-tetrabenzyl-1,4,8,11-tetraazacyclodecane in the presence of hexadecanoic acid in the organic phase have demonstrated that the resulting host-guest 'package' can be employed for the synergistic extraction of nickel(II) and copper(II). The observed extraction behaviour of systems such as this can be interpreted in terms of the operation of an 'assembly effect'. The origins of the latter are not straight forward but may include a favourable entropy term associated with the involvement of an assembled ligand package for complex formation as well as a variable contribution reflecting overall lipophilicity considerations.

Under defined conditions, an appreciation of this effect has the potential to provide an additional guide to the subtleties of metal complex formation alongside other well established 'effects' in coordination chemistry.

INTRODUCTION

The use of molecular design to achieve spacial and/or molecular complementarity between different molecular entities is a continuing theme in supramolecular (host-guest) chemistry. In the initial phase of the present study we have investigated one such area involving the formation of host-guest adducts between organic moieties which are themselves potential metal-ion ligands. In particular, we have been interested in the situation where the ligand components of a coordination sphere 'assemble' spontaneously in the absence of a complexing metal ion. In the presence of the metal ion, the corresponding metal complex will exist in solution *in equilibrium* with its corresponding ligand assembly.

When the stoichiometry of the ligand assembly approximates that required to occupy the coordination sphere of the metal then the prospect of enhanced metal binding exists - since the components of the coordination sphere are to a lesser or greater degree 'assembled' for complex formation. We propose the term 'assembly effect' to describe any enhanced stability arising from this source although other factors, such as those reflecting lipophilicity changes, may also contribute.

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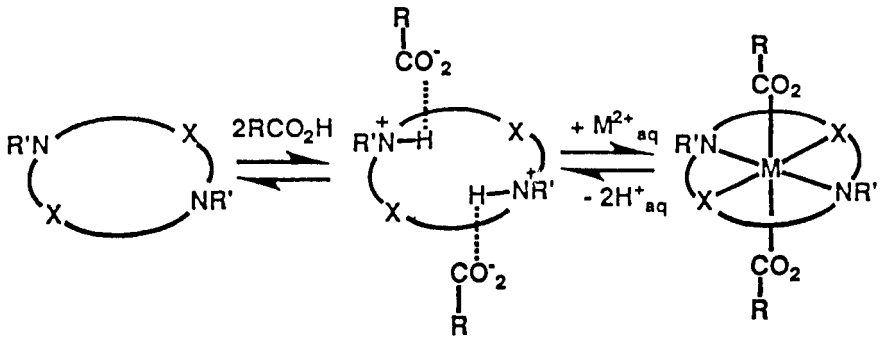
In view of the above, the implications of ligand assembly for metal complex formation has been a major concern of our study. It is emphasised that the proposed effect is of thermodynamic origin - being concerned with equilibria, such as of the type illustrated:



For an assembly effect to operate, the back equilibria to the (separated) free ligands should be unfavourable relative to formation of the assembled ligand package (it is noted that in a preliminary communication (ref. 1) we used the term 'pre-assembly effect' but now prefer 'assembly effect' since the effect will operate regardless of the order of addition of the ligand or metal components).

The assembly concept, which spans the areas of supramolecular host-guest chemistry and classical metal coordination chemistry, appears to have implications for the design of new reagents for use in solvent extraction systems. In particular, ligand assembly may contribute to particular examples of 'synergism' in the solvent extraction literature (for which a rationale is commonly absent}. From our studies so far, it seems likely that effects arising from ligand assembly in the organic phase may play a role in at least some of the observed behaviour of this type. There are now a many reported examples of solvent extraction experiments in which a mixture of ligands in the organic phase gives rise to 'synergistic' behaviour. While a great many of these appear not relevant to the concepts expressed here, others appear of direct relevance. For example, Aggett and Woollard (ref. 2) reported the synergistic enhancement of nickel(II) extraction when combinations of aromatic carboxylic acids and particular N- or C-alkylated diamines were employed as a mixed ionophore. Indeed, our group (ref. 3) and (ref. 4) have previously reported increased extraction efficiencies when a hexadecanoic acid/amine-containing macrocycle mixture was used as the extractant in heavy metal ion extraction studies. In other studies, a mixture of aza-crown-6 and hexadecanoic acid has been demonstrated to act in a synergistic fashion for the transport of silver(I) (ref. 5) and lead(II) (ref. 6) across a chloroform liquid membrane.

Overall, the aims of the present study were three-fold: (i) to investigate the formation of a wide range of molecular assemblies incorporating hosts and guests that are themselves potential metal-ion ligands; (ii) to probe the nature of the interaction between individual hosts and guests and (iii) to use molecular assemblies of the above type in selected solvent extraction experiments.

