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Redox Kinetics as a Probe of the Supramolecular Interaction of α- and β-Cyclodextrins with Amphiphilic Nickel(II) Complexes of Pentaazamacrocycles Bearing Aliphatic Tails

ROBERT I. HAINES and JAMES E. ROWLEY
Department of Chemistry University of Prince Edward Island, 550 University Avenue, Charlottetown, PE, Canada C1A 4P3,

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Abstract

Host–guest interactions between α- and β-cyclodextrins and nickel(II) polyazamacrocycles bearing aliphatic pendant arms (*n*-butyl, *n*-octyl and *n*-dodecyl) have been investigated, using redox kinetics as a probe, to estimate binding constants. Electrospray mass spectrometry shows the formation of inclusion complexes in aqueous solution. Cyclic voltammetric measurements show the cyclodextrins to have no effect on the redox potentials for the nickel(II/III) couples. Kinetics of oxidation of the nickel(II) complexes to the tervalent state exhibits rate retardation in the presence of the cyclodextrins. The outer-sphere oxidation of the nickel(II) macrocycles by aqua(5, 5, 7, 12, 12, 14-hexamethyl-1,4,8,11-tetraazacyclotetradecane-1-acetato)nickel(III), $[Ni(hmca)(OH_2)]^{2+}$ obeys the rate law:

$$\text{Rate} = k_{obs}[Ni^{III}(hmca)(OH_2)] = \frac{[k_2 + k_3 K_{CD}][Ni^{II}L][Ni^{III}(hmca)(OH_2)]}{(1 + K_{CD}[CD])}$$

where k_2 is the rate constant for oxidation of the nickel(II) macrocycle in the absence of cyclodextrins, and k_3 is that for oxidation of the {NiL.CD} inclusion complex.

Introduction

Cyclodextrins are well known as cyclic oligosaccharides composed of D(+)-glucopyranose units linked by an α-(1,4) glycosidic linkage [1]. The α- and β-cyclodextrins contain 6 and 7 glucopyranose units respectively. The cyclodextrins have toroidal truncated cone shapes (or ''lampshades''), that have hydrophilic peripheries that give rise to significant solubilities in water. They have lipophilic cavities, that readily encapsulate hydrophobic molecules of appropriate size [2]. A schematic representation of α-cyclodextrin is shown in Figure 1.

Cyclodextrins have received much attention in areas of molecular recognition [3], biotechnology [4] and as biomimetic materials [5], as well as in the rapidly growing field of supramolecular chemistry [6].

Macrocyclic chemistry has blossomed over the past 40 years, with the development of facile routes to the synthesis of a myriad of macrocycles in high yields [7]. Attention has been focussed on the reactivity of macrocycles, with a variety of donor atoms that complex to metal ions. In recent years there has been a great deal of interest in the functionalization of macrocycles, producing pendant-arm complexes [8]. Azamacrocycles having one alkyl pendant-arm can be incorporated into liquid membranes [9]. Catalytic activity in solution can be greatly affected by the ability of a reagent to aggregate in solution, forming structured assemblies such as micelles, vesicles and lipid bilayers. This ability is dependent on the reagent having certain structural and electronic characteristics, such as a charged hydrophilic ''headgroup'' and a long hydrophobic ''tail'' [10]. Hexaaza-macrocycles containing six attached long aliphatic tails have been prepared, and have been shown to form a tubular mesophase (liquid crystal) by stacking the macrocyclic units [11]. Amphiphilic ferrocene-containing micelles have been shown to be disrupted by oxidation to the Fe(III) state, but re-micellize on reduction back to Fe(II) [12]. More recently, there has been a significant interest aroused in the ability of amphiphilic complexes to exhibit liquid crystal behaviour [13]. While many of the systems were of penta- or octahedral coordination, improved liquid crystal behaviour is found for systems with square planar

* Author for Correspondence. E-mail: rhaines@upei.ca

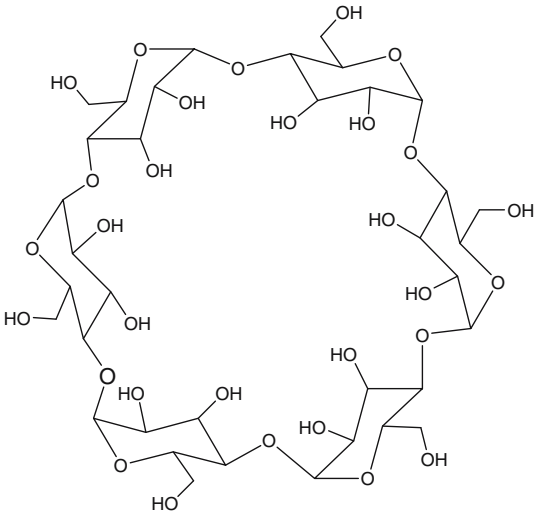

Figure 1. Structure of α-cyclodextrin.

geometry, since structural anisotropy of the ligand is not compromised. Medicinal applications of pendant-arm azamacrocycles, particularly as anti-HIV agents, has recently been reviewed [14].

