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Complexation of Macrocyclic Compounds with Nicotinamide in Dimethylsulphoxide and its Water Mixture

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The complexation behavior of nicotinamide with macrocyclic polyethers viz, 15-crown-5, benzo-15-crown-5, 18-crown-6, dicyclohexano-18-crown-6, dibenzo-18-crown-6, dibenzo-24-crown-8, 1,4,7,10,13,16-hexathiacyclooctadecane, monoaza-15-crown-5, 1,4,10-trioxa-7,13-diaza-cyclopentadecane, 5,6,14,15-dibenzo-1,4-dioxa-8,12-diazacyclo pentadecane, 7,16-dibenzyl-1,4,10,13-tetraoxa-7,16-diaza-cyclooctadecane, 1,4,7-tritosyl-1,4,7-triazacyclononane, 1,4,7,10-tetratosyl-1,4,7,10-tetraazacyclododecane and 1,4,8,11-tetraazacyclooctadecane has been studied in dimethylsulphoxide (DMSO) and 90% DMSO + water using differential pulse polarography and complexation constants have been reported. Nicotinamide forms stable complexes with six-membered coronand rings of the crown ethers. The nature of the atoms (oxygen, sulfur and nitrogen) in the coronand ring is observed to affect the stability of the complex. The stoichiometry and stability constants of the complexes were determined by monitoring the shifts in peak potentials of the polarograms of nicotinamide against the ligand concentration. The Gibbs free energy change turns out to be negative at 25°C, which indicates the spontaneity of the binding of nicotinamide with crown ethers. The mole ratio of nicotinamide to the macrocyclic compound was also determined and it was found that the complexes were of 1:1 type with respect to crown ethers. The tendency of nicotinamide to form complexes with macrocycles is found to be greater in DMSO than in DMSO + water.

Keywords: Nicotinamide; Crown ether; Polarography; Dimethylsulphoxide; Stability constants

INTRODUCTION

Nicotinamide (3-pyridine carboxylic acid amide) commonly known as Niacin or vitamin B_3 is a water-soluble vitamin, required for cell respiration. It helps in release of energy and the metabolism of carbohydrates, fats and proteins, proper circulation and healthy skin, functioning of the nervous system and normal secretion of bile and stomach fluid and so it is a pharmacologically important compound [1]. A deficiency of nicotinamide causes pellagra [2]. Biologically important molecules like NAD and NADH on decomposition give a small amount of nicotinamide, hence knowledge of the electrochemical properties of nicotinamide and its reduced forms are helpful in characterization of the nucleotides. Pedersen published the first report on crown compounds in 1967 [3]. Since then a wide range of applications of these compounds in different areas such as medicine [4], chemical sensors [5,6] and separation of metals by extraction [7] have been reported, most of which are based on their complexing property. The binding ability of organic molecules [8,9] with macrocyclic polyethers has received lesser attention in comparison to the complexes of such polyethers with metal ions [10,11]. Molecular recognition in biological systems by specific non-covalent interactions is quite prominent, especially crown ethers are of considerable interest in biological modeling of ion transport processes, enzyme catalysis and antibody antigen association [12–16]. In this respect, the studies concerning the structural and solvent aspect of interaction between macrocyclic receptors and biological compounds are useful in investigating biochemical processes and analytical applications as well. We have recently reported the complexation of pyridoxine hydrochloride with macrocyclic compounds in dimethylsulphoxide [17]

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and chemically modified electrode based on macrocyclic compounds for riboflavin [18] and *para*-aminobenzoic acid [19]. Although the interaction of nicotinamide with metal ions [20–22] and amino acids [23] has been reported, no electrochemical study dealing with the interaction of nicotinamide with macrocyclic compounds has appeared in literature. An important goal of the present study was to understand how structural variation of macrocyclic polyethers and solvent composition affect the ability of these species to bind organic molecules like nicotinamide. Binding selectivity is expected to be affected by ring sizes, number and identities of donor atoms and also on solvent effect.