NEW MOLECULAR ASSEMBLIES

A series of NMR titration studies in $CDCl_3$ (and some comparative studies in CD_3OD) were performed in an attempt to define the factors controlling the formation (or otherwise) of host-guest assemblies between amine-containing ligand hosts and carboxylic acid guests. The latter included benzoic, tert-butylbenzoic and hexadecanoic acids.

Initially, it was not clear to us what influence a low polarity $CDCl_3$ medium would have on the stoichiometries of carboxylic acid/amine ligand adducts when the host molecules incorporate amine sites having very different basicities (as judged by the respective pK_a values for their protonated forms in polar media such as water or water/methanol). Apart from its interest in relation to the present study, an

understanding of this aspect also has wider implications for a fuller understanding of other supramolecular systems incorporating interactions of the amine-carboxylic acid type.

Adduct formation in CD_3OD

It was of interest for comparison purposes to probe initially whether simple open-chain amine ligands might undergo adduct formation with benzoic acid in the relatively polar solvent CD_3OD. The following amines were used in such an investigation: 1,2-ethanediamine, 1,4-butanediamine, diethylenetriamine, triethylenetetramine, N,N-dimethyl-1,2-ethanediamine, N,N'-dimethyl-1,2-ethanediamine and N,N,N',N'-tetramethylethylenediamine.

In a typical experiment from these studies, incremental addition of benzoic acid to 1,2-ethanediamine in CD_3OD (held in an NMR tube) resulted in the following chemical shift changes in the ^1H and ^{13}C NMR spectra of the diamine: the ^1H spectra showed a final downfield shift for the methylene protons of around 0.5 ppm while the final upfield ^{13}C shift for the methylene carbons was approximately 5 ppm. Such behaviour is clearly in accord with the occurrence of significant interaction between the amine groups and benzoic acid. Although the perceived 'end points' are subject to some uncertainty, the shapes of the plots are consistent with the formation of both 1:1 and 2:1 adduct species in this case.

The above adduct between 1,2-ethanediamine and benzoic acid has been crystallised from methanol solution and its 1:2 stoichiometry confirmed by both X-Ray and neutron diffraction studies (ref. 7).

Related NMR titrations using benzoic acid as 'titrant' were also performed for each of the amines mentioned above. In all cases, the NMR evidence again indicated stepwise adduct formation. With the aid of the program EQNMR (ref. 8) the incremental induced shifts in the respective ^{13}C NMR spectra of the N,N'-dimethyl-1,2-ethanediamine/benzoic acid/ and N,N,N',N'-tetramethyl-1,2-ethanediamine/benzoic acid systems in CD_3OD were employed to calculate the corresponding 1:1 and 1:2 stepwise binding constants. In the first case, log K values (at 25°C) of 2.4 (1:1 adduct) and 1.5 (2:1 adduct) were obtained while, in the latter case, the corresponding log values were 4.1 (1:1 adduct) and 1.8 (1:2 adduct).

Adduct formation in $CDCl_3$

Initially, the stoichiometries of a selection of the open-chain amine/carboxylic acid systems just discussed were reinvestigated in the less polar solvent $CDCl_3$. Once again, clear evidence for stepwise adduct formation was obtained, with for most systems the results paralleling those obtained in CD_3OD. It is also noted in this context that the formation of adducts between the chiral resolving agent, (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine and a number of chiral carboxylic acids had also been demonstrated previously in NMR studies employing $CDCl_3$ and C_6D_6 as solvents (ref. 9).

As an extension of our studies [and in anticipation of subsequent water/chloroform extraction studies], an investigation of adduct formation between carboxylic acids and amine-containing macrocyclic ligands in $CDCl_3$ was undertaken. In part cyclic ligands were chosen because of their tendency to yield simpler speciation (often just 1:1) on interaction with a metal ion relative to related open-chain ligands.

Many amine-containing macrocycles, and especially mixed donor ones, have been synthesised in our laboratory over many years (ref. 10) and nearly all cases their protonation constants have been determined. In the present study, selected ligands from this series have been employed as guests together with a range of other macrocyclic systems taken from the literature. Collectively, these rings provide a matrix of cyclic hosts, against which structure/function relationships involving adduct formation has been able to be assessed. In this investigation, the guests were restricted to benzoic, *tert*-butylbenzoic, or hexadecanoic acid and the same 'titration' procedure ($CDCl_3$ as solvent) to that outlined above was employed.

