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ORIGINAL ARTICLE

Conductance study of the thermodynamics of complexation of amantadine, rimantadine and aminocyclohexane with some macrocyclic compounds in acetonitrile solution

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Abstract A conductance study concerning the interaction between cationic organic ammonium ions amantadine, rimantadine, and aminocyclohexane with 18-crown-6 (18C6), dicyclohexyl-18-crown-6 (DC18C6) and cryptand C222 in acetonitrile solution has been carried out at different temperatures. The stability constants of the resulting 1:1 cornplexes at various temperatures were determined from the computer fitting of molar conductance-mole ratio data. The enthalpy and entropy of complexation reactions were evaluated from the temperature dependence of the formation constants. The influences of different parameters such as steric hindrance of organic amines and macrocycles, conformations of the free and complexed ligands, and solvent-ligand interaction on the thermodynamic data are discussed.

Keywords Amantadine · Rimantadine · Aminocyclohexane · Macrocyclic ligands · Complexation · Acetonitrile · Molar conductance · Stability constant · Enthalpy · Entropy

Introduction

Rimantadine and amantadine (Scheme 1) are tricyclic aminohydrocarbons with antiviral activity directed uniquely against influenza A virus. Both compounds have a similar mechanism of action inhibiting the early phases of viral replication by preventing uncoating of the viral genome and virus-mediated membrane fusion. Both drugs are used in the prevention and treatment of influenza A infections [1, 2].

On the other hand, macrocyclic- [3] and macrobicyclic polyethers [4] have been extensively used as interesting model compounds for the study of molecular effect on membrane permeability [5–8], due to their many similarities to cyclic antibiotics and biological transport agents. Considerable attention has been focused on the interactions between different protonated amines and macrocyclic ligands in order to study the molecular effect on membrane permeability [9–16].

The thermodynamics of complexation of ammonium ion and different protonated amines with several crown ethers and cryptands in nonaqueous and mixed solvents have been reported in the literature [13–16]. In this paper, we report a conductance study of the thermodynamics of complexation of amantadine, rimantadine and aminocyclohexane (as a model compound) with 18C6, DC18C6 and cryptand C222 (Scheme 1) in acetonitrile and discuss the influence of several structural and medium parameters on the complexation reaction.

Experimental

All chemicals used were of the highest purity available. Amantadine was purchased from Merck and rimantadine from Roch companies. Perchlorate salts of amantadine, rimantadine, and aminocyclohexane were prepared from the 1:1 interaction of perchloric acid with amantadine hydrochloride, rimantadine hydrochloride, and aminocyclohexane, respectively. The resulting perchlorate salts were recrystallized three times from doubly distilled deionized water and vacuum dried for 24 h and stored over P_2O_5. Reagent grade acetonitrile from Merck was used as

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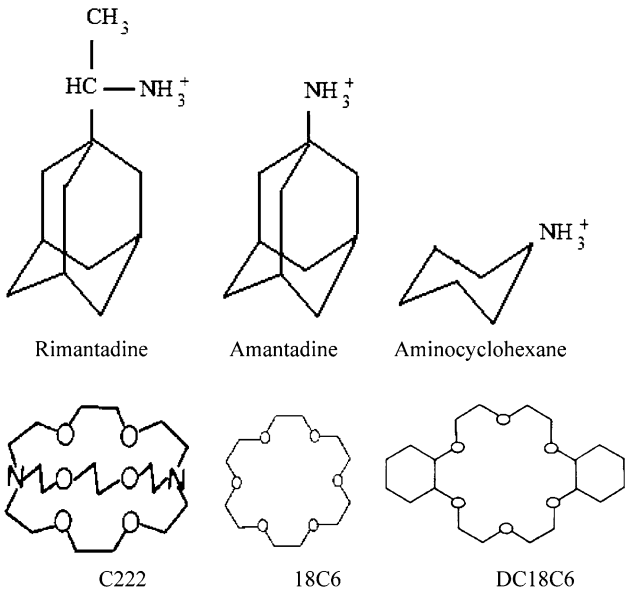


Scheme 1 Structure of ammonium-containing molecules (guest) and macrocyclic ligands (host)

the solvent. The conductivity of the solvent was less than $1.0 \times 10^{-7}\ S^{-1}\ cm^{-1}$.