DMSO is a dipolar aprotic solvent having moderate viscosity (1.996 mPa s, 25°C) and a fairly high relative permittivity (46.68, 25°C) [24,25]. The reduction mechanism of nicotinamide in DMSO has been well established [26], therefore, it is chosen as the medium for complexation studies. Also most of the macrocyclic compounds that are insoluble in water are easily soluble in DMSO. Earlier, we had reported the use of organic solvents in binary mixtures with water for solubilization of macrocyclic compounds and studied their effects on the stabilities of the complexes [27,28]. In the present work, the complexation behavior of nicotinamide in DMSO and 90% (v/v) DMSO + water, with certain oxa, aza and thia macrocycles (Scheme 1) viz., 15-crown-5, benzo-15-crown-5, 18-crown-6, dicyclohexano-18-crown-6, dibenzo-18-crown-6, dibenzo-24-crown-8, 1,4,7,10,13,16-hexathiacyclooctadecane, monoaza-15-crown-5, 1,4,10-trioxa-7,13-diaza-cyclopentadecane, 5,6,14,15-dibenzo-1, 4-dioxa-8,12-diazacyclopentadecane, 7,16-dibenzyl-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane, 1,4,7-tritosyl-1,4,7-triazacyclononane, 1,4,7,10-tetratosyl-1,4,7,10-tetraazacyclododecane and 1,4,8,11-tetraazacyclooctadecane were carried out by differential pulse polarography and cyclic voltammetry. The stability constants and Gibbs energy of complexation (ΔG) are reported herein.

The stability constant is related to the free energy of reaction because the free energy consists of enthalpy (ΔH) and entropy (ΔS), terms which frequently tend to compensate each other in dissociation process, more complete information about the factors governing complex formation can be gained by determining the stability constant and calculating the Gibbs energy.

EXPERIMENTAL SECTION

Solvents and Reagents

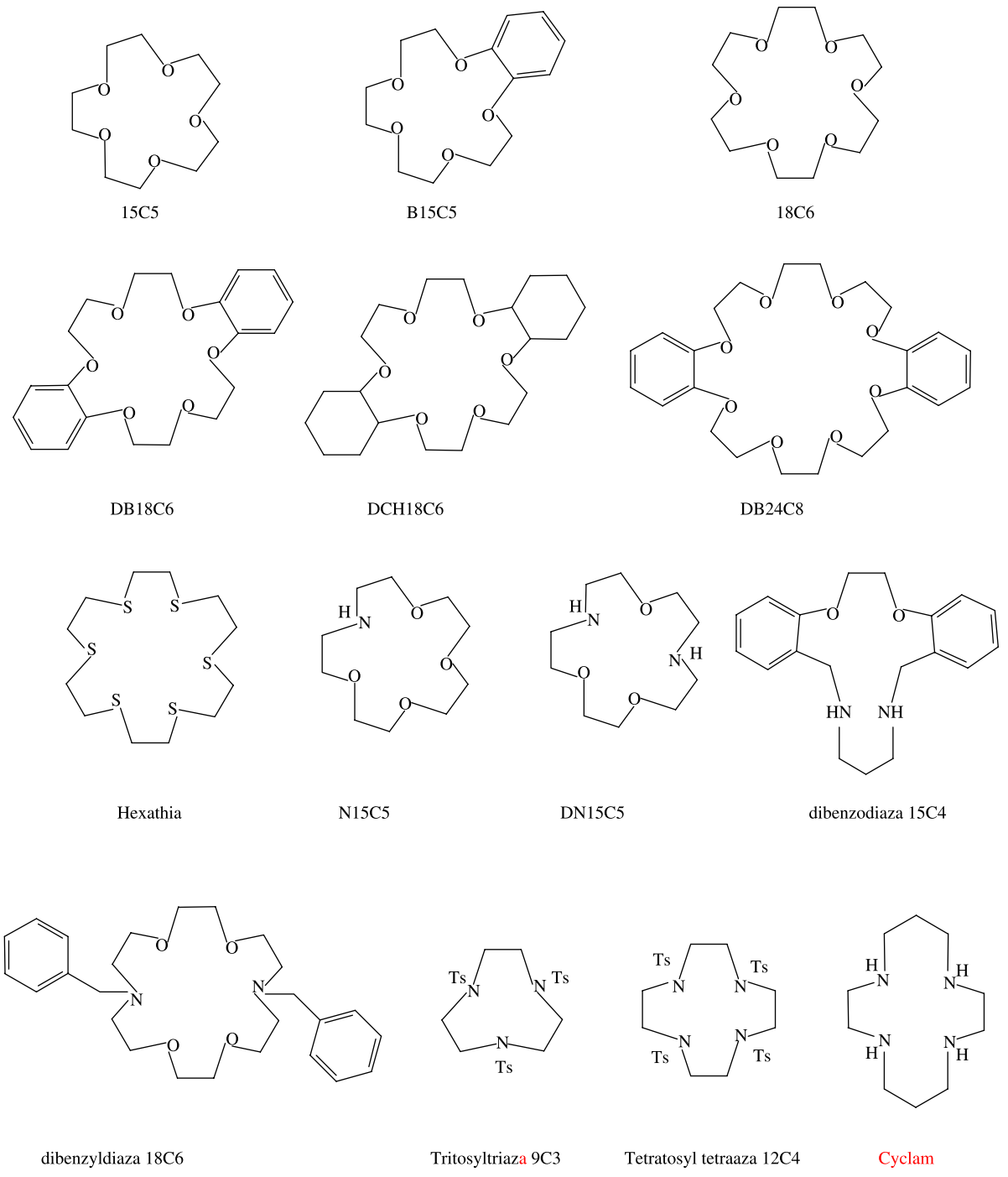
Double distilled, deionised water was used for preparation of all solutions. Commercially available DMSO (99% pure, SDFine, India) was held over sodium hydroxide for 3 hours at 90°C and distilled twice under reduced pressure [25]. Finally; a third distillation was carried out without any additive, under reduced pressure. The middle fraction, comprising about 80% was collected and kept over a thermally activated 4 Å molecular sieves prior to use. Both the solvents were stored in sealed containers to prevent atmospheric contamination. Appropriate volumes of DMSO and water were mixed to give 90% (v/v) DMSO + water solvent mixture. All the polarographic measurements were made at 25 ± 0.2°C.

