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# The Complexation of Some Amino Acids by Isomers of Dicyclohexano-18-Crown-6 and 18-Crown-6 in Methanol

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**Abstract**

The complexation of some amino acids (glycine, L-alanine, L-leucine, L-valine, and L-serine) by the *cis-syn-cis* and *cis-anti-cis* isomers of dicyclohexano-18-crown-6 (DC18C6) in methanol was studied by calorimetric titration measurements. Both isomers exhibited a significant ability to bind the amino acids mentioned above. The results obtained demonstrate that the structural isomers of DC18C6 are significantly different in terms of thermodynamics concerning their complexation with the amino acids. The stability constants and the thermodynamic data for the reaction of the amino acids under study in protonated form and 18-crown-6 (18C6) are reported.

## Introduction

It is well known that the selective complexation ability of crown ethers is one of their most attractive properties. Intermolecular and intramolecular hydrogen bonds and other noncovalent interactions are specific in molecular recognition [1–7]. Crown ethers are of considerable interest in biologically modeling of ion transport processes, enzyme catalysis, and antibody-antigen associations [8–16]. In this respect, the studies concerning the structural and thermodynamic aspects of interactions between macrocyclic receptors and biological compounds are useful in investigating biochemical processes and analytical applications as well.

The macrocyclic ligand dicyclohexano-18-crown-6 was employed in numerous studies concerning the complexation with different compounds, liquid–liquid extraction of some metal ions, and transport through liquid membranes [17–21]. According to the results reported in some publications, the *cis-syn-cis* and *cis-anti-cis* isomers of DC18C6 exhibit a different behavior in their complexation or extraction with various compounds [18, 22]. In the case of solvent extraction of strontium (II) and lead (II) from nitric acid solutions and various nitrate salts, a mixture of *cis* isomers of DC18C6 extracts metal ion slightly less than the pure *cis-syn-cis* isomer itself [23]. One explanation may be that the *cis-anti-cis* isomer shows much lower extraction. The effects of DC18C6 in the simultaneous determination of *p*-, *m*-, and *o*-nitrophenol, respectively were investigated and showed that DC18C6 is a good extractant but less efficient than dibenzo-18-crown-6 and 18-crown-6 under the specified conditions [24].

Although the ability of DC18C6 as an extractant or carrier through liquid membrane involved in metal ion separation has been extensively studied, few papers are dedicated to complexation of biological compounds [5, 25–27].

In our previous publications we presented different aspects of amino acids complexation by various macrocyclic ligands, as well as the liquid–liquid extraction of amino acids and the transport of amino acids through liquid membranes using the macrocyclic ligands as carriers [7, 10, 11, 28–30].

In this work we investigated some aspects of the complexation between the *cis-syn-cis* and *cis-anti-cis* isomers of dicyclohexano-18-crown-6 and several amino acids (L-alanine, L-leucine, L-valine, L-serine, and glycine) in methanol. The resulting data are compared with the complexation of the above mentioned amino acids by 18C6.

## Experimental

Dicyclohexano-18-crown-6 (DC18C6, see Figure 1) as a mixture of isomers was obtained from Janssen. The separation of the DC18C6 mixture into the individual isomers, namely *cis-syn-cis* and *cis-anti-cis* was carried out using Izatt's procedure [31, 32]. Reagent grade 18C6 was obtained from Merck (Figure 1) and used without further purification.

The following amino acids were employed: L-alanine (L-Ala, Fluka), L-leucine (L-Leu, Fluka), L-valine (L-Val, Fluka), L-serine (L-Ser, Fluka), and glycine (Gly, Fluka). They were of the highest purity commercially available and used without further treatment. Sodium tetraphenylborate (Fluka) was used without further purification. For the preparation of the corresponding tetraphenylborates the