In our initial study (ref. 11), 4-*tert*-butylbenzoic acid was shown to form a discrete host-guest assembly with the tetraazamacrocycle cyclam. The product was investigated by nmr titration, calorimetry, X-ray

diffraction, neutron diffraction and semi-empirical MO calculations. Thus monitoring the changes in the ^{1}H and ^{13}C nmr spectra during the incremental addition of 4-*tert*-butylbenzoic acid to a solution of cyclam in $CDCl_3$ clearly indicated the formation of a strong 2:1 host-guest complex; a parallel investigation using titration calorimetry confirmed this result. Crystallisation of a solution containing cyclam and 4-*tert*-butylbenzoic acid in a 2:1 ratio yielded a crystalline 4:1 complex. However, the X-ray structure of this product shows that only two 4-*tert*-butylbenzoic acid moieties interact directly with the cyclam molecule (via a network of hydrogen bonds involving all four amine groups). In this case the carboxylic acid moieties are orientated in 'axial' positions above and below the N_4-plane of the macrocycle which adopts a 'trans III' configuration; overall the product represents a system arranged for octahedral metal coordination. The X-ray and neutron studies also confirm the transfer of a carboxylic acid proton to an amine group of the macrocycle in each of the main hydrogen bonds linking the two bound carboxylate groups to the cyclam.

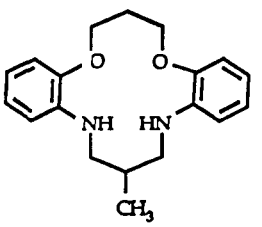
We have repeated the above NMR experiment using a D_2O/CD_3OD (5:95) mixture as the solvent. As before, 1:2 adduct formation was observed, with sharp inflections corresponding to stepwise interaction being again apparent - attesting to the strength of binding between host and guests in this system (in spite of the polarity of the medium in this case).

Many other amine-containing macrocycles have also been employed in similar studies (in $CDCl_3$) and in most instances stepwise adduct formation was apparent. A summary of the results obtained for the all-nitrogen donor macrocyclic systems is given below; the speciation (given in parenthesis) is based on the observed inflections in the respective titration plots; in isolated instances (especially where the binding is weak), it is subject to some uncertainty:
1,4,7-triazacyclononane(/*tert*-butylbenzoic acid (1:1, 1:2);
1,4,7,10-tetraazacyclodecane (cyclen)/4-*tert*-butylbenzoic acid (1:1, 1:2);
1,4,8,11-tetraazacyclotetradecane (cyclam)/benzoic acid (1:1, 1:2);
1,4,8,11-tetraazacyclotetradecane (cyclam)/hexadecanoic acid (1:1, 1:2);
Reduced Curtis macrocycle (tet-a)/hexadecanoic acid (1:2);
1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (tetramethylcyclam)/benzoic acid (1:1, 1:2);
1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (tetramethylcyclam)/hexadecanoic acid (1:1, 1:2);
1,4,8,11-tetrabenzyl-1,4,8,11-tetraazacyclodecane/benzoic acid (1:1, 1:2) [approximate stepwise stability constants (log values) 2.3 and 0.3];
1,4,8,11-tetrabenzyl-1,4,8,11-tetraazacyclodecane/benzoic acid (1:1, 1:2);[approximate stepwise stability constants (log values) 2.2 and 0.35];
Hexaaza-18-crown-6 (1:2, 1:3).

For the following mixed donor cyclic systems the following results were obtained:
1,10-diaza-18-crown-6/hexadecanoic acid (1:1, 1:2);
6,7,8,9,10,11,17,18-octahydro-5H-dibenzo[*e,n*][1,4]dioxa[8,12]diaza-cyclopentadecine/hexadecanoic acid (1:1);
1,12,15-triaza-3,4:9,10-dibenzo-5,8-dioxacycloheptadecane (1:1, 1:2).

It is clear from this series of studies that the stoichiometry of adduct formation depends on both the number and relative basicities of the individual nitrogen groups present in the respective structures, while being much less dependent on which carboxylic acid was employed for the individual experiments. An important outcome is that, under the conditions employed, *in all cases the stoichiometry of the respective adducts in $CDCl_3$ corresponded to the number of amine sites in the host ligand that had log protonation constants equal to or greater than about 6-7 in aqueous or aqueous/ methanol media.* Where all amine

sites were less basic than this, as occurs for example with **1, 2** and **3**, then no adduct formation was observed under the conditions employed.



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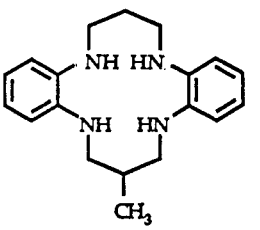

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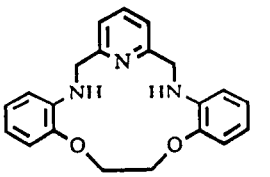

(3)

Apart from the applicability to host-guest studies of the present type, the above finding provides a 'rule of thumb' for use more generally in the design of other supramolecular systems.

