Anion and Cavity Effects on the Complexation Behavior of Di-Aza-Benzo-Crown-Ether Calix[4]arene towards Zn(II) Ions

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Abstract. A novel compound, 25, 27 - N, N' - di - ((2 - ethoxy)benzyl)butylenediamine - p - *tert*-butylcalix[4]arene, **1**, has been synthesized by reducing its Schiff base derivative. Inclusion studies by ^{1}H-NMR spectroscopy in a mixed solvent ($CD_3OD/CDCl_3$) of 25,27-N, N'-di-((2-ethoxy)benzyl)propylenediamine-p-*tert*-butylcalix[4]arene, **2**, and **1** with Zn(II) ions, where counter anions are Cl^-, Br^-, I^- and NO_3^-, show that both ligands can bind Zn(II) to a different extent depending on the counter anions and the cavity size of the ligands. The stability constants of ZnX_2–**1** (ZnX_2-**2**) complexes where X = Cl^-, Br^-, I^- and NO_3^- are 1.4 ± 0.1 (1.6 ± 0.1), 1.7 ± 0.1 (1.9 ± 0.1), 2.2 ± 0.1 (2.7 ± 0.1) and 4.7 ± 0.1 (6.0 ± 0.1), respectively. The calix[4]arene unit of the ligand **2** was found to have a structural change from cone to partial cone conformation upon binding to $ZnCl_2$, $ZnBr_2$ and ZnI_2.

Key words: Partial cone conformation, crown ether, anion effect, cavity size effect, conformational change, calix[4]arene.

1. Introduction

Calix[4]arene is a versatile building block used for many investigations in supramolecular chemistry, as shown in recent reviews [1–3]. The molecule possesses a well preorganized cavity. In particular, the lower rim of the calix[4]arene unit can be modified by methods of organic syntheses to connect useful moieties into the hydroxy unit [4–8]. This property makes calix[4]arene a very attractive compound that can be used as a starting platform for designing more sophisticated structures to bind specific guest atoms and molecules. Calix[4]arene possesses four possibilities of conformational isomerism: cone, partial cone, 1,2-alternate and 1,3-alternate [5, 9]. Among these four conformations, the cone conformation is favored because of the very strong intramolecular hydrogen bonding between the four OH groups at the lower rim of the calix. It was found from ^{13}C-NMR studies that the main cause of the conformation differences originates from steric rather than electronic effects [10]. Pochini *et al.* have demonstrated that the conformation of calix[4]arene depends on functional groups attached to the lower rim [11]. Fur-

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thermore, substituents on the *meta* position of phenol rings of the calix were also found to have effects on calixarene conformations [12].

We have been working on a class of calix[4]arene derivatives in which two OH groups of the lower rim have been modified by adding the di-aza-benzo-crown-ether moiety. We report herein the synthesis of 25,27-N, N'-di-((2-ethoxy)benzyl)butylenediamine-p-$tert$-butylcalix[4]arene, **1**, and its character-ization. In a similar manner to its congener macrobicyclic compounds such as cryptand[13], **1** can bind both metal ions and anions. In this report, we have examined the effect of counter anions and the cavity size of ligands on the com-plex stability of Zn(II) with the ligand **1** and its analogue, 25,27-N, N'-di-((2-ethoxy)benzyl)propylene diamine-p-$tert$-butylcalix[4]arene, **2**. We also observed the effects of counter anions on the conformation of the calix[4]arene unit.

2. Experimental

2.1. MATERIALS

The solvents, sodium hydroxide and 1,4-diaminobutane were obtained from Baker, Merck and Fluka Chemical Company, respectively. All chemicals were used with no further purification.

2.2. ANALYTICAL PROCEDURES

The ^{1}H-NMR spectra were recorded at 200 MHz on a Bruker ACF200. Mass spectra were obtained on a Jeol JMS-DX-300 mass spectrometer. Elemental analyses were carried out on a Perkin Elmer Elemental Analyzer 2400 CHN at the Scientific and Technological Research Equipment Center of Chulalongkorn University.

2.3. SYNTHETIC PROCEDURES

The preparation of 25, 27 - N, N' - di - ((2 - ethoxy)benzyl)butylenediimine - p - *tert* - butylcalix[4]arene, **Sb-1**, and 25, 27 - N, N' - di - ((2 - ethoxy)benzyl)-propylenediamine-p-*tert*-butylcalix[4]arene, **2**, have been reported previously [14, 15].

