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Solution thermodynamics of amino acid-18 crown 6 and amino acid-cryptand 222 complexation reactions

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Abstract – The thermodynamics of complexation between synthetic macrocyclic ligands (18 crown 6 and cryptand 222) and amino acids in methanol and ethanol is discussed. Attention is drawn to the enthalpy–entropy compensation effect of these ligands and amino acids in these solvents. From the thermodynamic data for these complexation reactions together with computer calculations, active sites of guest and host molecules are suggested. Transfer parameters from methanol to ethanol of amino acid–18 crown 6 complexes recently isolated, amino acids and the 18 crown 6 ligand from methanol to ethanol are discussed in relation to complexation data.

INTRODUCTION

Crown ethers (ref 1) and cryptands (ref 2) are able to interact with ammonium and substituted ammonium salts through hydrogen bond formation (refs 3–6). Electrostatic interactions between the nitrogen atom (positively charged) of the ammonium group and the oxygen donor atoms of the crown ether molecule may also contribute to the stabilisation of these complexes. A schematic representation of the interactions between 18 crown 6 and the ammonium cation is shown in Fig 1.

Encouraged by these findings and the observation that 18–crown 6 (1,4,7,10,13,16–Hexaoxa–cyclooctadecane) and cryptand 222 (4,7,13,16,21,24–Hexaoxa–1,10 diazabicyclo [8.8.8] hexacosane) enhance the solubility of amino acids in the alcohols (refs 7 & 8) we decided to focus attention on the energetics of the complexation process involving DL–amino acids and macrocyclic ligands (18 crown 6 and cryptand 222) in methanol (MeOH) and ethanol (EtOH) as the reaction media. In this paper we shall first show the main features so far observed on the thermodynamics of amino acid–crown and amino acid–cryptand complexation reaction in the alcohols. We shall then explore briefly the existence of any possible correlation between complexation and thermodynamic data for the transfer of the free and complexed amino acid, as well as the macrocyclic ligands among the alcohols. Finally, we shall discuss the implications of these results to areas of current interest.

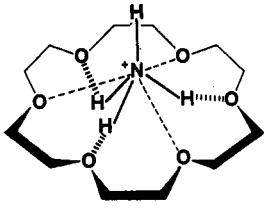

Fig 1. Ammonium–18 crown 6 interactions

TABLE 1. Stability constants (log K_s) and thermodynamic parameters of complexation of DL–alanine and DL–phenylalanine with macrocyclic ligands (18 crown 6 and cryptand 222) in methanol at 298.15K.

Amino acid	log K_s	$\Delta_cG°$ kJ mol^{-1}	$\Delta_cH°$ kJ mol^{-1}	$\Delta_cS°$ JK^{-1} mol^{-1}
DL–Ala (18C6)	3.59	–20.49	–45.94	–85.4
DL–Ala (222)	3.22[a]	–18.38[a]	–15.40[a]	10.0[a]
DL–Phe (18C6)	3.15	–17.98	–39.18	–71.1
DL–Phe (222)	3.48[a]	–19.86[a]	–10.21[a]	32.3[a]

[a]Data from Ref. 7

THERMODYNAMICS OF AMINO-ACID-MACROCYCLIC COMPLEXATION

In order to demonstrate the complexing abilities of 18 crown 6 (18C6) and cryptand 222 (222) in methanol some representative data for the stability constant (expressed as log K_s), and the thermodynamic parameters of complexation [free energy, $\Delta_cG°$, enthalpy, $\Delta_cH°$, entropy $\Delta_cS°$] of two amino acids [DL–alanine (DL–Ala) and DL–phenylalanine (DL–Phe)] with 18 crown 6 and with cryptand 222 in methanol at 298.15K obtained by titration calorimetry are listed in Table 1.

For monoamino monocarboxylic acids, the dipolar ion in which the amino group is protonated and the carboxylic group is dissociated is the predominant amino acid form in methanol and ethanol (ref. 7). Therefore complexation data are referred to the process

$$H_3\overset{+}{N}\cdot CH(R)\cdot COO^-(ROH) + 18C6(ROH) \longrightarrow 18C6\ H_3\overset{+}{N}\cdot CH(R)\cdot COO^-(ROH) \quad (1)$$

or

$$H_3\overset{+}{N}\cdot CH(R)\cdot COO^-(ROH) + 222(ROH) \longrightarrow 222\ H_3\overset{+}{N}\cdot CH(R)\cdot COO^-(ROH) \quad (2)$$