Nicotinamide purchased from Lancaster was used as such. The macrocycles viz. 15-crown-5 (15C5), benzo-15-crown-5 (B15C5), 18-crown-6 (18C6), dibenzo-18-crown-6 (DB18C6), dibenzo-24-crown-8 (DB24C8) and 1,4,7,10,13,16-hexathiacyclooctadecane (Hexathia) were purchased from Aldrich, dicyclohexano-18-crown-6 (DCH18C6), 1,4,10-trioxa-7,13-diaza-cyclopentadecane (DN-15C5), 5,6,14,15-dibenzo-1,4-dioxa-8,12-diazacyclopentadecane (dibenzodiaza 15C4), 7,16-dibenzyl-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (dibenzyldiaza 18C6), and 1,4,8,11-tetraazacyclooctadecane (cyclam) from Fluka and were used as supplied, monoaza-15-crown-5 (N15C5) 1,4,7-tritosyl-1,4,7-triazacyclononane (tritosyltriaza 9C3), 1,4,7,10-tetratosyl-1,4,7,10-tetraazacyclododecane (tetratosyltetraaza 12C4) were synthesized by reported method [29–31]. Tetraethylammonium perchlorate (TEAP) was prepared by adding a slight excess of perchloric acid (70% Loba, GR) to tetraethylammonium bromide (Sisco, India). The precipitate was washed several times with water to obtain the filtrate free from acid. The product thus obtained was recrystallized twice from water, dried in vacuum, and used as supporting electrolyte. Mercury used for the working electrode was triply distilled under reduced pressure. The reference electrode used for the polarographic studies in DMSO consisted of replacing the inner solution of the conventional Ag/AgCl electrode (No. 6.1414.010, Metrohm, Netherlands) with saturated LiCl in ethanol [32] and the outer chamber with saturated solution of tetramethylammonium chloride (TMACl) in pure DMSO. All potentials are quoted with respect to $Ag/AgCl/LiCl_{sat}$ (EtOH)/$TMACl_{sat}$ (DMSO) in DMSO and Ag/AgCl/3 mol L^{-1} KCl in water and its DMSO mixtures.

PROCEDURES

Voltammetric Measurements

The voltammetric system used for the studies was Electrochemical Work Station, model Autolab 30; the electrode assembly being a 663 VA stand with GPES computer software for recording and analyses of the polarograms was supplied by Eco Chemie,