Conductivity measurements were carried out with a Metrohm 712 conductivity meter. A dip-type conductivity cell made of platinium black, with a cell constant of 0.8641 cm^{-1} (at 25 °C) was used. In all measurements, the cell was thermostated at the required temperature ±0.05 °C, using a Hober poly state CC1 thermostate.

In a typical experiment, 5 mL of the protonted amine perchlorate solution (1.0×10^{-4} M) was placed in the titration cell, thermostated at the preset temperature and the conductance of the solution was measured after the solution reached thermal equilibrium. Then, a known amount of the macrocyclic solution (3.0×10^{-3} M) was added in a stepwise manner using a calibrated micropipette. The conductance of the solution was measured after each addition until the desired ligand-to-cation mole ratio was achieved.

The 1:1 binding of the protonated amines with macrocyclic ligands can be expressed by equilibrium $M^+ + L = ML^+$, and the corresponding equilibrium constant, K_f, is given by:

$$K_f = \frac{[ML^+]\quad f(ML^+)}{[M^+][L]f(M^+)f(L)} \tag{1}$$

where $[ML^+]$, $[M^+]$, [L] and f represents the equilibrium molar concentrations of complex, free cation, free ligand and the activity coefficients of the species indicated, respectively. Under the dilute conditions used, the activity coefficient of the uncharged ligand, f(L) can be reasonably assumed to as unity [17, 18]. The use of Debey-Huckel limiting law of 1:1 electrolytes [19] leads to the conclusion that $f(M^+) \approx f(ML^+)$, so that the activity coefficients in Eq. 2 cancel out.

Thus, the complex formation constant in terms of the molar conductance can be expressed as [20, 21]:

$$K_f = \frac{[ML^+]}{[M^+][L]} = \frac{(\Lambda_M - \Lambda_{obs})}{(\Lambda_{obs} - \Lambda_C)[L]} \tag{2}$$

$$[L] = C_L - \left\{ C_{M^+} + \frac{(\Lambda_M - \Lambda_{obs})}{(\Lambda_M - \Lambda_C)} \right\} \tag{3}$$

here, Λ_M is the molar conductance of the protonated amine before addition of the ligand, Λ_C the molar conductance of the complexed amine, Λ_{obs} the molar conductance of the solution during titration, C_L the analytical concentration of the macrocycle added, and C_M^+, the analytical concentration of the amine salt. The complex formation constant, K_f, and the molar conductance of the complex, Λ_C, were obtained by computer fitting of Eqs. (2) and (3) to the molar conductance-mole ratio data using a nonlinear least- squares program KINFIT [22].

Results and discussion

In order to evaluate the influence of adding macrocyclic ligands on the molar conductance of the protonated amines in acetonitrile solution, the conductivity at a constant salt concentration (1.0×10^{-4} M) was monitored while increasing the macrocycle concentration at 25, 35, and 45 °C. The resulting molar conductances vs. macrocycle/cation mole ratio plots are shown in Fig. 1. As is obvious from Fig. 1, in all cases studied, addition of the macrocyclic ligand to the protonated amine solutions caused a continuous decrease in the molar conductance of the solutions, indicating the lower mobility of the complexed cations compared to the solvated ones. In all cases, the slope of the molar conductance-mole ratio plots change sharply at the point where the ligand to cation mole ratio is one, indicating the formation of a relatively stable 1:1 complex between the macrocyclic ligands and the protonated amines used. The stability constants of the resulting 1:1 complexes were determined from the computer fitting of Eqs. 2 and 3 to the molar conductance-mole ratio data. A sample computer fit of the mole ratio data is shown in Fig. 2 and all K_f values are summarized in Table 1.