Amphiphilic transition metal macrocycles, bearing pendant alkyl chains are expected to undergo supramolecular assembly with cyclodextrins, where the aliphatic chains can ''thread'' the lampshade-shaped cyclic oligosaccharides. Supramolecular interactions between cyclodextrins and a wide range of guest molecules are studied by methods such as solubility, absorption spectroscopy, NMR, fluorescence, voltammetry and conductivity, as well as others [15]. Many of these methods cannot be used to study host–guest interactions between cyclodextrins and pendant-arm macrocyclic complexes of nickel(II) because, for example, (a) there are no fluorescent markers present; (b) there are no significant spectral changes in the UV/visible region upon complexation; and (c) nickel(II) tetraazamacrocycles, while diamagnetic in the solid state, coordinate water molecules in their axial positions in low ionic strength aqueous solutions, giving rise to octahedral high-spin, paramagnetic species. Hence, NMR signals are often broad and unsuitable for use in NMR titrations.

Recently, we have shown that the nickel(II) pendant-arm pentaazamacrocycles, bearing aliphatic pendant-arms (shown in Figure 2 below) are oxidized to the nickel(III) form in aqueous solution by a nickel(III) complex of the *meso*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane-1-acetate anionic macrocycle *via* an outer-sphere mechanism [16].

n the present study, we have used the kinetics of oxidation of the amphiphilic macrocyclic complexes to the nickel(III) forms as a probe to examine the supramolecular interactions between α- and β-cyclodextrins with the pendant aliphatic tails of the complexes.

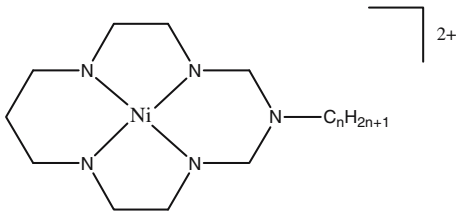

Figure 2. Structure of the nickel(II) pentaazamacrocyclic cations bearing aliphatic pendant-arms.

The complexes studied in this work are: (3-*n*-butyl-1,3,5,8,12-pentaazacyclotetradecane)nickel(II) perchlorate, $[NiL^4](ClO_4)_2$; (3-*n*-octyl-1,3,5,8,12-pentaazacyclotetradecane)nickel(II) perchlorate, $[NiL^8](ClO_4)_2$; and (3-*n*-dodecyl-1,3,5,8,12-pentaazacyclotetradecane) nickel(II) perchlorate, $[NiL^{12}](ClO_4)_2$. Hereafter, the abbreviated formulae will be used.

Experimental

Materials

All solutions were prepared using distilled, deionized water. The α- and β-cyclodextrins (Aldrich) were dried at 60 °C *in vacuo* overnight, prior to use. The nickel(II) complexes, $[NiL^{4,8,12}](ClO_4)_2$ were prepared, purified and characterized as described previously [16]. *Meso*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane-1-acetic acid (abbreviated hereafter as hmcaH, and its deprotonated form as $hmca^-$), and the aquanickel(II) complex, $[Ni(hmca)(OH_2)]^+$ (shown in Figure 3 below) were prepared according to the literature [17]. Solutions of the nickel(III) form were prepared *in situ* by oxidation with a stoichiometric deficiency of hexaaquacobalt(III) [18], as described previously [19]. All other reagents and solvents were of AnalaR grade and were used as received.

Caution! Compounds containing perchlorate anions must be regarded as potentially explosive and should be handled with caution.

Cyclic voltammetry

Cyclic voltammograms were measured using a Princeton Applied Research model 482 fast-scanning electrochemical apparatus, in aqueous 0.10 M trifluoromethanesulphonic acid, under an argon atmosphere. A 1mm diameter Pt disk working electrode, a platinum wire counter electrode and a Ag/AgCl (sat. KCl) reference electrode were used.