In summary, the NMR titration technique involving both ^{1}H and ^{13}C NMR has proved to be a valuable method for detecting adduct formation in solution and for yielding the stoichiometry of the host-guest product(s) formed. Although not explicitly discussed above, it is also generally useful for indicating the sites of interaction between host and guests.

METAL-ION SOLVENT EXTRACTION

We have now investigated in some detail the use of selected ligand 'packages' of the type discussed above as assembled reagents in metal-ion solvent extraction studies. The results from these studies clearly indicate that ligand assembly may contribute to metal complex formation (and stability) under appropriate conditions. In our extraction studies this has normally been manifested as enhanced (synergistic) metal ion uptake behaviour when an appropriate ligand assembly, representing the components of a coordination shell, is present in the organic phase. This may be illustrated by reference to the tetrabenzylated cyclam/hexadecanoic system.

From the stepwise stability constants (see above), the interaction of 1,4,8,11-tetrabenzyl-1,4,8,11-tetraazacyclodecane with hexadecanoic acid in $CDCl_3$ is rather weak; nevertheless the NMR titration data give clear evidence for 1:1 and 1:2 adduct formation.

In a series of solvent extraction experiments (water/chloroform), the aqueous phase contained unbuffered copper(II) nitrate solution (10^{-3} mol dm^{-3}), maintained at pH 5.00 ±0.05, while the $CHCl_3$ phase incorporated 1,4,8,11-tetrabenzyl-1,4,8,11-tetraazacyclodecane (10^{-3} mol dm^{-3}) and varying amounts of hexadecanoic acid. Equal volumes of the aqueous and organic phases were employed and shaking was carried out for one hour at 25°C. The changes in the visible spectra of the organic layer were monitored as the concentration of hexadecanoic acid was increased. The results indicated an initial sharp rise in the amount of copper extracted on addition of hexadecanoic acid which, however, tapered off considerably after the hexadecanoic acid:macrocyclic ligand ratio rose above about two. Under the conditions employed hexadecanoic acid alone does not extract copper(II) while the extraction of this metal by the tetrabenzylated ligand alone is no more than about six percent (as determined by Atomic Absorption spectroscopy from the loss of copper from the aqueous phase). In the presence of a 2:1 ratio of hexadecanoic acid to macrocycle, extraction of copper(II) rose to 34 percent. Clearly, the macrocycle/carboxylic acid combination leads to synergistic extraction of copper in this case.

Under identical conditions, similar behaviour was also observed for nickel(II) but in this case the overall extraction efficiency was (not unexpectedly) considerably lower. In the absence of hexadecanoic acid, extraction of this ion by the macrocycle was negligible while it rose to three percent when both ligand components were present in the $CHCl_3$ phase - indicating that a degree of synergism also occurs in this case.

As mentioned briefly already, two somewhat subtle factors may be dominant in such behaviour. First, if the ligands are present in solution as an assembly of the required stoichiometry (rather than being mutually dispersed throughout the bulk solution), this will be expected to result in a favourable contribution towards metal-ion complexation since an element of coordination shell preorganisation is present. That is, the entropy term for complexation by the assembled ligands should be more favourable (on average) than for the situation in which the equilibrium lies towards the corresponding dissociated ligand species. Namely, less loss of disorder on complex formation will occur in the former case.

Secondly, host-guest formation in the organic phase may affect the overall lipophilicity of the system; reagent lipophilicity is an important factor influencing the efficiency of solvent extraction behaviour. In this context, we have already demonstrated for a particular systems that if adduct formation occurs between a somewhat hydrophobic amine-containing ligand and a lipophilic long-chain fatty acid, then bleeding of the amine component from the organic phase to the aqueous phase is inhibited. For example, this was shown to be the case for cyclam on the addition of hexadecanoic acid. In a related manner, if the long-chain acid forms part of the coordination sphere of the subsequent metal complex generated in the organic phase, then this will enhance complex lipophilicity and hence also reduce its loss from the organic phase. By such means, the overall efficiency of extraction may be increased.

CONCLUDING REMARKS

In view of the widespread interest in hydrogen bonded host-guest complexes, it was of some surprise that little information was available concerning the relationship between the basicity of amine sites in aqueous media relative to their ability to undertake hydrogen-bond formation in non-aqueous solvents such as chloroform. The present investigation of this relationship thus appears of fundamental importance to a number of areas across supramolecular chemistry.

Similarly, application of the assembly concept clearly has the potential to systematise a range of already reported metal-ion complexation behaviour. However, perhaps more importantly, it also has implications for the design of new reagents for metal-ion discrimination and especially ones for use in metal-ion solvent extraction systems.

ACKNOWLEDGMENT

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