In order to obtain a better understanding of the thermodynamics of the complexation reactions, it is useful to consider the enthalpic and entropic contributions to these reactions. The enthalpy and entropy of the complexation reactions were determined by measuring the formation constants as a function of temperature. A typical series of molar conductance vs. mole ratio plots at different temperatures is shown in Fig. 3. All the calculated formation

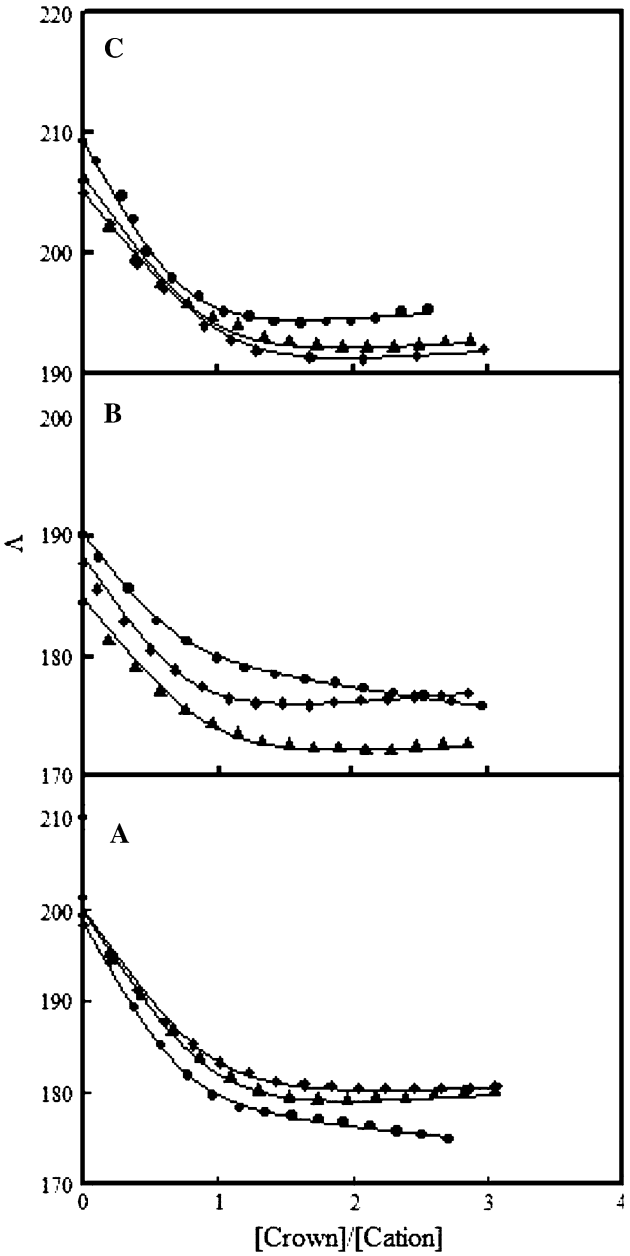


Fig. 1 Molar conductance against macrocycle/cation mole ratio at 25 °C: (**a**) aminocyclohexane; (**b**) amantadine; (**c**) rimantadine. (●) C222; (▲) DC18C6; (♦) 18C6

constants obtained at various temperatures are summarized in Table 1. Plots of log K_f vs. 1,000/T for different protonated amine- macrocycle complexes are shown in Fig. 4. The enthalpies and entropies of complexation were determined from the slopes and intercepts of the plots in Fig. 4 and the results are also included in Table 1.

It is well known that, in the host–guest interactions between macrocyclic ligands and different cations, a number of host and guest parameters play a very fundamental role. The important structural properties of macrocyclic ligands as host include cavity size, type and number of donating atoms