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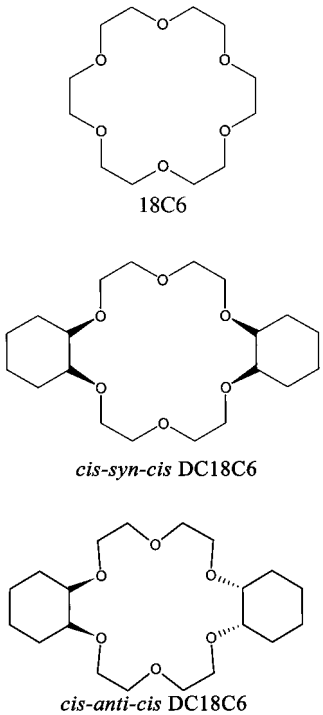


*Figure 1.* Chemical structures of the ligands used: 18C6, DC18C6 *cis-syn-cis*, and DC18C6 *cis-anti-cis*.

amino acids were dissolved in water and hydrochloric acid (known concentration) and an aqueous solution of sodium tetraphenylborate was added. The tetraphenylborate salts of the amino acids precipitated. The resulting precipitates were filtered, washed and dried in vacuum. Anhydrous methanol (Merck; $H_2O$ content less than 0.01%) was used as solvent. The stability constants and the reaction enthalpies were determined using calorimetric titrations (Tronac Model 450). To perform calorimetric titrations solutions of the ligand ($1.6 \times 10^{-2}$ mol/L) were titrated into a solution of the amino acid ($1 \times 10^{-3}$ mol/L). All measurements were repeated five times. The calculation of the stability constant and reaction enthalpy was performed according to the measured thermogram [33].

## Results and discussion

The values of the stability constants, the reaction enthalpy and entropy for the complexation of several tetraphenylborate salts of L-amino acids and glycine with both isomers of DC18C6 in methanol are presented in Table 1.

As can be seen from Table 1, the stability constants for the reaction of the L-Ala with *cis-syn-cis*-DC18C6 are two orders of magnitude higher than the corresponding value for the same amino acid with *cis-anti-cis*-DC18C6. There are not many differences in the values of the reaction enthalpies for the complexation of L-Ala with both isomers of DC18C6.

The values of the stability constants of the amino acid complexes under study with both isomers of DC18C6 and with the crown ether 18C6 (Table 2) were comparable having the same order of magnitude. It is well known that crown ether 18C6 is a good molecular receptor for the ammonium group [4].

*Table 1.* Stability constants log $K$ ($K$ in $dm^3\ mol^{-1}$) and thermodynamic parameters $\Delta H^\circ$ and $T\Delta S^\circ$ (in kJ $mol^{-1}$) for the complexation of some amino acids$*HBPh_4$ with *cis-syn-cis*-DC18C6 and *cis-anti-cis*-DC18C6 in methanol at 25 °C

| Ligand and amino acid | Log $K$ | $-\Delta H^\circ$ | $T\Delta S^\circ$ |
|---|---|---|---|
| *cis-syn-cis*-DC18C6 | | | |
| Gly | $3.18 \pm 0.03$ | $63.0 \pm 0.4$ | $-44.8 \pm 0.6$ |
| L-Ala | $4.35 \pm 0.01$ | $12.9 \pm 0.3$ | $11.9 \pm 0.8$ |
| L-Leu | $2.56 \pm 0.04$ | $7.4 \pm 0.2$ | $7.2 \pm 0.5$ |
| L-Val | $2.52 \pm 0.02$ | $3.6 \pm 0.5$ | $10.8 \pm 0.7$ |
| L-Ser | $2.54 \pm 0.03$ | $2.6 \pm 0.6$ | $11.9 \pm 0.5$ |
| *cis-anti-cis*-DC18C6 | | | |
| Gly | $2.55 \pm 0.02$ | $13.8 \pm 0.6$ | $0.8 \pm 0.7$ |
| L-Ala | $2.57 \pm 0.01$ | $8.8 \pm 0.5$ | $5.9 \pm 0.8$ |
| L-Leu | $2.54 \pm 0.02$ | $5.8 \pm 0.4$ | $8.7 \pm 0.6$ |
| L-Val | $2.56 \pm 0.01$ | $2.3 \pm 0.7$ | $12.3 \pm 0.5$ |
| L-Ser | $2.48 \pm 0.04$ | $0.8 \pm 0.5$ | $13.3 \pm 0.3$ |

