The First Thermodynamic Data on the Complexation of Amino Acids with Cryptand 222 in Methanol at 298.15 K

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The macrobicyclic ligand cryptand 222 can interact with amino acids in methanol to form stable 1 : 1 complexes; thermodynamic data for these complexation reactions are first reported and together with computer calculations, these suggest active sites on both guest and receptor molecules.

Although the main interest in macrocyclic ligands has centred on their complexation with metal ions (particularly s block cations),[1] in recent years a new, but nevertheless interesting aspect of the chemistry of macrocyclic ligands has emerged. This is related to their ability to form hydrogen bond complexes with alkylammoniuum salts[2] and with amine ligands of metal complexes.[3] Although each individual bond is relatively weak, the collective interaction is sufficiently strong to give stable, isolable complexes. Therefore, we decided to explore the possibility of using cryptands as receptors for amino acids, $^{+}H_3N{\cdot}CH(R)CO_2^{-}$.

Our success using thermodynamics in studies on the complexation of metal cations with cryptands,[4—7] led us to focus attention on the energetics of the process involving cryptands and amino acids. These data are of significant importance to several areas of research, such as: (i) the transport of amino acids across cell membranes; (ii) solubility enhancement of amino acids in organic solvents; (iii) the use of cryptands for amino group protection in peptide synthesis; (iv) separation of amino acids and their isomeric forms. Herein we report the stability constant (expressed as $\log K_s$)

Table 1. Thermodynamic parameters of amino acids and cryptand 222 in methanol at 298.15 K.

Amino acid	$\log K_s$	ΔG_c° /kJ mol^{-1}	ΔH_c° /kJ mol^{-1}	ΔS_c° /J K^{-1} mol^{-1}
Gly	3.48 ± 0.01	−19.86	−41.77 ± 0.14	−73.5
DL-Ala	3.22 ± 0.10	−18.38	−15.40 ± 0.94	10.0
DL-Phe	3.48 ± 0.15	−19.86	−10.21 ± 0.64	32.3
L-Phe	3.75 ± 0.20	−21.41	−6.39 ± 1.06	50.4
D-Phe	3.47 ± 0.15	−19.80	−5.69 ± 0.38	47.3
DL-Ser	3.64 ± 0.02	−20.78	−15.74 ± 0.23	16.9
DL-Pro	2.46 ± 0.05	−14.04	−5.20 ± 0.56	29.6
DL-Trp	3.72 ± 0.20	−21.23	−7.92 ± 0.78	44.6

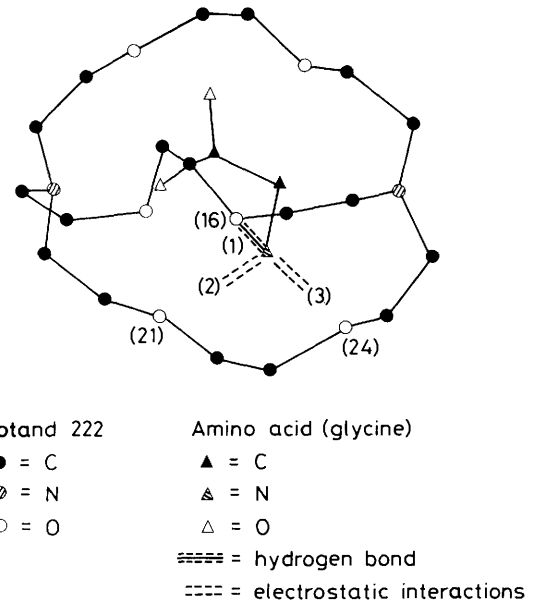

Figure 1. Computer modelling for the cryptand 222–amino acid (glycine) interaction.