2.3.1. *Preparation of 25,27-N, N'-di-((2-ethoxy)benzyl)butylenediamine-p-tert-butylcalix[4]arene·2HCl (**1**·2HCl)*

To a solution of **Sb-1** (2.00 g, 2.04 mmol) was added sodium borohydride (1.17 g, 40.72 mmol). The mixture was stirred under a nitrogen atmosphere for 2 h. Water was then added to quench the excess of sodium borohydride. After evaporating to dryness, the solid residue was then extracted with dichloromethane. The organic layer was dried over sodium sulfate and evaporated to dryness. The solid was acidified with a hydrochloric acid solution in methanol (0.74% v/v) until the pH

of the solution reached 1. The hydrochloride product was obtained as a white precipitate upon reducing the volume of the solvent (1.73 g, 81%).

Characterization data for **1·2HCl**: ^{1}H-NMR (CDCl$_3$): δ (ppm) 9.13 (s, broad, 4H, N*H*), 7.40–7.17 and 6.87–6.74 (m, 8H, aromatic protons), 6.97 (s, 4H, HOAr*H*), 6.78 (s, 2H, ArO*H*), 6.68 (s, 4H, ROAr*H*), 4.60 (s, broad, 4H, Ar—C*H*$_2$—NH—), 4.32 and 3.15 (AB system, $J_{\text{H···H}}$ = 13.0 Hz, 8H, ArC*H$_A$H$_B$*Ar), 4.18 (s, broad, 8H, OC*H*$_2$C*H*$_2$O), 3.18 (s, broad, 4H, NC*H*$_2$CH$_2$), 2.26 (s, broad, 4H, CH$_2$C*H*$_2$C*H*$_2$CH$_2$), 1.23 (s, 18H, HOAr—*t*-C$_4$*H*$_9$), 0.85 (s, 18H, ROAr—*t*-C$_4$*H*$_9$). FAB positive: 1074 m/z. *Anal. Calcd.* for C$_{66}$Cl$_2$H$_{86}$O$_6$N$_2$: C, 73.74; H, 8.01; N, 2.61. *Found*: C, 73.68; H, 8.16; N, 2.49.

2.3.2. *Preparation of 25,27-N,N'-di-((2-ethoxy)benzyl)butylenediamine-p-tert-butylcalix[4]arene (1)*

To a methanolic solution (25 mL) of **1·2HCl** (2.00 g, 2.0 mmol) was slowly added a methanolic solution (50 mL) of sodium hydroxide (0.16 g, 4.0 mmol). Concurrently, the mixture was stirred. After the solution reached pH 10, it was evaporated to dryness. The residual was redissolved in methylene chloride and extracted with water. The organic phase was then dried over anhydrous sodium sulfate. Upon slowly adding methanol, a white solid precipitated and was isolated from the methylene chloride solution (1.12 g, 59%).

Characterization data for **1**: ^{1}H-NMR (CDCl$_3$): δ (ppm) 7.30–7.17 (m, 4H, aromatic protons), 6.92 (t, 2H, aromatic protons), 6.82 (d, 2H, aromatic protons), 7.03 (s, 4H, HOAr*H*), 6.73 (s, 4H, ROAr*H*), 4.39 and 4.31 (s, broad, 8H, OC*H*$_2$CH$_2$O), 4.39 and 3.27 (AB system, $J_{\text{H···H}}$ =13.0 Hz, 8H, ArC*H$_A$H$_B$*Ar), 3.82 (s, broad, 4H, Ar—C*H*$_2$—NH—), 2.43 (t, 4H, NC*H*$_2$CH$_2$), 4.27 (m, broad, 4H, CH$_2$C*H*$_2$C*H*$_2$CH$_2$), 1.27 (s, 18H, HOAr—*t*-C$_4$*H*$_9$), 0.91 (s, 18H, ROAr-*t*—C$_4$*H*$_9$). FAB positive: 1001 m/z. *Anal. Calcd*. for C$_{66}$H$_{84}$O$_6$N$_2$: C, 79.16; H, 8.45; N, 2.80. *Found*: C, 79.60; H, 8.31; N, 2.60.