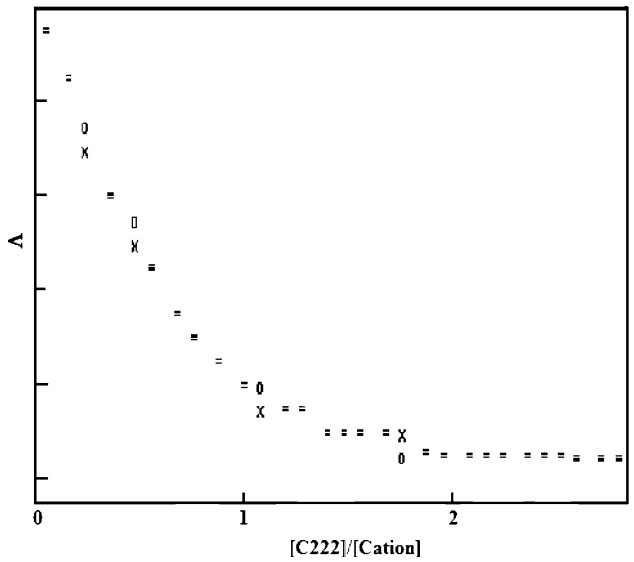


Fig. 2 Computer fit of the molar conductance-mole ratio data for the C222- aminocyclohexane system at 25 °C in AN; (x) experimental point; (o) calculated point; (=) experimental and calculated points are the same within the resolution of the plot

in the ring, nature of the ring substituent and ring conformation [23, 24]. The 18-membered rings provide the most convenient configuration for the binding of the tetrahedral ammonium ions to the three available heteroatoms of the macrocyclic ring (Scheme 2). On the other hand, due to different binding mechanisms involved, the guest parameters for organic ammonium ions differ from those of metal ions. In the cation–ligand binding process, metal ions penetrate inside the macrocyclic cavity, whereas the binding of the organic ammonium ions occurs via hydrogen bonding of the amine protons and available ring donor atoms [24–26]. Since $N^+H\cdots N$ hydrogen bonding is stronger than $N^+H\cdots O$ [9, 25, 27], it is not surprising to observe a significant increase in the stability of the protonated amine complexes in the case of C222 macrocyclic ring.

The important guest parameters of organic ammonium ions include the number of hydrogen atoms available for H-bonding, steric hindrance to ligand–cation approach by the organic moiety of the guest and electronic effects on the H-bonding donicity of the guest. All the protonated organic amines used in this study are of the first kind with three hydrogen atoms available for H-bond formation. They form complexes with selected macrocycles, which are less stable than the corresponding NH_4^+ complexes (Table 1).

This observation obviously revealed that the steric hindrance of the R- groups of RNH_3^+ guest molecules would result in their decreased tendency for H-bonding to donor atoms of the macrocycles. As seen from Table 1, generally, the stability constants of the resulting host-guest adducts vary in the order aminocyclohexane > amantadine > rimantadine. Obviously, aminocyclohexane with the least steric hindrance forms

Table 1 Formation constants, enthalpies and entropies for different ammonium-crown ether complexes in acetonitrile solutions

Cation	Crown	Log K_f^a			ΔH° (kJ mol^{-1})	ΔS° (J mol^{-1} K^{-1})	ΔG° (kJ mol^{-1})
		25 °C	35 °C	45 °C			
Aminocyclohexane	18C6	4.24	4.21	4.19	−4.54 (±0.44)	65.84 (±1.42)	−24.16
	DC18C6	4.45	4.32	4.17	−25.37 (±1.52)	0.15 (±4.95)	−25.33
	C222	5.02	4.96	4.92	−9.08 (±0.88)	65.52 (±2.85)	−28.60
Amantadine	18C6	4.45	4.37	4.30	−13.61 (±1.07)	39.5 (±3.5)	−25.63
	DC18C6	4.04	3.94	3.86	−16.34 (±0.59)	22.46 (±2.4)	−23.03
	C222	4.66	4.42	4.23	−39.03 (±1.90)	−41.8 (±6.3)	−26.57
Rimantadine	18C6	4.16	4.14	4.11	−4.52 (±0.61)	64.37 (±1.97)	−23.70
	DC18C6	4.0	3.95	3.89	−9.96 (±0.71)	43.0 (±2.31)	−22.77
	C222	4.42	4.40	4.38	−3.62 (±0.07)	72.36 (±0.23)	−25.18
NH_4^{+b}	18C6	5.56	5.46	5.33	−21	36.2	
	DC18C6	5.9	5.77	5.53	−39.8	−19.6	
	C222	>6					

[a] Standard deviations for all log K_f values are less than (±0.05)