The most notable feature of the thermodynamic data on amino acid macrocyclic complexation reactions (involving eighteen DL–amino acids for each ligand) is the small variation in the stability constant data (hence free energy of complexation). Undoubtedly, the stability constant values (relatively large) reflect that the 18 crown 6 and the cryptand 222 ligands are able to interact with amino acids in methanol. The only likely site of interaction of the guest molecule with either 18 crown 6 or cryptand 222 is through the amino group of the amino acid and the donor atoms of the ligand. This has been confirmed from the results obtained from pH titrations and from calorimetric studies using 18 crown 6 and N–blocked amino acids in methanol. However, the free energy data clearly reflect that 18 crown 6 and cryptand 222 are unable to selectively recognise these amino acids in methanol. Selectivity (as reflected in the free energy term) can be achieved by a decrease or an increase in the number of hydrogen atoms available for bond formation in the guest molecule. Thus, a drop in stability was observed for DL–proline (an amino acid containing a secondary amino group) and these two ligands in methanol, whilst 2:1 complexes were found for lysine (diamino monocarboxylic acid) with 18 crown 6 (Fig. 2) and cryptand 222 in this solvent. It should be emphasised that formation of 2:1 complexes of crown ethers and cryptands with diammonium guest cations have been reported (refs. 3 & 9).

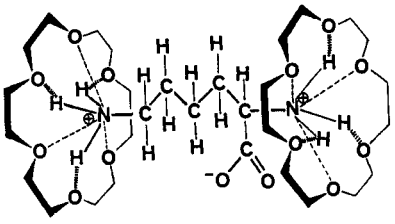

Fig. 2. Computer modelling for the 18 crown 6–lysine complex.

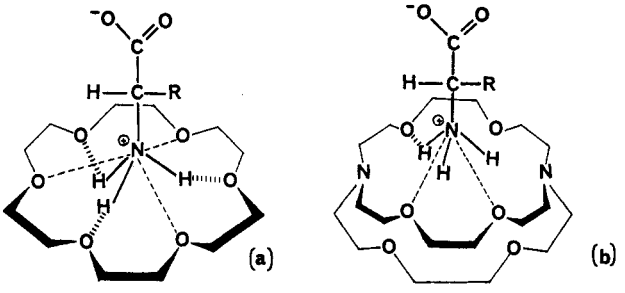

Fig. 3. Suggested interactions of amino acids with (a) 18 crown 6 and (b) cryptand 222.

The representative data shown in Table 1 reflect that two different combinations of Δ_cH° and Δ_cS° values lead to the observed free energies (almost constant) of complexation of amino acids and these ligands in methanol. Thus, for 18 crown 6 the process is enthalpically controlled, whilst for these amino acids (except glycine) and cryptand 222, the process is enthalpically and entropically favoured (ref. 7). This may be explained in terms of the structural differences between crown ethers and cryptands. The former ligands described by Gutsche (ref. 10) as loops are able to interact more effectively with the amino acids than the latter ligands, characterised by a three dimensional cavity. As a result, an increase in enthalpic stability is observed for amino acids complexed with 18 crown 6 in methanol with respect to the same amino acids complexed with cryptand 222 in this solvent. These findings are in accord with the results obtained from computer calculations (Fig.3) which suggest that, unlike amino acid–18 crown 6 interactions (three N–H···O and three N^+–H···O) the complexation of amino acids with cryptand 222 is likely to occur through the formation of one hydrogen bond and two N^+···O electrostatic interactions (ref. 7)

Rather interesting was to investigate the effect of the medium on the binding of macrocyclic ligands and DL–amino acids. Comparison of the data for 18 crown 6 and DL–alanine (log K_s = 3.69; Δ_cG° = –21.06 kJ mol^{-1}; Δ_cH° = –54.52 kJ mol^{-1}; Δ_cS° = –112.2 JK^{-1} mol^{-1}) and DL–phenylalanine (log K_s = 3.36; Δ_cG° = –19.18 kJ mol^{-1}; Δ_cH° = –56.57 kJ mol^{-1}; Δ_cS° = –125.7 JK^{-1} mol^{-1}) (refs 7 & 8) in ethanol and those in methanol (Table 1) shows that (unlike free energies) enthalpies and entropies of complexation are quite sensitive to solvent variation. In fact, there is a substantial amount of experimental evidence suggesting that the binding of amino acids to macrocyclic ligands is enthalpically selective. Indeed, significant enthalpy changes are observed for i) a given ligand and the various amino acids, ii) a given amino acid and the various ligands and iii) different reaction media (methanol to ethanol). It is generally observed that an increase in enthalpic stability (Δ_cH° more negative) is accompanied by a decrease in entropy (Δ_cS° more negative). In conclusion, the relatively small variation in the free energy term (Δ_cG°) is the result of a remarkable enthalpy – entropy compensation effect (refs 11 & 12). An illustration of this effect is the linear relationship shown in Fig. 4.

The lower (cryptand 222) and middle (18 crown 6) portion of the line mostly reflect the ligand effect on the Δ_cH° and Δ_cS° in methanol. The solvent effect on these parameters is shown in the middle (methanol) and upper (ethanol) portion of this line.