2.4. INCLUSION STUDIES OF COMPOUNDS **1** AND **2** WITH ZnX$_2$ (X = Cl, Br, I, NO$_3$, ClO$_4$) BY ^{1}H-NMR SPECTROMETRY

Generally, metal salts (0.2 mmol) in CD$_3$OD (2 mL) and the ligands (0.125 mmol) in CDCl$_3$ (2.5 mL) were mixed in a NMR tube by varying the Zn(II) : ligand ratio from 0–3. We monitored the chemical shift displacement (experimental δ_{obsd}) of the ArC*H*$_2$NH— or —[NC*H*$_2$]$_2$CH$_2$ proton signals. Analyses of the data at equilibrium in order to estimate the stability constant can be performed using the following equations:

$$M + L \overset{K}{\rightleftharpoons} ML \qquad M = Zn^{2+}, \quad L = \mathbf{1} \text{ or } \mathbf{2}$$
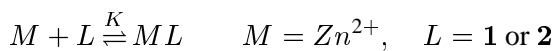
$$K = [ML]/[M][L]$$

$$\delta_{\text{obsd}} = \delta_L X_L + \delta_{ML} X_{ML} \tag{1}$$

$$X_L \text{ is the mole fraction of } L, \quad X_L = [L]/C_L^0 \tag{2}$$

$$X_{ML} \text{ is the mole fraction of } ML, \quad X_{ML} = K[M][L]/C_L^0. \tag{3}$$

Mass balance equation:

$$C_L^0 = [L] + [ML] \quad \text{and} \quad [L] = C_L^0/(1 + K[M]) \tag{4}$$

$$C_M^0 = [M] + [ML] \text{ and } [M] = C_M^0/(1 + K[L]). \tag{5}$$

The set of equations was solved by iteration [16,17]. Starting with an initial estimate of the free metal concentration $[M]$, the first value of $[L]$ could be obtained from Equation (4) and used to calculate a more accurate estimate of $[M]$ from Equation (5). This procedure was repeated until convergence occurred. The converged values of $[M]$ and $[L]$ were used in the calculation of the mole fraction from Equations (2) and (3). The value of K was obtained by fitting the calculated δ_{obsd} (Equation (1)) to the experimental values.

3. Result and Discussion

3.1. SYNTHESIS AND CHARACTERIZATION

The crown ether-p-tert-butyl calix[4]arene **1** was prepared by hydrogenating the Schiff base calix[4]arene, 25,27-N, N'-di-((2-ethoxy)benzyl)butylenediimine-p-tert-butylcalix[4]arene (**Sb-1**), Scheme 1, in the same manner as its analogue **2** [15]. Signals of —NH_2^+— and methylene protons of ArCH_2NH$_2^+$— appear at 9.13 ppm and 4.60 ppm, respectively. They shifted relatively downfield as compared to the starting compound **Sb-1** [14] due to the deshielding effect of the positive charge on the nitrogen atom. The mass spectrum of this compound shows an intense signal at m/z 1001 corresponding to **1·2HCl** with less HCl molecules which may be stripped off during the characterization process. The elemental analysis, however, supports the existence of **1·2HCl**.