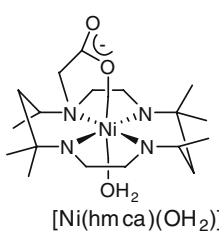

Figure 3. Structure of the $[Ni^{II}(hmca)(OH_2)]^+$ cation.

Electrospray mass spectra

The mass spectrometry measurements were obtained on a VG quadrupole mass spectrometer with an atmospheric pressure electrospray source. Samples, in distilled water, were introduced into the source at a flow rate of 5 mL min^{-1}.

Kinetics

Kinetic measurements were made using a Hi Tech SF61-DX2 stopped flow spectrometer, thermostatted to ± 0.1°C with a Lauda model RM6 refrigerated recirculating water bath. Pseudo-first-order conditions were maintained, using an excess of the appropriate nickel(II) amphiphilic macrocycle. A constant ionic strength ($NaClO_4/HClO_4$) was maintained for all experiments. The reactions were followed by monitoring net absorbance changes at 440 nm due to formation of the $[NiL^{4,8}]^{3+}$ products. Pseudo-first-order rate constants were determined by non-linear least squares fitting of absorbance-time data, using Hi Tech's ''Kinetasyst'' software, on a Dell 466MHz Pentium III computer.

Due to the low solubility of the $[NiL^{12}](ClO_4)_2$ complex in water, it was not possible to study its oxidation kinetics in the absence of cyclodextrins.

Results and discussion

Electrospray mass spectra of $[NiL^{4,8,12}]^{2+}$ in the presence of α- and β-cyclodextrins

The electrospray mass spectral data of aqueous solutions of $[NiL^n]^{2+}$ (10^{-4} M, $n = 4, 8$ and 12) containing 10^{-3} M α- and β-cyclodextrin are reported in Table 1. For all systems studied, the major species present is the free $[NiL^n]^{2+}$ cation. The $[NiL^n](ClO_4)^+$ ions were also detected, with higher concentrations being detected in solutions containing the shorter aliphatic-tailed complexes. 1:1 adducts, $[NiL^n(CD)]^{2+}$ were observed for all complexes, for both α- and β-cyclodextrins. From the peak intensities, the relative abundance (%BPI) of the 1:1 adducts is in the order $[NiL^8]^{2+} \gg [NiL^4]^{2+} > [NiL^{12}]^{2+}$. 1:2 adducts were also detected, but at an order of magnitude lower abundance than their 1:1 analogues. In the $[NiL^{12}]^{2+}$/α-CD system, a strong peak was seen at 1466 u. This corresponds to an approximate stoichiometry of 2:5 (calculated stoichiometry1:2.57) for $[NiL^{12}]^{2+}$: α-CD. A corresponding peak was not observed for the β-cyclodextrin system. For the $[NiL^n]^{2+}$/β-CD series, much lower amounts of the adducts were detected compared with the corresponding α-CD systems, with only trace amounts of the 1:2 adducts being detectable.

Electrochemistry

We previously [16] showed the cyclic voltammogram for reversible one-electron oxidation of the $[NiL^4]^{2+}$ cation in aqueous triflic acid. We have found, in this work, that the presence of 1×10^{-3} M α-cyclodextrin has no effect on the cyclic voltammogram, within experimental error. Oxidation of the nickel(II) centre to nickel(III) is reversible (peak separation 69 mV), with a half-wave potential of 0.72 ± 0.01 V *versus* S.H.E, for all complexes, in the presence of either α- or β-cyclodextrin. The value of $E_{1/2}$ (which corresponds to $E°$) is identical to that in the absence of α-cyclodextrin. The results are reported in Table 2. Further, the value remained constant for a series of concentrations of both α- and β-cyclodextrin. We have also shown previously [16] that the length of the aliphatic tails also does not affect the redox potentials of the $[NiL^n]^{2+}$ complexes.

