Calorimetric Titration of Selected Divalent Transition Metal Cations with a Novel Macrocyclic Diamide

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Complex stability constant (*β*) and thermodynamic parameters ∆H, ∆G, and ∆S as changes in enthalpy, Gibbs free energy and entropy, respectively were determined in methanol at 25 ⁰C for the observed stoichiometric 1:1 complexation of a novel macrocyclic diamide, 1 with selected nitrate salts of divalent transition metal cations (Co(II), Ni(II), Cu(II), and Zn(II)) using isothermal titration calorimetry. Compound 1 was more stable and selective toward Co(II) cation over other divalent cations which was revealed by favorable *∆G* (-33.68 kJ/mol) and *∆S* (20 J/mol.K) upon complexation in methanol. The preference of 1 for Co(II) was probably due to the favorable desolvations of Co(II) and 1 and conformational changes in methanol. Thermodynamically, complexation of Co(II) and Zn(II) with 1 was driven by enthalpy effect, Ni(II) and Cu(II) complexes were compensated by enthalpy-entropy effect, and 1 selectivity for Co(II) was governed by free Gibbs energy and entropy contribution in methanol.

Key Words: Host-guest complexation, stability, complex, thermodynamic binding

INTRODUCTION

Macrocyclic diamides are recently recognized as important ligands in which nitrogen donor atoms are incorporated for binding with metal cation guest (Shamsipur et al. 2001; Pearson 1963). These compounds have been successfully used as ionophores in the development of ion selective electrodes (Shamsipur et al. 2002), as extraction or complexation agents of picrate containing cation from aqueous to organic media (Kimura et al. 1998), and as catalysts in the reduction of ketones to their corresponding alcohols (Fonseca and König 2003). Recently, there is a growing interest to look into the fundamental thermodynamic parameters of their complexation with cations. The metal-ligand complexation depends on the type of donor atoms, ligand cavity size and complexation bond energies. The presence of nitrogen atom in the macrocyclic ligands helps discriminate metal cations in solution due its "hard" and basic properties which shows affinity for hard transition metal cations because of "hard-hard" interactions in solution (Liu et al. 1998). The investigation of energetic parameters is very essential to understand deeper the effect of host character upon complexation with guest cation and its environment, the solvent. This implies that there is a need to rationalize molecular structures in terms of binding energies, a task that is difficult in spite of some very promising theoretical developments and steady accumulation of experimental results. The parameters include Gibb's free energy of binding (ΔG), enthalpy of binding (ΔH), and entropy of binding (ΔS). They can be measured using isothermal titration calorimetry (Gherrou et al. 2005; Arnaud-Neu 2003; Buschmann 1998; Izatt 1976; Lamb 1980; Jelesarov 1999).

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MATERIALS AND METHODS

The novel compound **1** was prepared following procedure described elsewhere (Sharghi and Eshghi 1995). DB18-crown-6 (Fluka) and nitrate salts of cobalt (Merck), zinc (APS Ajax FineChem), copper (UNIVAR), nickel (Fluka) and barium nitrate (Merck) were all of analytical grade and dried *in vacuo* prior to use. Reagent-grade methanol was refluxed over magnesium turnings and distilled fractionally to give dry methanol. The ligands DB18-crown-6 and novel cyclic diamide, **1** were dissolved in dry methanol to make the titrand solution of 2-5 and 1-2 mM concentration, respectively, while nitrate salts were dissolved in the same solvent to make titrant solution of 0.01-0.05 M concentration.

Experimental Procedure
Calorimetric titration were carried out under normal atmospheric pressure in a temperature controlled water bath maintained at 25°C using TAM 2277 precision Thermometric calorimeter connected to a computer with DIGITAM® 4.1 software for automated titration and processing. Two identical 4 ml stainless steel cylindrical ampoules were used as sample and reference cells. The working and reference cells were filled with sample solution and solvent, respectively. In a typical run, a nitrate salt solution of divalent metal cations was added continuously at a rate of 25 μL/sec into a solution of **1** placed in a calorimeter. Methanol solutions of compound **1** and the different salts were titrated separately to the solvent to determine if there were heats of dilution in the reaction. The net heat of metal-ligand complexation was obtained by subtracting the heat of dilution of salt and **1** solutions. Data were processed in which titration curve was obtained by plotting the heat measured in μJ against the amount of **1** from which the complex stability constant and enthalpy change were directly calculated. The condition and performance of calorimeter and reliability of the method used were ascertained using Ba(II) complexation with DB18-crown-6 in methanol at 25°C (Fruh et al. 1979). The average enthalpy of complexation (-19.98 ± 0.2 kJ/mol) and log β (4.325 ± 0.001/M) do not deviate significantly from the reported literature values ($\Delta H = -21.17$ kJ/mol and log $\beta = 4.28$/M). Reliability of the instrument and calculation procedures were doubly checked by titrating DB18-crown-6 with barium nitrate in methanol of which comparison of the obtained data with the reported literature values were made to give satisfactory results