[b] Refs. [13, 14]

Values in parentheses are standard deviations

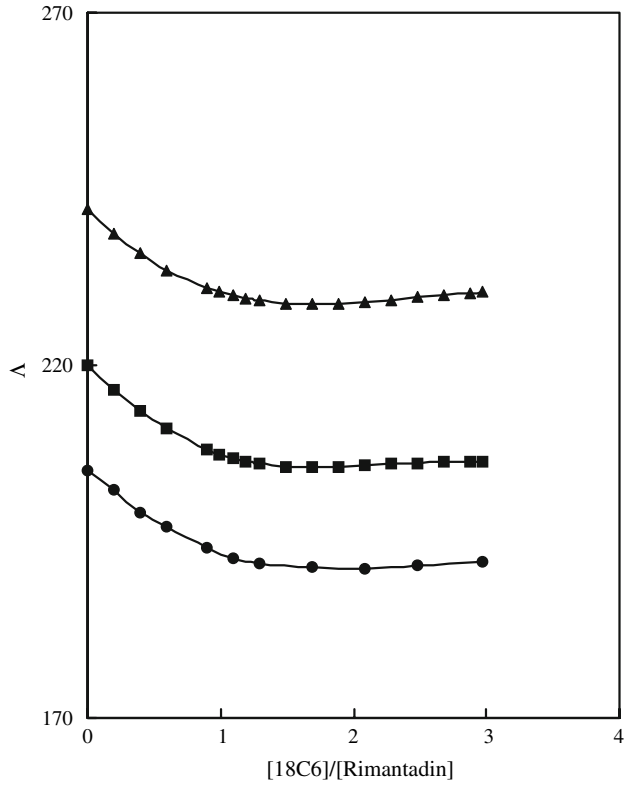


Fig. 3 Molar conductance against 18C6/rimantadine mole ratio at (●) 25 °C; (■) 35 °C; and (▲) 45 °C

the most stable complexes and rimantadine with the most steric hindrance shows the weakest complexes with the macrocycles.

In the case of aminocyclohexane, the stability of the complexes decreases in the order: C222 > DC18C6 > 18C6. This order is consistent with the previous observations [24–26]. The tetrahedral NH_4^+ and R–NH_3^+ ions can nicely bind to three of the six available oxygen atoms in the 18C6 ring to form a stable complex. In this case, the R group presumably protrudes upward from the center and perpendicular to the plane of the oxygens. Electron pumping of cyclohexyl groups of DC18C6 is a major reason that its complexes with organic ammonium cations are more stable than those with 18C6, most possibly due to the increased basicity of the oxygen atoms of the ring, as H-bond acceptors. In the case of C222, the highest stability constants observed can be attributed to the bicyclic geometry of the ligand and the resultant cryptate effect in the system [14, 28], and the presence of two donating nitrogen atoms in its three-dimensional cavity, as better H-bond acceptors than oxygen atoms [9, 25, 27].

The data given in Table 1 revealed that, except for the case of C222-amantadine system, in all cases the complexes are both enthalpy and entropy stabilized. However, in the case of C222-amantadine complex, the system is enthalpy stabilized but entropy destabilized.

Enthalpies and entropies of complexation reactions show that, in most cases, the reaction is entropic controlled although, in all cases, a negative value of enthalpic change is also obtained. This observation is most probably due to the steric hindrance of the guest molecules, which does not let the ammonium moiety to approach donor atoms of macrocyclic molecules for convenient overlapping of the orbitals involved in H-bonding. Comparison of ΔH° values of complexation of the protonated organic amines used in this study with those for NH_4^+ ion (Table 1) clearly revealed that the steric hindrance in organic ammonium ions is an