SCHEME 1 Macrocyclic compounds studied in the present investigation

The Netherlands. Experiments were performed with the three-electrode cell consisting of static mercury drop as working electrode, graphite as an auxiliary and $Ag/AgCl/LiCl_{sat}$ (EtOH)/ $TMACl_{sat}$ (DMSO) in pure DMSO solvent and $Ag/AgCl/3\,mol\,L^{-1}$ KCl electrode in DMSO + water medium as the reference electrodes. Before each measurement a stream of pure nitrogen deaerated the solution. A known volume of supporting electrolyte $0.05\,mol\,L^{-1}$ TEAP in DMSO or 90% DMSO + water was taken in sample cell and polarogram was run. To this solution, a concentrated solution of the vitamin was added to get the desired working concentration in the cell and the polarogram was run. Then a step-by-step increase in concentration of macrocyclic compound was made using a micropipette until the total concentration of the macrocycle was approximately thrice the concentration of the vitamin. The potential scans were recorded using the differential pulse polarographic technique at a scan rate of $10\,mVs^{-1}$ and pulse amplitude of 100 mV. Cyclic voltammetry and chronocoulometry were used to study the redox mechanism

of nicotinamide on mercury electrode. The area of mercury electrode (0.00459 cm^2) was determined by carrying out cyclic voltammetry in $Cd(NO_3)_2$ or $Pb(NO_3)_2$ in 1 mol L^{-1} KNO_3 solution.

THEORY

Polarographic Studies

The determination of stability of complexes by polarography is based on the shifts in the half wave potentials on complexation [33]. The relation between the shift in half wave potential and the stability constant is as follows:

$$\Delta E_{1/2} = (E_{1/2})_s - (E_{1/2})_c = (0.05916/n) \log B_p + (0.05916p/n) \log C_L \quad (1)$$

where $(E_{1/2})_s$ and $(E_{1/2})_c$ are the half wave potentials of the free and complexed cations, respectively, B_p is the stability constant, C_L the total ligand concentration, and "p" is the vitamin to ligand ratio. The half wave potential obtained by sampled DC can be correlated to the peak potential (E_p) as obtained by differential pulse polarography (DPP) by the following equation:

$$E_{1/2} = E_p + \Delta E/2 \quad (2)$$

As the shift in peak potentials can be measured more accurately than the half wave potentials, Eq. (1) can be replaced by

$$\Delta E_p = (E_p)_s - (E_p)_c = (0.05916/n) \log B_p + (0.05916p/n) \log C_L \quad (3)$$

Equation (3) indicates that the plot of ΔE_p *vs.* log C_L would provide the values of (0.05916 p/n) log B_p as intercept and 0.05916 p/n as slope. These plots are used to calculate the stability constants and the value of 'p' was found to be between 0.9 and 1.0 in all cases, which indicates 1:1 complexation with crown ether.

RESULTS AND DISCUSSION

Electrochemical Behavior of Nicotinamide

The differential pulse polarograms of nicotinamide in 0%, 20% and 90% DMSO + water are given in Fig. 1, and in pure DMSO is given in Fig. 2. It is observed from Fig. 1 that nicotinamide shows only one reduction peak at −1.6 V in aqueous medium, which shifts to −1.64 V in 20% DMSO + water. Whereas, it shows two well separated reduction peaks in 90% DMSO + water at −1.97 V and −2.485 V and in pure DMSO at −1.82 V and −2.24 V.

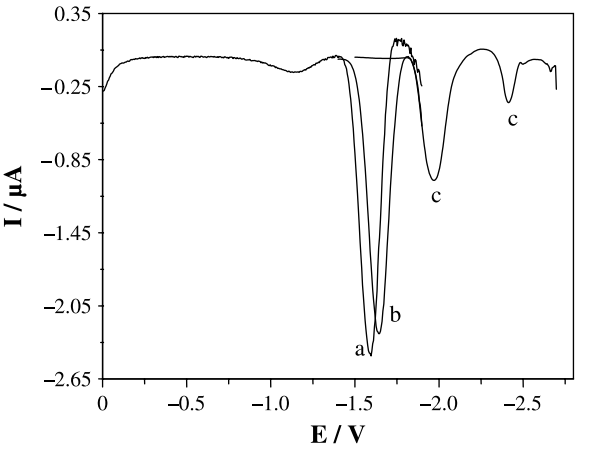


FIGURE 1 Differential pulse polarogram of nicotinamide in 0 (a), 20 (b) and 90% DMSO + water (c).