RESULTS AND DISCUSSION

The binding model with 1:n stoichiometric metal-ligand (M-L) complexation in methanol was used in which stability constants, β_n and enthalpy change, ΔH_n were calculated using non-linear least square fit in the following equations:

$$M + L_n = ML_n; \; \beta_n, \Delta H_n \qquad (1)$$
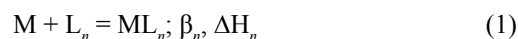
$$\beta_n = \frac{[ML_n]}{[M][L]} \qquad (2)$$

$$Q_{calc} = (V_{tit} + V_{tid}) \sum \Delta H_n [ML_n] \qquad (3)$$

where $n=1,2$ or 3, *M* and *L* represented titrant and titrand, respectively. Q_{calc} was the amount of heat calculated, V_{tit} and V_{tid} were the volumes of titrant and titrand, respectively.

A typical ITC plot from the titration of novel ligand **1** with copper cation in methanol at 25 °C is depicted (Figure 1). It displays the raw data which is the heat evolved over time. Initial injections produce a large signal from the complexation of the added guest, the metal cation solution. Over time, this response decreases because binding sites become saturated. A binding isotherm is generated by
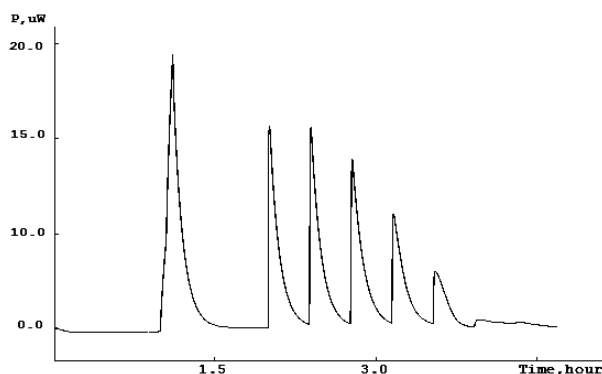

Figure 1. Plot of raw data of copper-ligand complex

integrating each peak and plotting the resulting data versus the mole ratio. A separate titration for both titrant and titrand to solvent is conducted which is then subtracted from the raw data to produce the final binding curve (Figure 2). At high concentration of the titrant the heat of dilution produced is quite substantial while the titrand produced a negligible heat effect.

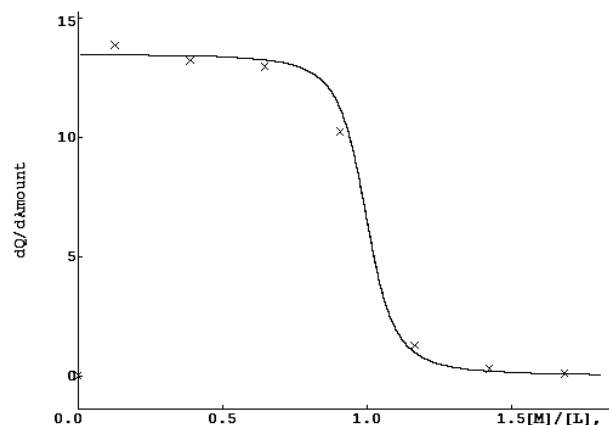Using the DIGITAM 4.1® software, the non linear least square fit with 1:1 binding model is shown as a smooth

Figure 2. Binding isotherm of copper-ligand complex

curve corresponding to the theoretical fit of binding curve of the ligand with the host. The points marked "x" are experimental binding curve. It can be seen, that binding in 1:1 model closely resembles the theoretical fit. At some point in a host-guest design reaction, the percentage of the ligand that is bound to the guest decreases from close to 100% to close to 0%. The decrease may be gradual or sharp depending on the association equilibrium constant (K) and the concentration of both host and guest. The sharp drop of the curve corresponds to the stoichiometric binding of the complex, i.e., n is equal to one. The y-intercept gives the heat of binding which is the enthalpy of complexation.