Neutralization of **1·2HCl** with NaOH gave the basic form **1**. The ^{1}H-NMR spectrum shows a signal of methylene protons of ArCH_2NH— at higher field (3.83 ppm) due to disappearance of the positive charge, thus decreasing the deshielding effect. Although we could not find a signal due to the NH protons, evidence from the mass spectrum and elemental analysis suggest the existence of compound **1**. Compound **1** was assigned to have a cone conformation as established by two p-tert-butyl signals and one AB system for the methylene protons on the lower rim with a coupling constant of 13.0 Hz; the same as its Schiff base precursor, **Sb-1**, [14] and similar to its analogous compound, **2**.
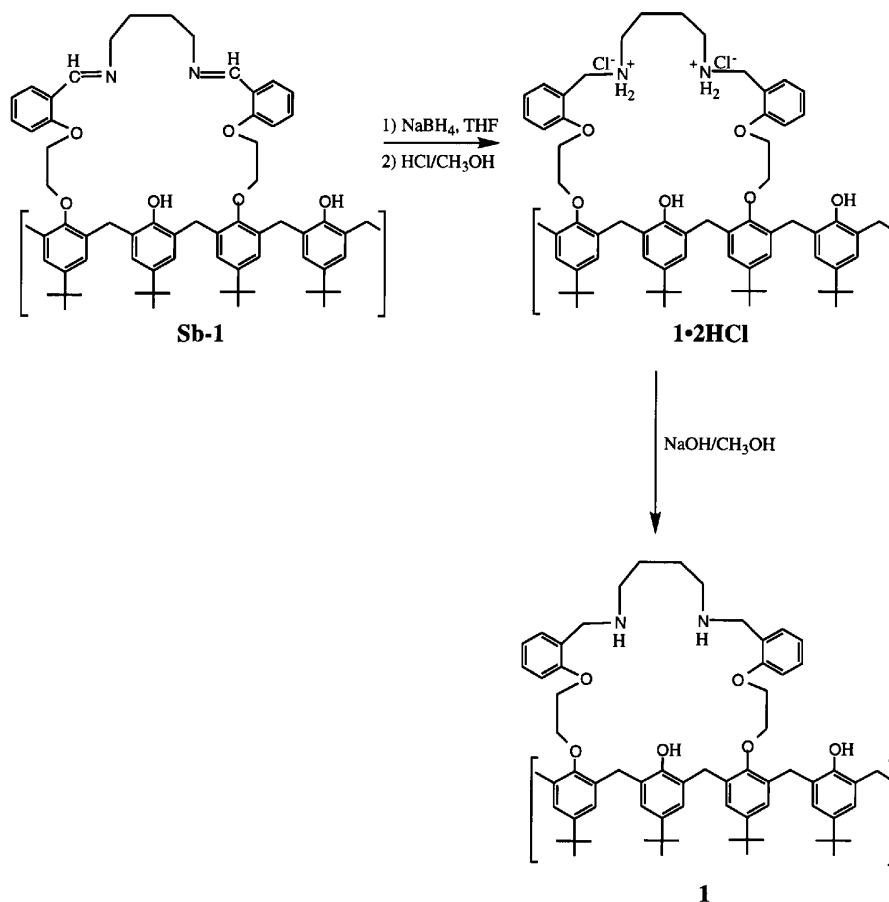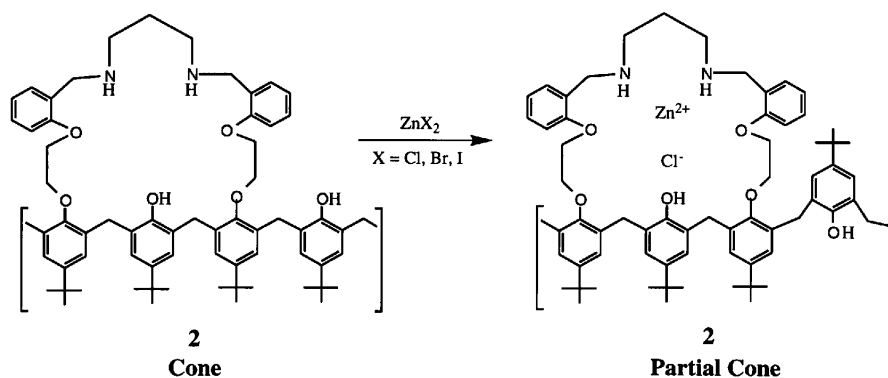
Scheme 1.

3.2. INCLUSION STUDIES OF COMPOUND *2*

Both compound **1** and **2** are calixarene derivatives which contain N and O donors. A study of the inclusion of compound **2** with $Zn(ClO_4)_2 \cdot 6H_2O$ has been previously described [15]. ^{1}H-NMR studies indicate that ligand **2** forms complexes with Zn(II) in 1-to-1 (Zn(II):**2**) and 2-to-1 (2Zn(II):**2**) fashions. The latter occurs when an excess amount of Zn(II) was added to the ligand **2**. The complexation of the second Zn(II) takes place very slowly (26 days for the reaction to reach equilibrium). The equilibrium constants are estimated to be log $K_1 = 3.6$ and log $K_2 = 3.0$ for **ZnL** and **Zn$_2$L**, respectively. These values are very low compared to the stability constant, log $K = 8.41$, of Zn [12]aneN$_3$, a model complex for carbonic anhydrase, which possesses three N and one O donors [18, 19].