The cyclic voltammograms of nicotinamide in 90% DMSO + water are given in Fig. 3. It has been observed that the reversibility of both peaks occurs only at higher scan rates. Similar observation is reported in literature [26]. The two peaks in 90% DMSO + water and pure DMSO are due to the two electron exchange which has been reported earlier [26,34,35]. The reduction mechanism of nicotinamide is presented in Scheme 2. Nicotinamide (1) undergoes, initial single electron addition to form a neutral free radical (2) which dimerizes (3) at the sixth position; the neutral free radical again undergoes reduction to form 1,6-dihydro pyridine (4). At a potential considerably more positive than that of the first reduction peak, the dimer (3) can be oxidized back to nicotinamide and at still more positive potential the 1,6-dihydro species (4) can also be oxidized to nicotinamide. The oxidation of dimer and 1,6-dihydro species are notified at −1.97 V and −1.1 V, respectively (Fig. 3) in 90% DMSO + water at very high scan rate.

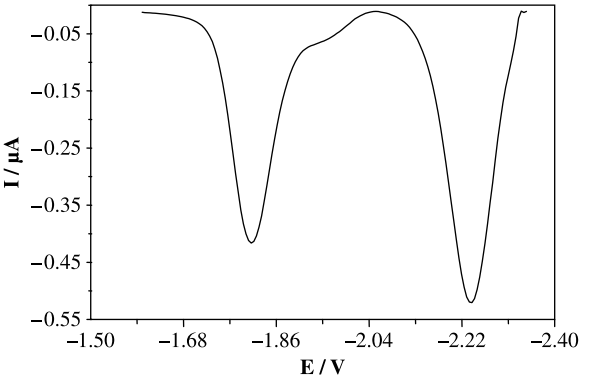


FIGURE 2 Differential pulse polarogram of 8×10^{-4} mol L^{-1} nicotinamide in DMSO.

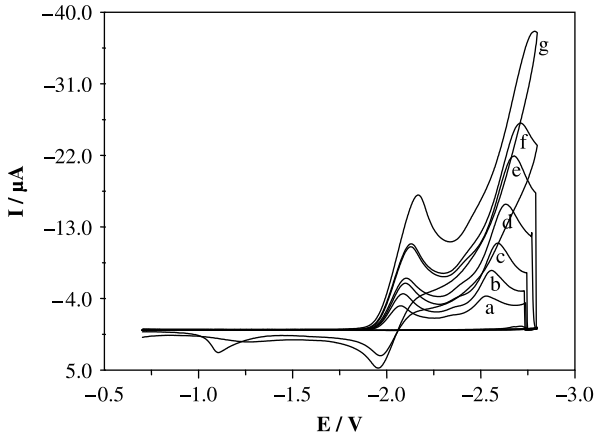


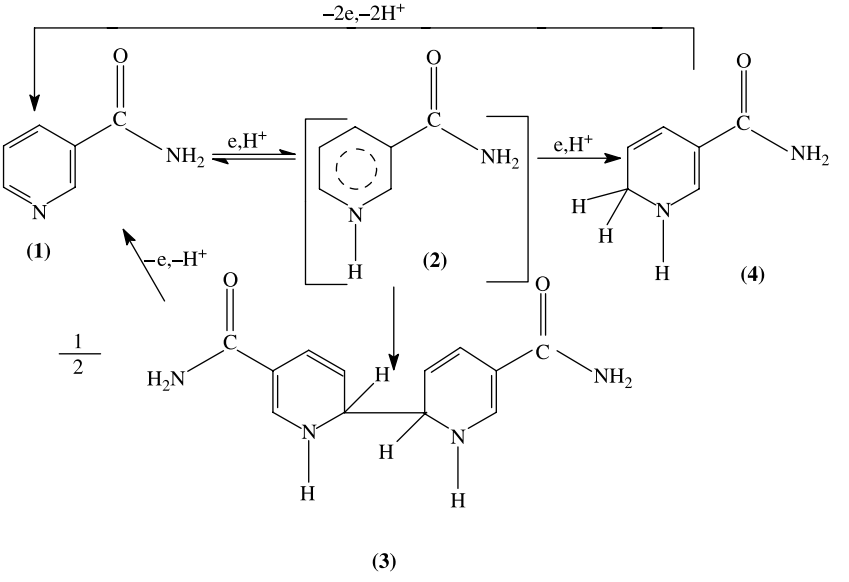
FIGURE 3 Cyclic voltammogram of nicotinamide (3.45 $\times 10^{-3}$ mol L^{-1}) in 90% (V/V) DMSO + water at varying sweep rates:- a) 50, b) 100, c) 200, d) 500, e)1000, f) 2000 and g) 6000 mVs^{-1}.

