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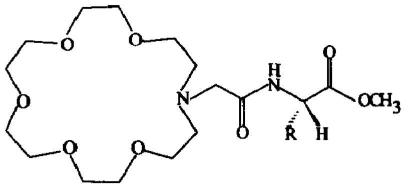
Equilibrium Cation Binding Constants of the Dipeptide Derived Lariat Ethers in Methanol Determined From Circular Dichroism Measurements

Danlin Gu, Birdella D. Kenney, Banita White Brown*

Department of Chemistry, University of North Carolina at Charlotte, Charlotte, NC 28223, USA

Abstract: Circular Dichroism Spectropolarimetry has proven to be a useful alternative for determining cation binding constants for Na^+, K^+, and Ca^{2+} of the dipeptide derived lariat ethers in anhydrous methanol. The determination of log K_S for Ca^{2+} for derivatives of **2** involved using a new application of CD called ligand-ligand competitive CD.

The dipeptide derived nitrogen pivot lariat ethers (**1** and **2**) are potentially useful as neutral carriers of alkaline earth metal cations. Recently, Gokel et al.[1] reported that derivatives of **2** exhibited extraordinarily high Ca^{2+} binding strengths and the highest Ca^{2+}/Na^+ ion selectivities known for nitrogen pivot bibracchial lariat ethers (BiBLEs) in aqueous solution. The equilibrium binding constants (log K_S) for Ca^{2+} were determined directly using a calcium ion selective electrode. Kataky et al.[2] have also studied the binding properties of these ligands in aqueous solution and reported similar trends in calcium selectivity using potentiometric methods.



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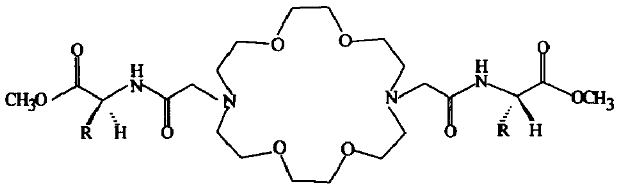

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Attempts to determine Ca^{2+} ion binding of the dipeptide BiBLEs in methanol in a competitive method with the Na^+ ion using a sodium ion selective electrode were unsuccessful.[3,4] No competition between Na^+ and Ca^{2+} ions was observed, which indicated strong complexation to Ca^{2+}. Since calcium ion selective electrodes are incompatible in methanol solvent,[4] another method of assessing Ca^{2+} ion binding strengths of these ligands is needed. We report here results from using circular dichroism (CD) spectropolarimetry for determining cation binding strengths of the dipeptide lariat ethers. Since the molecules possess a chiral center near a chromophore accessible in the ultraviolet region of the electromagnetic spectrum, circular dichroism measurements are possible. The advantage of using the CD method is that binding information about the ligand may be obtained for a variety of cations in a variety of solvents. Information about the solution conformation of the complexed and uncomplexed ligands may also be obtained from CD measurements.

The equilibrium stability constants determined for derivatives of **1** and **2** and various cations are shown in Table 1 and are reported as log K_S values. The equilibrium constants were calculated from changes in CD measurements of crowns **3-12** as cation concentration was increased.

In order to test the validity of the method, log K§ for Na^+ and K^+ was obtained first since values for Na^+ and K^+ have been determined previously by Gokel et al.[3,5] in methanol solutions using the sodium and potassium ion selective electrodes, respectively. For the single armed nitrogen pivot derivatives, **3-7**, log K_S for Na^+ ranges from 4.18 to 4.30 ± 0.1 and log K_S for K^+ ranges from 5.22 to 5.62 ± 0.2. The binding constant values and K^+/Na^+ selectivity are essentially the same as those observed by Gokel . The values for the dipeptide BiBLEs, **8-12**, are as follows: log K_S for Na^+ ranges from 4.20 to 4.46 ± 0.12 and log K_S for K^+ ranges from 4.34 to 4.81 ± 0.13. The binding constants for Na^+ of the dipeptide BiBLEs are almost identical to those obtained from the sodium ion selective electrode. Our K^+ binding constants are slightly higher than those determined by Gokel, but are of the same order of magnitude.

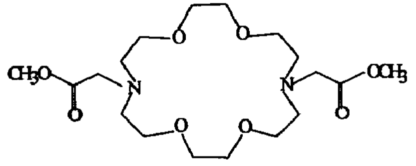
Table 1. Binding Constants for Na^+, K^+, and Ca^{2+} with Peptide Derived Nitrogen Pivot Lariat Ethers

		Log K_S (MeOH, 25°C)		
Compound	R	Na^+	K^+	Ca^{2+}
		Single-armed Derivatives		
3	Me	4.18	5.31	6.29
4	*s*-Bu	4.25	5.60	7.18
5	*i*-Bu	4.30	5.34	6.82
6	benzyl	4.20	5.62	6.51
7	*i*-Pr	4.25	5.22	6.53
		Two-armed Derivatives		
8	Me	4.46	4.34	9.13
9	*s*-Bu	4.20	4.53	9.06
10	*i*-Bu	4.25	4.52	8.82
11	benzyl	4.34	4.81	9.16
12	*i*-Pr	4.23	4.40	9.21

Log K_S for Ca^{2+} was then determined using circular dichroism measurements since CD proved to be a useful alternative. The binding constants for the one-armed dipeptides (**1**) range from 6.29 to 7.18 ± 0.2. Very strong complexation to Ca^{2+} is observed.