It has been shown [20] that cyclic voltammetry is an excellent indicator of host–guest complex formation for addition of β-cyclodextrin to substituted viologens. In that system, where redox occurs *via* two one-electron transfers at the individual pyridyl rings of the viologen, each wave is shifted as its corresponding pyridyl ring is encapsulated by a β-cyclodextrin. Thus when the host cyclodextrin envelops one pyridyl ring, only one wave

Table 1. Electrospray mass spectral data

Species	*m/e* (calc.)	*m/e* (found)	%BPI
$[NiL^4]^{2+}$	158.5	157.5 (major)	100
$[NiL^4](ClO_4)^+$	416	416	5.99–11.59
$[NiL^4(\alpha\text{-CD})]^{2+}$	645	644 (strong)	11.50
$[NiL^4(\alpha\text{-CD})_2]^{2+}$	1132	1130.4	1.34
$[NiL^4(\beta\text{-CD})]^{2+}$	726	724.5	1.54
$[NiL^4(\beta\text{-CD})_2]^{2+}$	1294	1293	0.01
$[NiL^8]^{2+}$	186.5	185.6 (major)	100
$[NiL^8](ClO_4)^+$	472	470.3	2.17–5.19
$[NiL^8(\alpha\text{-CD})]^{2+}$	673	672.2 (strong)	29.75
$[NiL^8(\alpha\text{-CD})_2]^{2+}$	1160	1158.4	3.77
$[NiL^8(\beta\text{-CD})]^{2+}$	754	753.2 (strong)	9.49
$[NiL^8(\beta\text{-CD})_2]^{2+}$	1321.5	1320.9	0.48
$[NiL^{12}]^{2+}$	215	213.8 (major)	100
$[NiL^{12}](ClO_4)^+$	528.5	528.3	0.48–3.22
$[NiL^{12}(\alpha\text{-CD})]^{2+}$	701	700.3 (strong)	7.82
$[NiL^{12}(\alpha\text{-CD})_2]^{2+}$	1188	1186	0.81
$[(NiL^{12})_2(\alpha\text{-CD})_5]^{2+}$	1431	1466.5 (strong)	29.93
$[NiL^{12}(\beta\text{-CD})]^{2+}$	782	781 (strong)	6.29
$[NiL^{12}(\beta\text{-CD})_2]^{2+}$	1350	1349 (weak)	0.29

Table 2. Electrochemical data for $[NiL^{4,8,12}]^{2+}$ in both the presence and absence of cyclodextrin, in 0.10 M triflic acid

Sample	$E°$ (V)
0.001 M $[NiL_4]^{2+}$	0.72 ± 0.01
0.001 M $[NiL_8]^{2+}$	0.72 ± 0.01
0.001 M $[NiL_{12}]^{2+}$ + 0.002 M α-CD	0.71 ± 0.02
0.001 M $[NiL_4]^{2+}$ + 0.002 M α-CD	0.72 ± 0.01
0.001 M $[NiL_8]^{2+}$ + 0.001 M α-CD	0.73 ± 0.02
0.001 M $[NiL_8]^{2+}$ + 0.002 M α-CD	0.72 ± 0.02

$E°$ values are reported versus the Ag/AgCl electrode at 298 K.

shifts in the cyclic voltammogram and the wave due to electron transfer at the exposed end of the viologen is unaffected. In the electrochemical study of the interaction of β-cyclodextrin with carboxycobalticenium [21], addition of β-cyclodextrin to the system causes an anodic shift of 57 mV in the reversible one-electron anodic wave, indicative of inclusion of the sandwich complex inside the β-cyclodextrin's cavity.

In the present study, addition of α- and β-cyclodextrins to each of the three nickel(II) macrocycles had no effect on their cyclic voltammograms. Thus, while the electrospray data show the presence of $\{[NiL^n].CD\}^{2+}$ host–guest complexes in solution, the lack of dependence of $E_{1/2}$ on [CD] indicates that the cyclodextrins do not envelop the nickel redox centre. Rather, the supramolecular complexation occurs at the alkyl tail portions of the complexes. This is not unexpected, since the approximate diameters of the α- and β-cyclodextrin cavities are 5.7 and 7.8 Å respectively, while the width of the nickel-macrocycle is 6.7 Å. Thus the latter moiety is clearly too large to enter the cavity of α-cyclodextrin. Although the nickel(II) macrocycle is theoretically able to fit within the cavity of β-cyclodextrin, the probability of such an event would be very low, given the hydrophobic nature of the cavity and the hydrophilic character of the doubly charged metal complex. Further, the positively charged nickel(II)-macrocycle centre would be repelled by the hydrophobic cavity of the cyclodextrins. The inclusion of the alkyl tails could not be shown by NMR, since, as noted in the Introduction, the complexes exhibit paramagnetic character in aqueous solution, due to coordination of solvent water in the axial positions at the nickel centre, resulting in a high-spin octahedral nickel(II) species.