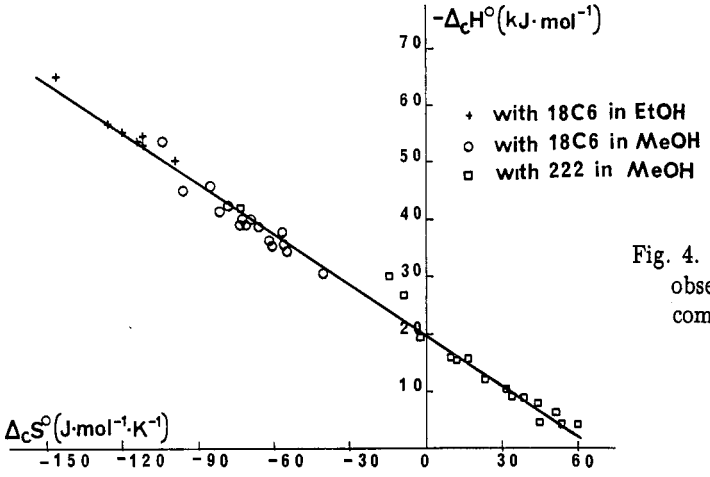

Fig. 4. Enthalpy–entropy compensation effect observed in amino–acid – macrocyclic complexation reactions.

Significant findings as far as enthalpies are concerned are those related with the higher enthalpic stability observed for DL–amino acids relative to corresponding data for D and L amino acids and these macrocyclic ligands in methanol. This is exemplified by complexation data for cryptand 222 and DL (Δ_cH° = –10.21 kJ mol^{-1}), D (Δ_cH° = –5.69 kJ mol^{-1}), L (Δ_cH° = –6.39 kJ mol^{-1}) phenylalanine in methanol (ref 7). Enthalpy data for D and L amino acids and these ligands are again largely compensated by entropy data. Since hardly any variation is found in the free energy, therefore, Δ_cH° and Δ_cS° data for these amino acids fall within the linear relationship shown in Fig. 4. Further experimental work is now in progress in order to establish whether or not the enthalpy increase observed for DL–amino acids and these ligands is associated with cooperativity effects resulting from the racemic mixture.

THERMODYNAMIC PARAMETERS OF TRANSFER

In a recent paper presented at the Fourth International Symposium on Solubility Phenomena, Danil de Namor (ref 13) emphasised the need of accurate transfer data for the host, guest and resulting complex in the interpretation of binding processes involving macrocyclic–substrate complexation reaction in different reaction media.

FREE ENERGY OF TRANSFER

Eq. 3 illustrates the relationship between the free energies of complexation Δ_cG° in the two solvents (MeOH and EtOH) and corresponding data for the transfer, Δ_tG° of the amino acid (AA), the crown ether (18C6) and the complexed amino acid (AA–18C6) from the reference solvent (MeOH) to ethanol.

$$\Delta_cG^\circ\ (MeOH) - \Delta_cG^\circ\ (EtOH) = \Delta_tG^\circ\ (AA\text{–}18C6) - \Delta_tG^\circ\ (18C6) - \Delta_tG^\circ\ (AA) \qquad \text{(eq. 3)}$$

Since for most amino acids studied, Δ_cG°(MeOH) $\cong$ Δ_cG°(EtOH) and given that Δ_tG°(18C6) (MeOH $\rightarrow$ EtOH) = 0.05 kJ mol^{-1} (ref 8) the following correlation holds

$$\Delta_tG^\circ(AA\text{–}18C6) \cong \Delta_tG^\circ\ (AA) \qquad \text{(eq. 4)}$$

This interpretation is further corroborated by the results shown in table 2 for the transfer free energies of DL–amino acids and DL–amino acid–18 crown 6 complexes (recently isolated) from methanol to ethanol derived from direct solubility measurements of these compounds in methanol and ethanol.

TABLE 2. Representative data for the transfer free energy of amino acids and amino acid–18 crown 6 complexes from methanol to ethanol at 298.15 K (ref 8).

AA	Δ_tG° kJ mol^{-1}	AA–18C6	Δ_tG° kJ mol^{-1}
DL–Ala	3.70	DL–Ala–18C6	4.92
Gly	3.35	Gly–18C6	4.69
DL–Phe	5.30	DL–Phe–18C6	3.93
DL–Val	5.40	DL–Val–18C6	6.64

Gly and Val are the abbreviations for the amino acids glycine and valine; respectively.

When an amino acid interacts with 18 crown 6 through the amino group, the solvation shell of this group is most likely to be replaced by the donor atoms of the ligand. The transfer free energy data suggest that the differences in solvation of the amino acid–18 crown 6 complexes in the two alcohols do not differ significantly from the differences in solvation of the free amino acids in these solvents.