In this article, we studied the effect of counter ions on the complexation of Zn(II) ions and the ligand **2** by varying the counter ions from Cl$^-$ to Br$^-$, I$^-$ and

NO_3^-. Generally, we observed continuous shifting of the methylene proton signals due to —ArCH_2NH— and —[NCH_2]$_2$CH$_2$ of the ligand **2** to more downfield positions when the amount of Zn(II) increased. Therefore, the Zn(II) ion in **ZnX$_2$-2** complexes must reside in the N_2O_2 cavity of the RO—Ar—CH$_2$—NH—(CH$_2$)$_3$— NH—CH$_2$—Ar—OR moeity, Scheme 2. We employed the chemical induced shifts to estimate the stability constants for the zinc complexes of the ligand **2** as described in the experimental section. The ground-state structure of the calixarene unit of the ligand **2**, *cone conformation*, gives two signals of methyl protons of t-C$_4H_9$ArOH and ROAr–t-C$_4H_9$ at 1.25 and 0.84 ppm, respectively. ^{1}H-NMR studies of binary compounds of Zn(II) ions, ZnX$_2$ when $X = Cl^-$, Br$^-$ and I$^-$, with the ligand **2** in a mixture of CD$_3$OD and CDCl$_3$, however, showed interesting features. When $X = Cl^-$, a signal due to the methyl protons at 1.25 ppm split into two lines at 1.29 and 1.20 ppm, respectively. The integral ratio of these two lines was found to be equal, and the intensity of the signals increased upon addition of ZnCl$_2$. This suggests the structure of the calix[4]arene unit in **2** changed from a cone to a partial cone conformation (Scheme 2). A similar conformational change has been previously observed in the potassium picrate complex of 1,3-dimethoxy-*p-tert*-butylcalix[4]arene-crown-5 [20]. Table I illustrates the mole fraction of the cone and partial cone conformation where the ratio of ZnCl$_2$ and the ligand **2** are varied from 0 : 1 to 3.0 : 1. The relationship between the mole ratio ZnCl$_2$: **2**, illustrated in Figure 1, thus shows evidence that a 1 : 1 complex is formed. This behavior is different from the complex possessing ClO$_4^-$ as a counter ion mentioned earlier where the 2 : 1 complex of 2Zn(II) : **2** has been observed [15]. We assume that the Cl$^-$ ion must be located close to the Zn(II) center by occupying a cavity of four phenolic-oxygen donors at the lower rim and thus induces the conformational change of the calixarene unit to facilitate its coordination. Br$^-$ and I$^-$ ions gave similar results to the Cl$^-$ ion. Stability constants, log K_s, of ZnX$_2$-**2** complexes where X = Cl$^-$, Br$^-$ and I$^-$ are 1.6 ± 0.1, 1.9 ± 0.1 and 2.7 ± 0.1, respectively. This indicates that larger halide ions form more stable complexes. The results, however, are different from those of a relevant work performed by Kimura *et al.* The Zn[12]aneN$_3$·H$_2$O forms complexes with Br$^-$ and I$^-$ ions and gives stability constants, log K_s, of 1.6 and 1.5, respectively. [18] Compared to the ZnX$_2$-**2** system, these values give the opposite order of the complex stability, i.e. Br$^-$ > I$^-$.

Upon changing from halide to oxo anion such as NO_3^- and ClO$_4^-$, there was no splitting of signals from the methyl protons of t-C$_4H_9$ArOH due to the conformational change as found in the halide cases. The stability constant of Zn(NO$_3$)$_2$-**2** was calculated to be log $K = 6.0 \pm 0.1$. Similar to the halide counter ions, NO_3^- does not give the 2 : 1 species at all. This oxo ion must, therefore, be located in a position where the coordination of the second Zn(II) ion is forbidden.

Scheme 2.

Table I. Mole fraction of cone and partial cone conformation upon varying the mole ratio of $ZnCl_2 : 2$.