Table 3. Second-order rate constants, $k_{obs}/[NiL^{4,8,12}]_{tot}$ as a function of increasing [CD] at 25 °C

Complex	α – CD		β – CD	
	10^3[CD]/M	k_4/mol^{-1} dm^3 s^{-1}	10^3[CD]/M	k_4/mol^{-1} dm^3 s^{-1}
$[NiL_4]^{2+}$	0	8287	0	8391
	0.908	8435	1.74	8505
	1.82	7929	3.48	8480
	3.63	8514	5.22	8474
	2.73	7958	6.58	8565
	4.54	8300		
	5.45	8380		
	6.36	8213		
$[NiL_8]^{2+}$	0.907	8410	0	8000
	1.81	7700	0.435	7850
	2.72	7430	0.87	7695
	3.63	7040	1.74	7605
	4.54	6970	2.61	7540
			3.48	7485
			4.35	7295
			5.22	7230
			6.09	6975
$[NiL_{12}]^{2+}$			0.348	4873
			0.783	4642
			1.22	4337
			1.65	4273
			2.09	4236
			2.96	4171

Constant concentrations of 1.00×10^{-4} M and 1.00×10^{-5} M were maintained for $[NiL^{4,8,12}]^{2+}$ and $[Ni(hmca)(OH_2)]^{2+}$ respectively.

Kinetics

Oxidation of $[NiL^n]^{2+}$ by $[Ni(hmca)(OH_2)]^{2+}$ has been shown to occur *via* an outer-sphere mechanism, the reaction being first-order in both $[NiL^n]^{2+}$ and $[Ni(hmca)(OH_2)]^{2+}$ and is independent of $[H^+]$ [16]. Addition of α- or β-cyclodextrin causes retardation of the rate of oxidation. Table 3 lists the second-order rate constants, $k_{obs}/[NiL^{4,8,12}]_{tot}$, for the reaction in the presence of a series of concentrations of α- or β-cyclodextrin at 25 °C. The rate decreases with increasing cyclodextrin concentration, corresponding to rapid equilibrium host–guest complexation, followed by oxidation of the nickel(II) centres in the "free" and complexed species, according to the following scheme:

$$[NiL^n]^{2+} + CD \rightarrow [NiL^n\{CD\}]^{2+} \quad K_{CD} \qquad (1)$$

$$[NiL^n]^{2+} + [Ni(hmca)(OH_2)]^{2+} \rightarrow [NiL^n]^{3+} + [Ni(hmca)(OH_2)]^{+} \quad k_2 \qquad (2)$$

$$[NiL^n\{CD\}]^{2+} + [Ni(hmca)(OH_2)]^{2+} \rightarrow [NiL^n\{CD\}]^{3+} + [Ni(hmca)(OH_2)]^{+} \quad k_3 \qquad (3)$$

Hence,

$$\text{Rate} = k_{obs}[Ni(hmca)(OH_2)] = k_2[NiL] + k_3[NiL\{CD\}][Ni(hmca)(OH_2)] \qquad (4)$$

Using the Law of Mass Balance, the equilibrium concentrations of [NiL] (Equation 2) and [NiL{CD}] (Equation 3) may be expressed in terms of the total concentration of NiL^n present, $[Nil]_{tot}$, as:

$$[NiL] = [NiL]_{tot}/(1 + K[CD]), \text{ and } [NiL\{CD\}] = K[CD][NiL]_{tot}/(1 + K[CD])$$

Substitution into Equation (4) gives the overall rate law:

$$\text{Rate} = k_{obs}[Ni^{III}(hmca)(OH_2)] = \frac{[k_2 + k_3K_{CD}][Ni^{II}L][Ni^{III}(hmca)(OH_2)]}{(1 + K_{CD}[CD])} \qquad (5)$$

whence

$$k_{obs} = [k_2 + k_3K_{CD}][Ni^{II}L]/(1 + K_{CD}[CD]) \qquad (6)$$

The kinetic data for the $n = 8$ and 12 complexes were fitted to Equation (6) using a non-linear least squares method, to estimate values of the binding constant, K_{CD} and the rate of electron transfer from the $[NiL^n\{CD\}]^{2+}$ host–guest complex, k_3. Estimates of K_{CD} and k_3, are reported in Table 4. Plots of $k_{obs}/[Ni^{II}L]$ *versus* [β-CD] for the three complexes, shown in Figure 4, illustrate the immeasurably small binding for the L^4 complex (using the kinetic probe method); reasonable binding for the L^8 complex; and very strong binding for the L^{12} complex.