This is in accord with the suggested model (Fig. 3) which shows that in the amino acid–18 crown 6 complex, most of the amino acid molecule is exposed to the solvent. As far as solvation is concerned, the free energy is the most relevant thermodynamic parameter. Therefore, we conclude that not appreciable differences are found in the transfer free energy of amino acids and their complexes among these two solvents.

ENTHALPY AND ENTROPY OF TRANSFER

Amino acids are not soluble enough in methanol and ethanol as to carry out direct measurements of their heats of solution in these solvents. Consequently, transfer enthalpies of amino acids from methanol to ethanol could not be obtained from solution enthalpies. This is not the case for 18 crown 6 and amino acid–18 crown 6 complexes. In fact, the solubility of these complexes is considerably higher than the solubility of these amino acids in these solvents. Therefore, enthalpies of transfer of 18 crown 6 and amino acid–18 crown 6 complexes were the result of direct measurements of their heats of solution in these solvents. Representative values for the transfer enthalpies of amino acid–18 crown 6 complexes from methanol to ethanol are given in table 3, together with corresponding data for 18 crown 6.

TABLE 3. Enthalpies of transfer of 18 crown 6 and amino acid–18 crown 6 complexes from methanol to ethanol at 298.15K.

Compound	$\Delta_t H^\circ$/kJ mol^{-1}
18C6	2.45
DL–Ala–18C6	1.92
Gly–18C6	2.05
DL–Phe–18C6	2.76
DL–Val–18C6	3.60

Analysis of the data given in Table 3 suggests that,

$$\Delta_t H^\circ \text{ (18C6) (MeOH} \rightarrow \text{EtOH)} \cong \Delta_t H^\circ \text{ (AA18C6) (MeOH} \rightarrow \text{EtOH)} \quad \text{(eq. 5)}$$

Therefore, taking into account eq. 3 expressed in terms of ΔH, it emerges that

$$\Delta_c H^\circ \text{ (MeOH)} - \Delta_c H^\circ \cong \Delta_t H^\circ \text{ (AA) (MeOH} \rightarrow \text{EtOH)} \quad \text{(eq. 6)}$$

Eq. 6 explains very well the differences in enthalpies of complexation of 18 crown 6 and amino acids as a result of solvent variation. The $\Delta_t H^\circ$ values for the DL–amino acids from methanol to ethanol (DL–Ala; 8.05 kJ mol^{-1}; Gly; 10.72 kJ mol^{-1}; DL–Phe; 17.80 kJ mol^{-1}; DL–Val; 21.73 kJ mol^{-1}) calculated from a rearrangement of eq. 3 (expressed in terms of enthalpy) indicate that the process is endothermic. Consequently, amino acids are enthalpically more stable in methanol than in ethanol. Our results show that the lower is the enthalpic stability of an amino acid in a reaction medium, the greater is the enthalpy of complexing of that amino acid and 18 crown 6 in that medium. In fact, the enthalpy term reflects a competition between the solvent and the ligand for the amino acid. Since there is a compensation effect between enthalpies and entropies, a similar effect is observed in terms of entropies. For the free amino acids, $\Delta_t S^\circ$ values (DL–Ala; 14.6 JK^{-1} mol^{-1}; Gly; 24.7 JK^{-1} mol^{-1}; DL–Phe; 41.9 JK^{-1} mol^{-1}; DL–Val; 55.4 JK^{-1} mol^{-1}) indicate that this process is intropically favoured. Therefore, as discussed in previous sections; $\Delta_c S^\circ$ of amino acids and 18 crown 6 in methanol are more favoured (less negative) than corresponding data in ethanol. However, it must be emphasised that in terms of entropy, the differences observed in the entropies of complexation of these amino acids and 18 crown 6 in these two solvents (MeOH and EtOH) seem to be related not only to the transfer free entropy of the amino acid but also to the transfer entropy of the ligand (ref. 8).

Finally, we stress that the free energy of transfer of the free and complexed amino acid (table 2) is the result of an enthalpy–entropy compensation effect which requires further investigations.

FINAL REMARKS

The enhancement in the solubility of biologically important compounds by the addition of macrocyclic ligands is an area of considerable interest. The influence of cryptands on the solubility of electrolytes has been discussed by Cox and Schneider (ref. 14). An immediate consequence of amino acid–macrocyclic complexation reactions is the higher solubility of the complex with respect to the free amino acids in the alcohols. Thus, the solubility value for glycine is 4.26×10^{-3} mol cm^{-3} in methanol at 298.15K (ref. 15) and that for the glycine–18 crown 6 complexation in the same solvent at the same temperature is 1.63×10^{-1} mol dm^{-3}. It is quite clear that the process of complexation of 18 crown 6 with amino acids leads to the formation of compounds of different solubility properties to that of the free amino acid.

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