The two-electron reduction mechanism of nicotinamide in DMSO is confirmed by chronocoulometry technique at a mercury electrode. The potentials controlled at the values on the diffusion plateau of first peak (−2.0 V) and second peak (−2.5 V) showed that one (0.94) Faraday per mole of electroactive material is consumed for first peak and two (1.92) Faradays per mole of electroactive material are consumed for complete reduction.

Complexation of Nicotinamide with Crown Ether

The complexation behavior of nicotinamide with crown ethers viz. 15C5, B15C5, 18C6, DCH18C6, DB18C6, DB24C8, hexathia, N15C5, DN15C5, dibenzodiaza 15C4, dibenzyldiaza 18C6, tritosyltriaza 9C3 and tetratosyltetraaza 12C4 in 90% DMSO + water and DMSO has been studied. Also complexation with cyclam has been studied in 20% DMSO + water and in water medium. The complexation studies involving cyclam in DMSO could not be performed, as it is insoluble in it.

The differential pulse polarograms of nicotinamide and its mixture with DB18C6 in pure DMSO are given in Fig. 4. Nicotinamide shows two reduction peaks at −1.82 V and −2.24 V. The peak at −1.82 V corresponds to the reduction of nicotinamide to form a free radical and peak at −2.24 V due to reduction of neutral free radical to form a 1,6-dihydro nicotinamide. On gradually increasing the concentration of DB18C6 from 1.6×10^{-4} to 2.5×10^{-3} mol L^{-1} in the cell containing 1.015×10^{-3} mol L^{-1} nicotinamide results in the shift in potential towards less negative side with decrease in current of both peaks. The shift in potential and decrease in current are observed till the concentration of DB18C6 was exactly equal to nicotinamide concentration. With excess of DB18C6, no change in peak current and peak potential was observed indicating that the complex has 1:1 stoichiometry. The ΔE_p vs. $-\log C_L$ plot of second peak for nicotinamide-DB18C6 is used to calculate the stability constant (Fig. 5). The similar type of behavior was observed for the complexation of nicotinamide with 18C6, DCH18C6, hexathia and dibenzyldiaza 18C6 in DMSO and 90% DMSO + water, and dibenzodiaza 15C4 in DMSO. The positive shift in the peak potential of the vitamin on progressive addition of crown ethers in all the cases continued up to [L] ≈ [VH] indicating 1:1 complexation. In Table I, the stability constants and Gibbs free energy of nicotinamide with crown ethers in pure DMSO and 90% DMSO + water are summarized. The log K values of the complexes



SCHEME 2

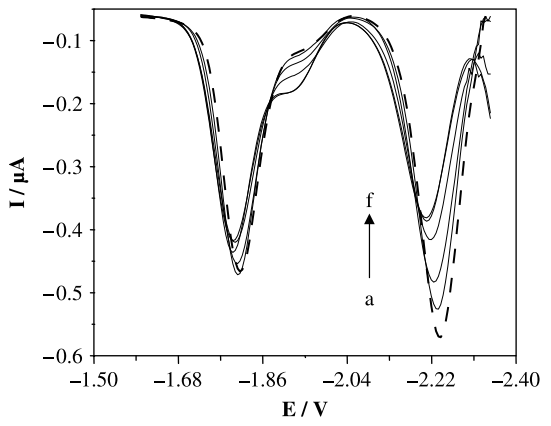


FIGURE 4 Differential pulse polarogram of 1.015×10^{-3} mol L^{-1} nicotinamide (--) solution containing 0 (a); 0.32×10^{-3} (b); 0.61×10^{-3} (c); 0.75×10^{-3} (d); 0.9×10^{-3} (e) and 1.02×10^{-3} mol L^{-1} (f) of DB18C6 (—) in pure DMSO.

with 1:1 stoichiometry fall in the range of 0.68 to 3.62 with a standard deviation of <0.06 ($5 \leq n \geq 9$). It is observed that all crown ethers form stable complexes with nicotinamide, with shift in potential towards less negative side and decrease in peak current. The Gibbs free energy change comes out to be negative at 25°C in all cases (Table I), which indicates the spontaneity of the binding of all nicotinamide with crown ethers.