The rate of electron transfer from the host–guest complex decreases as the aliphatic tail length increases. This trend was not observed for oxidation of the amphiphilic complexes in the absence of cyclodextrins [16], and may be due to steric effects of the cyclodextrins that encompass the pendant tails. There is a marked trend in binding constants. For α-CD, the binding with $[NiL^4]^{2+}$ was too weak to give a meaningful estimate. Very strong binding was observed for $[NiL^8]^{2+}$, where the tail is expected to be fairly linear, and the cross-section of the aliphatic tail matches the cavity of α-CD, leading to an excellent fit. The binding with $[NiL^{12}]^{2+}$ could not be measured, due to lack of solubility of the amphiphile under the kinetic conditions. The inability of the complex to dissolve sufficiently to meet the pseudo first-order conditions suggests that binding with α-CD is weak, since strong binding is expected to enhance the solubility of the complex.

In the case of β-cyclodextrin, observations similar to α-CD were made with $[NiL^4]^{2+}$. For $[NiL^8]^{2+}$, the binding constant with β-CD was found to be an order of magnitude less than that for α-CD. This is understandable since the cavity of β-CD is larger than that of α-CD, leading to weaker Van der Waals interaction between the host cavity walls and the guest's periphery. Interestingly, the binding constant for β-CD with $[NiL^{12}]^{2+}$ is the largest of all. It is possible that the long aliphatic tail is flexible enough to fold inside the host cavity, giving a tighter fit, with stronger Van der Waals interactions.

The trends in binding constants correlate well with the electrospray mass spectral data.

Conclusions

Redox kinetics at the metal macrocycle centre can be used as a probe of supramolecular properties of pendant aliphatic groups. The length of the aliphatic tail has a minimal effect on the redox kinetics of the Ni(II/III) centre. Cyclodextrins that engulf the aliphatic tails do not encompass the metal centre, evidenced by the independence of redox potential on [CD]. There is a very weak interaction between the CDs and the L^4 complex. α-CD has a strong affinity for the L^8 complex; β-CD has a strong affinity for the L^{12} complex. Current work in our laboratory focusses on developing pendant-arm macrocycles with fluorescent markers in the pendant groups, to allow comparison of binding constants measured by two independent methods.

Table 4. Estimated values of k_2 , k_3 and K_{CD}, obtained from fitting of kinetic data in Table 3 to Equation (6)

Complex	CD	$k_2/M^{-1}\ s^{-1}$	$k_3/M^{-1}\ s^{-1}$	K_{CD}
$[NiL^4]^{2+}$	α	8250 ± 210	–	–
	β	8480 ± 100	–	–
$[NiL^8]^{2+}$	α	9800 ± 500	6000 ± 400	1200 ± 200
	β	8100 ± 500	6400 ± 500	200 ± 100
$[NiL^{12}]^{2+}$	β	7500 ± 200	4060 ± 30	8500 ± 650

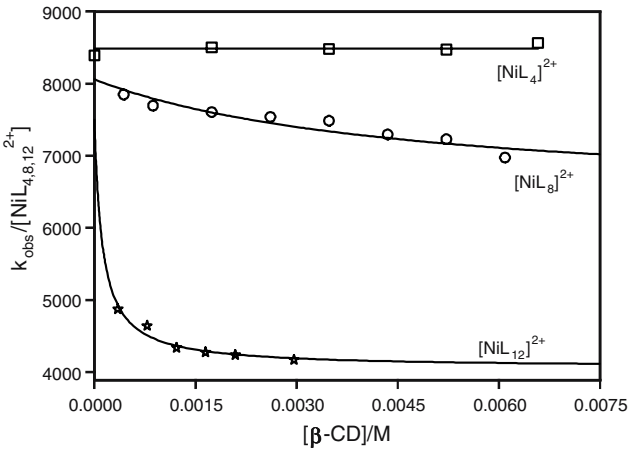

Figure 4. Plot of the second-order rate constants $k_{obs}/[NiL^{4,8,12}]_{tot}$, as a function of increasing [β-CD] at 298K. Constant concentrations of 1.00×10^{-4} mol dm^{-3} and 1.00×10^{-5} mol dm^{-3} were maintained for $[NiL_{4,8,12}]^{2+}$ and $[Ni(hmca)(OH_2)]^{2+}$ respectively.

Acknowledgements

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