Cation Preferential Binding and Complex Stability
The thermodynamic quantities and stability constant, β, obtained for binding of compound **1** (Figure 3) with selected divalent metal cations are summarized in Table
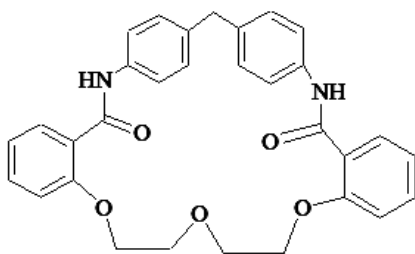

Figure 3. Structure of **1** ligand.

1. Results are reported as the average values of five independent experimental trials ± standard deviations.

Among cations tested, **1** shows preference for cobalt cation in methanol in terms of complex stability and preferential binding. At **1**'s concentration range (0.001-0.002 M), there is no observable complexation other than 1:1 (Metal(II):**1**) ratio. The electron density on nitrogen atoms is reduced due to the electron withdrawing effect of benzene moiety attached to them. However, the presence of carbonyl and ether groups provide polarization effects on the molecule which help contribute to the enhanced stability and binding selectivity of **1** towards cobalt cation over other cations tested.

Thermodynamic Parameters
Results on the enthalpy change (Table 1) display that the interaction of **1** with cobalt and zinc cations are enthalpy driven while its interaction with nickel and copper ions under the same experimental conditions are compensated by enthalpy-entropy contributions. This implies that the spatial arrangement and orientation of the **1**'s donor atoms in solution have favorable conformations for complexation with cobalt and zinc cations in methanol. Data also indicate that complexation with zinc has slight favorable gain in enthalpy change being the most negative (-33.44 kJ/mol) over cobalt ion (-27.3 kJ/mol) which can be attributed to the strong ion-dipole interaction and greater covalent character of the bonds formed between the solvent methanol and the oxygen donor atoms of **1**. However, zinc has small ionic radius (0.74 Å) compared with cobalt (0.885 Å) which suggests that in solution zinc cation moves freely in the cavity of the compound **1** with most favorable conformational change. Conversely, complexation with nickel and copper resulted in positive enthalpy change (37.18 and 13.38 kJ.mol^{-1}, respectively) which can be attributed to the less conformational change that takes place upon complexation in methanol. The stability of Cu(II)-**1** and Ni(II)-**1** complexes were attributed to the favorable entropy effects which compensate the large positive enthalpy contribution upon complexation in methanol.

Examining other thermodynamic quantity, the Gibbs free energy is calculated using Gibbs-Helmholtz relationship.

Table 1. Complex formation constants and thermodynamic parameters for different metal complexes of **1**.

Metal(II)-**1**	β (x 10^5) (M^{-1})	ΔH (kJ.mol^{-1})	ΔG (kJ.mol^{-1})	ΔS(J.mol^{-1}K^{-1})
Co(II)-1	7.96 ± 0.001	-27.30 ± 0.02	-33.68	+20.00
Zn(II)-**1**	1.35 ± 0.001	-33.44 ± 0.02	-28.97	-50.00
Ni(II)-**1**	1.92 ± 0.001	+37.18 ± 0.02	-30.16	+220.00
Cu(II)-**1**	2.36 ± 0.001	+13.38 ± 0.01	-30.65	+150.00

Results in Table 1 show that all Metal(II)-**1** complexes have comparable magnitude of ΔG signifying stable complexes at equilibrium due to favorable desolvation as well as conformational changes of both compound **1** and cations upon complexation. The Co(II)-**1** stability is not the result of less enthalpic gain but due to the entropic loss in the system compared with zinc. The endothermic complexation of Ni(II)-**1** and Cu(II)-**1** was still favored which are accompanied by positive ΔS large enough to offset the unfavorable $+\Delta H$. Therefore, it is essential that designing a novel compound **1**, variable functional binding groups such as oxygen and nitrogen donor atoms should be incorporated in the macrocycle as well as the benzo groups for structure rigidity in order to give binding affinity towards transition metal cation in solution. Hence, the research findings show that compound **1** can be used as a viable complexation agent and that ITC has the potential for probing the structure-interaction thermodynamic parameters for metal-ligand binding in methanolic solution.

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