A comparison of the values of stability constants given in Table I indicates that log K values of nicotinamide with 18C6 (log K 1.15) and DCH18C6 (log K 1.08) are observed to be almost similar in DMSO, whereas in the case of DB18C6 (log K 3.31), the complex shows greater stability. Such behavior has been observed earlier in the case of transition metal ions [10]. A relative higher stability with DB18C6 could be due to the unsaturated benzo-group substituent. On comparison of other oxa crown ethers containing five and eight membered rings, the five member ring like 15C5 and B15C5 do not form the complex because of small ring size, whereas DB24C8 shows an increase in peak current of both the peaks without shift in potential. All these observations, shift in peak potentials and change in peak currents show that there is an interaction between nicotinamide with crown ethers. The site of the interaction of nicotinamide with the crown ether may be pyridine ring with the N atom of the ring approaching the crown cavity with the nicotinamide molecule being directly perpendicular to the plane of the crown ether. The interactions of amino acid with oxa crown ethers have been well studied [36]. In these cases, each H atom from NH_3^+ of an amino acid interacts with one O atom of the crown ether via hydrogen bonding and the N atom bonds with three O atoms via electrostatic attraction. A full participation of all macrocyclic donor atoms with the complexed cation is expected to give the highest possible stability to the resulting complex. This does not seem to be the case with nicotinamide since only nitrogen in pyridine ring is available for complexation. Such behavior is reflected in the weak stability of the complex [17]. The interaction of nicotinamide with crown ether takes place through N atom present in the pyridine ring was confirmed by 1:1 complexation reported between six-membered N-Heteroaromatic cations and crown ether by Kiviniemi and co-workers [37].

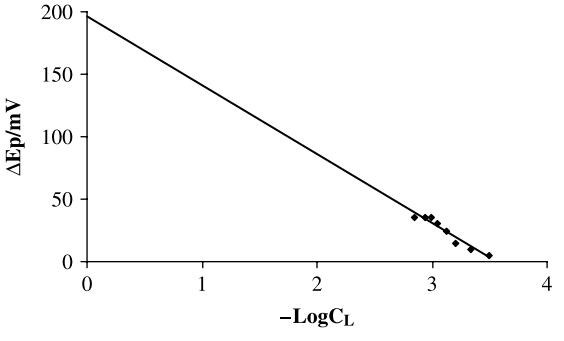


FIGURE 5 Plot of ΔE_P *vs.* $-\log C_L$ for DB18C6–nicotinamide system.

It is found that the heteroatom present in macrocycle can also affect the stability of complexes. Thus replacement of O with S or N in the coronand ring is observed to improve the stability of the complex. This behavior is observed during complexation with hexathia having the log K 2.06, which is more than 18C6 (log K 1.15). The effect of nitrogen in the macrocyclic ring was studied by taking different mono, di, tri and tetra aza crown ethers. Out of all aza crown ethers, N15C5 and DN15C5 do not form complexes, which may be due to smaller ring size. Thus replacement of one or two oxygen atoms of 15C5 by nitrogen does not attract the nicotinamide molecule. Other diazamacrocyclic compounds like, dibenzodiaza 15C4 and dibenzyldiaza 18C6 form good complexes in pure DMSO, this may be due to the presence of benzyl group, with its pi electron cloud, which makes the interactions possible. Tosylated crown ethers which are used in the present study, tritosyltriaza 9C3 and tetratosyltetraaza 12C4 containing three and four nitrogen atoms in macrocyclic ring are expected to form the stronger complex with nicotinamide, but they are electroactive in the same potential range where nicotinamide undergoes reduction therefore could not be studied. Cyclam containing four nitrogen atoms was then tried, but it is insoluble in DMSO and 90% DMSO + water. Hence, its complexation has been tried in 20% DMSO + water and water. Nicotinamide shows a single reduction peak at a potential at -1.64 V and -1.6 V in 20% DMSO + water and in pure water, respectively. With addition of increasing amounts of cyclam to the cell containing 1×10^{-3} mol L^{-1} nicotinamide, the peak

TABLE I Summary of the stability constant (log K/mol. L^{-1}) and Gibbs free energy ($-\Delta G$) of nicotinamide with macrocyclic compounds in DMSO and 90% DMSO + water

	DMSO		90% DMSO + water	
Macrocycles	Log K	$-\Delta$ G (KJ mol^{-1})	Log K	$-\Delta$G (KJ mol^{-1})
18C6	1.15	6.56	0.72	4.11
DCH18C6	1.08	6.16	0.68	3.88
DB18C6	3.31	18.88		
Hexathia	2.06	11.75	1.23	7.02
Dibenzodiaza15C4	1.63	9.30		
Dibenzyldiaza 18C6	2.84	16.20	2.12	12.09
Cyclam	3.62[†]	20.65	3.42[‡]	19.51