It is interesting to note that the values for Ca^{2+} for the single armed analogues are of the same order of magnitude as those of the dipeptide BiBLEs in aqueous solution.[1] However, the Ca^{2+}/Na^+ selectivity is not as high. This is probably due to the increased Na^+ binding of the ligand in the methanol solvent. The data show cation selectivity in the expected order, $Na^+<K^+<Ca^{2+}$. The binding constants (log K_S) increase by approximately an order of magnitude for each cation.

Calcium binding for the dipeptide BiBLE, **10**, was then attempted from CD measurements. Strong complexation to Ca^{2+} was evident from the CD spectra. The CD spectrum for a solution containing a mixture of crown and cation in a 1:1 ratio closely resembled that of a solution containing an excess of cation with the crown. Because of the similarity in the spectra, the formation of the 1:1 complex was near completion and a value for calcium could not be accurately calculated (see Figure 1). Therefore, it was necessary to design an alternative approach to determine its binding constant for Ca^{2+} from CD measurements. The method involved a ligand-ligand competition where two ligands compete for the same cation (Ca^{2+}). It was required that the competing ligand be non-CD active and exhibit strong binding to Ca^{2+}. Compound **13** (log K_S = 6.78, MeOH, 25°C)[6] was used in this study as the competing ligand.



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It was possible to calculate log K_S values from changes in the CD spectrum of the 1:1 dipeptide BiBLE and Ca^{2+} solution with increasing concentrations of **13** (see Figure 2). The values of log K_S for Ca^{2+} and derivatives of **2** determined using this competitive approach are shown in Table 1. The binding constants range from 8.82 to 9.21 ± 0.1. Values of this magnitude were expected. Gokel observed that Na^+ binding constants determined in water and in methanol differ by approximately two orders of magnitude.[1] Since cation binding strengths are solvent dependent, similar differences between Ca^{2+} binding constants determined in water[1,2] and in methanol were anticipated. Indeed, the values we obtained in methanol differ from those reported in water by about two orders of magnitude. These high Ca^{2+} binding constants confirm the effect of sidearm polarity of the lariat ethers on calcium selectivity.[6] The more polar sidearms prefer

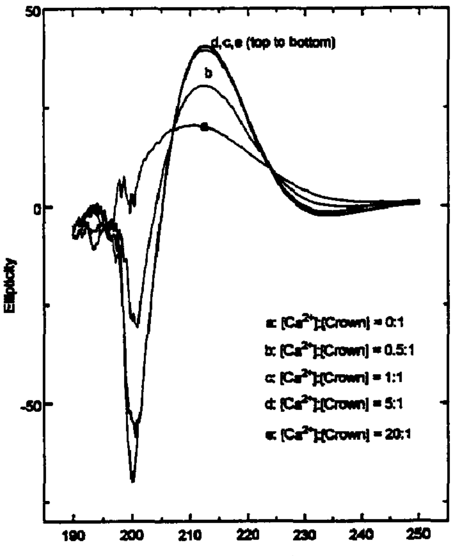

Figure 1. CD spectra of **10** with various various $[Ca^{2+}]$: [crown] ratios.

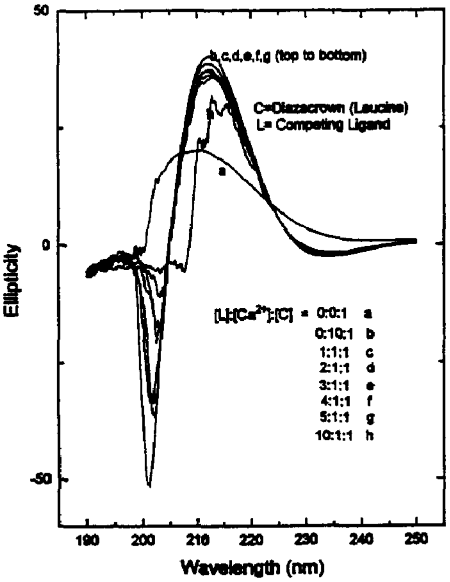

Figure 2. CD spectra of **13**, **10**, and Ca^{2+} with various [**13**] : $[Ca^{2+}]$: [**10**] ratios.

charge dense calcium ions. Circular dichroism studies of complexation interactions between these ligands and other metal cations are forthcoming.

At this point, concrete information about the solution conformation of the complexed and uncomplexed ligand is not available from our data. However, the increase in ellipticity with increasing cation concentrations suggests that the peptide derived lariat ethers have more rigid conformations in the complexed form than in the uncomplexed form. Further CD studies along with NMR studies could provide additional information about the conformation these ligands adopt in solution.

In conclusion, circular dichroism measurements have proven to be a useful technique for determining binding constants of this group of specialized ligands and various cations in anhydrous methanol. The ligand-ligand competition method employed for determining Ca^{2+} binding for derivatives of **2** from CD measurements also proved to be successful.

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