Mole ratio $ZnCl_2 : 2$	Mole fraction	
	Partial cone	Cone
0 : 1	0	1
0.2 : 1	0	1
0.4 : 1	0.137	0.863
0.6 : 1	0.187	0.713
0.8 : 1	0.437	0.563
1.0 : 1	0.652	0.348
1.2 : 1	1	0
1.5 : 1	1	0
2.0 : 1	1	0
2.5 : 1	1	0
3.0 : 1	1	0

3.3. EFFECTS OF THE CAVITY SIZE: INCLUSION STUDIES OF 1

In contrast to the ligand **2**, **1** has a bigger cavity around the N_2O_2 donor group of the RO—Ar—CH_2—NH—$(CH_2)_4$—NH—CH_2—Ar—OR moiety due to an additional methylene carbon of the diamine backbone and does not show any conformational changes upon formation of complexes with ZnX_2 (X = Cl, Br, I and NO_3^-). We also observed continuous shifting of methylene proton signals due to —ArCH_2NH— and —[NCH_2]$_2CH_2$ protons of the ligand **1** to more downfield positions when the amount of Zn(II) increased. We thus propose that the structures of the ZnX_2-**1** complexes should be similar to those of ZnX_2-**2**. However, complexation of **1** with Zn(II) ions occur very slowly. The time required for reactions to reach their equilibrium are 13, 32 and 35 days for I^-, Br^- and Cl^- counter ions, respectively, as indicated by ^{1}H-NMR studies. Stability constants, log K_s, of the
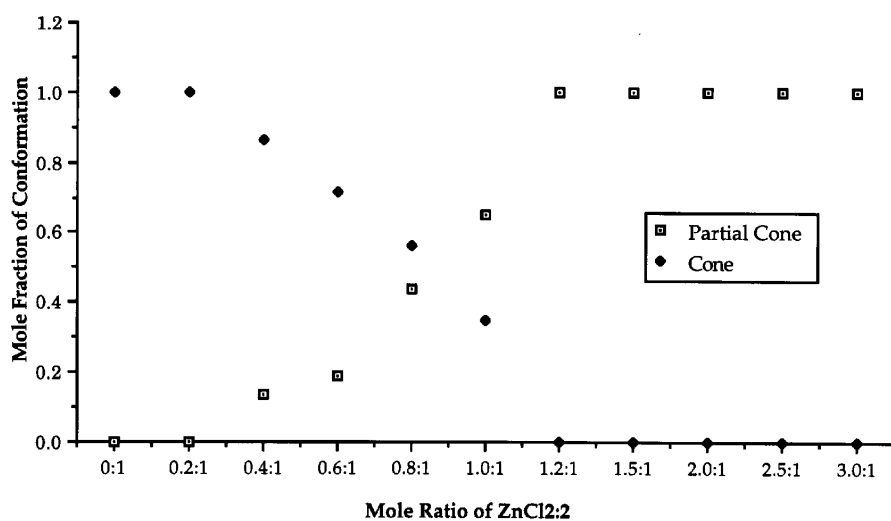
Figure 1. Plot of the relationship between mole ratio of $ZnCl_2 : 2$ and mole fraction of conformation.

ZnX_2-**1** complexes were estimated to be 1.4 ± 0.1, 1.7 ± 0.1, 2.2 ± 0.1 and 4.7 ± 0.1 where $X = Cl^-$, Br^-, I^- and NO_3^-, respectively. Compared to the ligand **2** system, ZnX_2-**1** complexes are generally less stable than ZnX_2-**2** complexes. This may result from a larger cavity of the N_2O_2 donor group of the ligand **1** which weakens the interaction of a Zn(II) ion with N and O donors. Nevertheless, the order of the complex stability is similar to that of the ZnX_2-**2** complexes.

4. Conclusion

A new aza-benzo-crown-ether derivative of calix[4]arene, 25,27-N, N'-di-((2-ethoxy)benzyl)butylenediamine-p-*tert*-butylcalix[4]arene (**1**), has been synthesized and characterized. We have determined effects of counter ions and ligand cavity size upon the complexation of Zn(II) with the ligand **1** and its analogue **2**. ^{1}H-NMR studies indicate that the order of stability of the complexes of ZnX_2 with ligand **1** and **2** varied upon changing counter ions X: $NO_3^- > I^- > Br^- > Cl^-$. The result suggests that complexes Zn(II)-**1** and Zn(II)-**2** can recognize certain anions to a different extent. Furthermore, the ligand **2** displays a conformational change upon interacting with halide anions such as Cl^-, Br^- and I^-. It may therefore be applied as an anion sensor [21]. Future work will be focused on the isolation of solid complexes of ZnX_2-**1** and ZnX_2-**2**. Their structures will be elucidated by X-ray crystallography.

Acknowledgments

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