*Table 2.* Stability constants log $K$ ($K$ in $dm^3\ mol^{-1}$) and thermodynamic parameters $\Delta H^\circ$ and $T\Delta S^\circ$ (in kJ $mol^{-1}$) for the complexation of some amino acids$*HBPh_4$ with 18C6 in methanol at 25 °C

| Amino acid | Log $K$ | $-\Delta H^\circ$ | $T\Delta S^\circ$ |
|---|---|---|---|
| Gly | $3.32 \pm 0.02$ | $63.4 \pm 0.3$<br>59.6[a] | $-44.5 \pm 0.4$ |
| L-Ala | $3.26 \pm 0.04$ | $47.2 \pm 0.6$<br>47.9[a] | $-28.6 \pm 0.6$ |
| L-Leu | $2.94 \pm 0.01$ | $56.7 \pm 0.8$ | $-40.0 \pm 0.3$ |
| L-Val | $3.16 \pm 0.02$ | $32.6 \pm 0.5$<br>35.1[a] | $-14.5 \pm 0.7$ |
| L-Ser | $3.02 \pm 0.05$ | $8.2 \pm 0.7$ | $9.0 \pm 0.8$ |

[a] From [28].

Large differences were obtained for the values of the reaction enthalpies and entropies for the complexes of amino acids with isomers of DC18C6 and with the ligand 18C6. The complexation of L-Ala, L-Leu and L-Val with 18C6 was mainly favored by the enthalpic contributions. In the case of L-Ser there is a similar situation concerning the reaction enthalpies and entropies for the complexation with both isomers of DC18C6 and crown ether 18C6, respectively. The values of the reaction enthalpy obtained for the complexation of L-Ala, Gly, and L-Val (except L-Ser) in protonated forms with 18C6 are in agreement with those already presented [31]. The structural isomers of DC18C6 displayed differences in the thermodynamics of their complexation with the amino acids under study. The complexation of *cis-syn-cis*-DC18C6 with L-Leu is both enthalpically and entropically stabilized. The stability constants for the complexation of L-Val with both isomers of DC18C6 are nearly identical. In conclusion, small values of the reaction enthalpies for complexation of L-Val with both isomers of DC18C6 were obtained. In this case, the complex forma-

tion is mainly favored by entropic contributions. The results given in Table 1 indicate a small variation in the values of stability constants for the complexes of L-Ser by both isomers of DC18C6 in methanol. The values of the reaction enthalpies are small and the values of the reaction entropies are positive. The same results were obtained for complexation of both amino acids in protonated forms with 18C6 (Table 2).

The effect of both isomers of DC18C6 was very clear for the complexation of *cis-syn-cis*-DC18C6 and *cis-trans-cis*-DC18C6 with Gly. Thus, a large negative value of the reaction enthalpy is observed for the complexation of glycine with *cis-syn-cis*-DC18C6 accompanied by a large negative value of reaction entropy. In the case of glycine the highest value of the reaction enthalpy was obtained for the complexation with *cis-syn-cis*-DC18C6 comparable with the complexation of glycine by 18C6. For the complexation of glycine with *cis-anti-cis*-DC18C6 a small value for reaction enthalpy was obtained. The values of the stability constants for complex formation between glycine and *cis-syn-cis*-DC18C6 compared to those of complex formation between glycine and 18C6 proved to be are nearly identical. A small value for the stability constant was obtained in the complexation of glycine with *cis-anti-cis*-DC18C6.

## Conclusion

Our experimental results indicate that both the *cis-syn-cis* and *cis-anti-cis* isomers of DC18C6 and 18C6 exhibit the ability to complex the amino acids. The values of the stability constants obtained for complexation of the selected amino acids with both isomers of DC18C6 were comparable with the results for the complexation of the same amino acids in protonated forms with 18C6. However, differences can be observed for the results of reaction enthalpy and entropy in this case. Further work on this topic is in progress.

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