and the thermodynamic parameters [free energy (ΔG_c°), enthalpy (ΔH_c°), and entropy (ΔS_c°)] of a number of amino acids [glycine (Gly), DL-alanine (DL-Ala), DL-phenylalanine (DL-Phe), DL-serine (DL-Ser), DL-proline (DL-Pro), and DL-tryptophan (DL-Trp)] and the macrobicyclic ligand cryptand 222 (222) in methanol (MeOH) at 298.15 K. Titration calorimetry was used to obtain these data. The stoicheiometry of the reaction for the amino acid/cryptand complex as confirmed by this technique is 1 : 1. Potentiometric titration (pH measurements) indicated that in methanol, amino acids are zwitterionic; therefore the data (Table 1) refer to the process in equation (1). These results are analysed in terms of the guest molecule (the amino acid), the receptor cryptand (222) and the reaction medium (methanol).

$$^+H_3NCH(R)COO^-(MeOH) + 222(MeOH) \rightarrow 222^+H_3NCH(R)COO^-(MeOH) \quad (1)$$

As far as the guest molecule is concerned the only likely interaction with cryptand 222 is through the amino group of the guest molecule and the donor atoms of the ligand. This is confirmed by the results (Table 1) for the amino acid DL-Pro, where the number of hydrogen atoms available for interaction with cryptand 222 is reduced with respect to other amino acids in this series. The decrease in stability ($\log K_s$) of the DL-Pro 222 complex with respect to other amino acids is the most notable feature. Further evidence that the amino group is the active site in the guest molecule is found in our recent data for the cryptand–lysine (2 : 1) complex in methanol.

For these amino acids (except glycine) the process is enthalpically and entropically favoured. It should be noted that all amino acids except glycine contain one asymmetric carbon. The stability (in enthalpic terms) for these complexes follows the sequence Gly > DL-Ala ≃ DL-Ser > DL-Phe > DL-Trp. The opposite sequence is observed in terms of entropy. These trends seem to be the outcome of steric factors as a result of the presence of substituent groups on the α-carbon of the amino acid. For amino acids containing aromatic groups (DL-Phe and Trp), steric factors are enhanced.

It is rather interesting to compare the ΔH_c° and ΔS_c° values for D-, L-, and DL-Phe; although no significant variation is observed for D- and L-Phe, it is surprising to find that these values differ significantly for those shown for DL-Phe. Indeed, the ΔH_c° value for the latter amino acid–cryptand complex is about twice that observed for the D- or L-Phe–cryptand 222 complexes. We are investigating this further by considering other D- and L-amino acid–cryptand 222 complexes in methanol.

As far as the receptor is concerned, the possibility of inclusion complexes of cryptand 222 with amino acids is ruled out exclusively on the basis of cavity size limitations. The results of our computer calculations using a COSMIC package[8] indicate that the conformation which corresponds to the formation of the lowest energy (highest stability) cryptand 222–amino acid (glycine) complex is that shown in Figure 1. The $-NH_3^+$ group of the guest molecule interacts with the oxygen atoms of the ligand. This interaction seems to occur through the formation of one hydrogen bond N–H(1)··O(16) (calc. distance 1.57 Å). Distances of 3.41 Å for N–H(2)··O(21) and 3.18 Å for N–H(3)··O(24) are considered to be too long for hydrogen bond formation and N^+··O electrostatic interactions are more likely to occur. Thermodynamic studies carried out with these amino acids and 18-crown-6 as receptors support this interpretation.[9] Calorimetric data indicate that no complexation takes place between these amino acids and cryptand 222 in water; a good solvating medium for amino acids such as water excludes complex formation with cryptand 222, as previously stated by us.[5]

We conclude that our most important findings are: (i) complexation of amino acids with cryptand 222; (ii) thermodynamic data associated with the formation of 1 : 1 complexes (for amino acids containing one amino group) in methanol are first reported (for most amino acids, the process in enthalpically and entropically controlled); (iii) active sites in the guest and receptor molecules are suggested from interpretation of thermodynamic data and computer calculations. Finally, we report that semi-quantitative studies on the solubility of amino acids in methanol, ethanol, and propan-1-ol, indicate that the addition of cryptand 222 to saturated solutions of amino acids in the alcohols results in a significant increase of their solubility in these reaction media. These findings have encouraged us to proceed with quantitative studies.

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