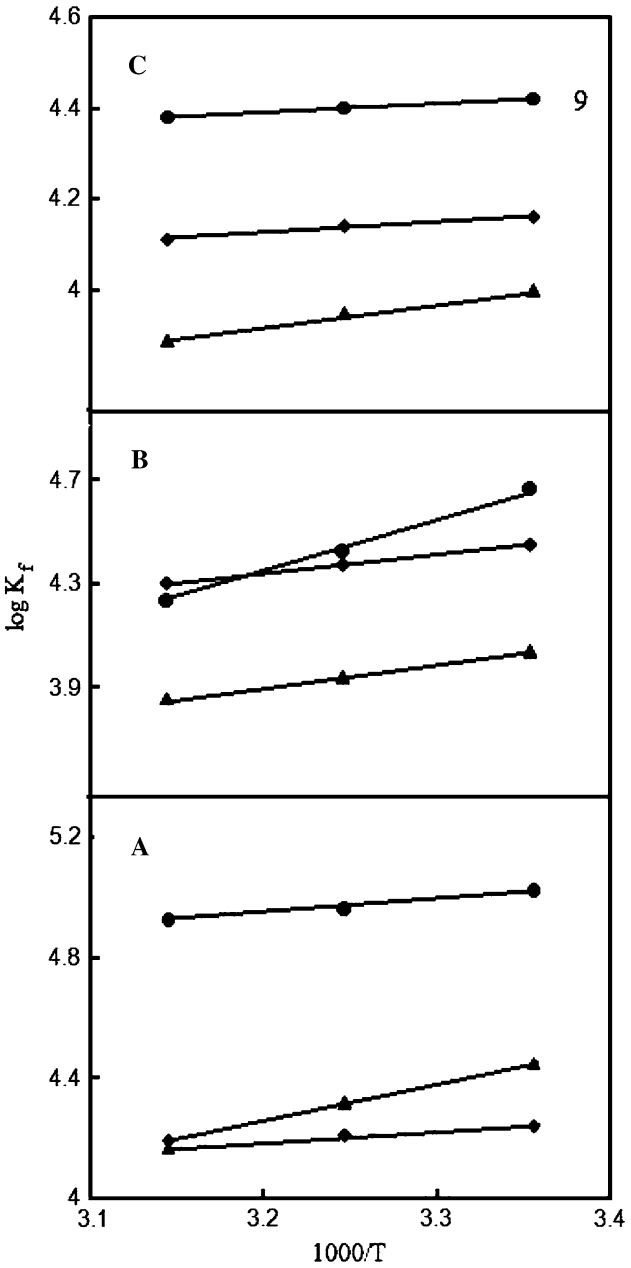
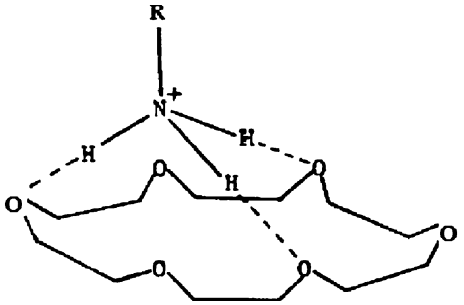


Fig. 4 log K_f against 1,000/T for different complexes: (**a**) aminocyclohexane; (**b**) amantadine; and (**c**) rimantadine with (●) C222; (▲) DC18C6; (♦) 18C6



Scheme 2 Schematic presentation of complexation between ammonium ion and18C6

important factor in enthalpy changes in the process of complexation reactions.

On the other hand, in most cases, the entropy changes during complexation reactions are quite favorable. The entropic change during the complex formation is in fact affected by several factors including the change in flexibility of the reactants in the course of complexation reaction and the differences between the extent of solvation–desolvation of the uncomplexed and complexed species. In the case of the complexation reactions of 18C6 with all organic ammonium cations, a large positive ΔS° was obtained. This observation seems to be due to strong solvation of 18C6 by AN [29–31]; during the process of complex formation with the organic ammonium ions, these solvent molecules are liberated, causing a favorable entropic change. Interestingly to note, a comparison between the ΔS°, ΔH° and ΔG° values reported in Table 1 reveals that generally a decrease in ΔH° value is accompanied with an increase in ΔS° in such a way that the free energy change ΔG° will remain more or less constant (last column of Table 1). Such enthalpy-entropy compensation effect was observed earlier in the case of complexation reactions of macrocyclic ligands with many organic and inorganic guest species [32].

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