In all the cases the standard deviation was <0.06 ($5 \leq n \geq 9$).[†] Complexation of nicotinamide with cyclam in 20% DMSO + water; [‡] Complexation of nicotinamide with cyclam in water.

potential shifted towards less negative side with increase in peak current in the said mediums. The complexation results in increasing peak currents with maximum shift in peak potential of 27 mV at 1:1 ratio of cyclam to nicotinamide in water. Figure 6 shows the differential pulse polarogram of nicotinamide with cyclam in pure water. Similar trends of increase in stability constant with increase in DMSO % were observed for cyclam in 20% DMSO + water (log K 3.62) and water (log K 3.42). The thermodynamic data reflects the effect of the donor atoms of the legand in the complexation process involving these solvents. Thus, the more polarizable nitrogen atoms afford much stronger dipolar interaction as reflected in the higher stability of cyclam and hexathia with nicotinamide.

It has been shown from previous studies of crown ether complexation in various solvents that the metal complex stabilities are more in organic solvents as compared to that in water [11]. A similar trend has been observed in the present investigation where all the macrocyclic compounds show higher stability in pure DMSO compared to 90% DMSO + water media. The increase in stability, which is observed in the case of DB18C6 compared to 18C6 and DCH18C6 due to presence of benzene ring was not observed in the presence of water, as DB18C6 does not form a complex with nicotinamide in 90% DMSO + water. Also, dibenzodiaza 15C4 is observed to form a complex in pure DMSO but not in 90% DMSO + water. Table I shows that the solvent composition has an important effect on the stability of the resulting complexes. In all cases, the stability of the complex is more in solvent having less solvating power, as expressed by the Gutmann donor number, which is 29.8 and 33.0 for DMSO and water, respectively. Thus, the pure DMSO has the lowest donicity and therefore shows the least competition for the crown molecules for the vitamin, which in turn results in the most stable complex. This explains the low stability of complexes in 90% DMSO + water solvent as compared to pure DMSO based on the log K values obtained in this study. The stability trend for nicotinamide complexes observed is found to be in the order of cyclam > DB18C6 > dibenzyldiaza 18C6 > hexathia > dibenzodiaza15C4 > 18C6 > DCH18C6.

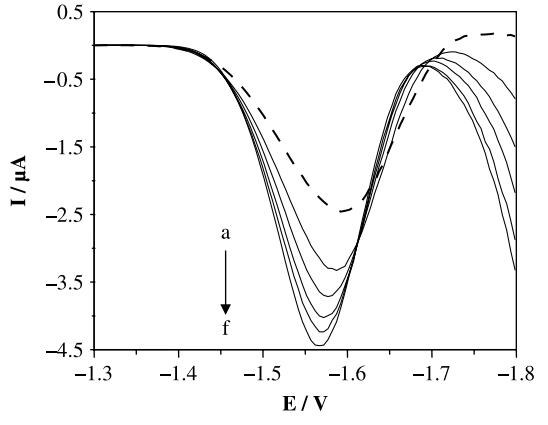


FIGURE 6 Differential pulse polarogram of 0.917×10^{-3} mol L^{-1} nicotinamide (--) solution containing 0 (a); 0.21×10^{-3} (b); 0.332×10^{-3} (c); 0.567×10^{-3} (d) 0.792×10^{-3} (e) and 1.076×10^{-3} mol L^{-1} (f) of cyclam (—) in water.

CONCLUSION

The stability constants of nicotinamide with oxa, aza and thia crown ethers in DMSO have been obtained by the shift in peak potential. It is observed that the stability of complex is affected not only by the size of the coronand ring, but also, solvating property of solvent, nature of heteroatom and substituted group present in the macrocycles. A relatively high stability is noticed by substitution of benzo group to macrocycles or replacement of O by S or N atoms in the coronand ring; a similar trend was observed in our previous work [17]. It is expected that such interaction studies would provide guidelines for development of some useful electrochemical sensors in the form of chemically modified electrodes and ion selective electrodes based on aza crown ether for the analysis of nicotinamide in different matrices or its separation by chromatographic techniques.

Acknowledgements

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