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# Cation-Induced Shifts in the Proton NMR Spectroscopy of Dioxydiacetamide Ionophores

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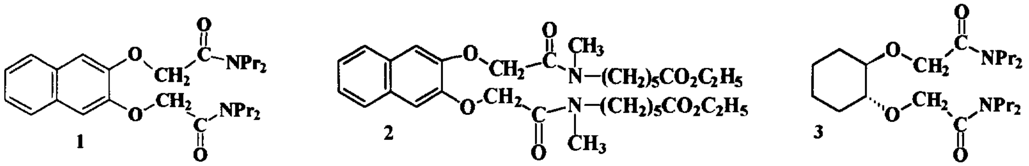
**Abstract :** Complexation of 1,2-disubstituted dioxydiacetamides with Group II cations in MeOH-$d_4$ results in downfield $^1$H NMR shifts. These cation induced shifts (CATIS) can be used to estimate the stoichiometry of cation/ligand binding. The shifts decrease in the order: $Ca^{2+} > Mg^{2+} > Sr^{2+} > Ba^{2+}$ while the order of binding is $Ca^{2+} > Sr^{2+} > Ba^{2+} >> Mg^{2+}$. The shifts are independent of the nature of the anion except for $Mg^{2+}$ where the CATIS decreases in the order: $I^- > Br^- > Cl^- > ClO_4^-$. © 1997 Elsevier Science Ltd.

Some years ago we reported the synthesis of a series of dioxydiacetamides such as N,N,N',N'-tetrakis-(n-propyl)-2,3-naphthalenedioxydiacetamide **1**, the N-methyl N-carboethoxypentyl compound **2**, and related aryl and alicyclic analogs.[1-5] We found that these compounds selectively bind Group II cations in methanol in the order: $Ca^{2+} > Sr^{2+} > Ba^{2+} > Mg^{2+}$ *via* Scatchard plots based on UV changes.[1,2] These studies were done in very dilute solution ($10^{-4}$ to $10^{-5}$ M) which encouraged 1:1 salt/ligand stoichiometry. While we were developing this UV method, we also studied the effects of cation binding on the 60 MHz $^1$H NMR spectra of these compounds in the hope of developing an alternate method for estimating binding strength.[6]

We found that the addition of various Group II cation salts to **1**, **2**, and related compounds in methanol-$d_4$ caused downfield shifts going to a maximum, of many of the protons, especially those near the complexation sites. These cation induced shifts (CATIS) ranged from very little (0 or 0.01 ppm for $CaCl_2$ with the ethyl protons of **2** to -0.47 ppm for the $CH_2$ protons next to the ether oxygens).[1b,7] The complexation sites, ether and carbonyl oxygens, had been confirmed by a single crystal X-ray analysis of the $CaBr_2$ and $MnBr_2$ complexes of the *trans*-cyclohexyldioxydiamide **3**[8] and $^{13}$C NMR studies on several analogs[1b]. These original studies were done at 60 MHz which necessitated the use of 0.22 M solutions. At such a moderate concentration, the stoichiometry of binding was not cleanly 1:1 ligand/salt but also 2:1 ligand/salt..[2a] The curves leveled off near 1:1 salt/ligand which indicated that the stoichiometry of the major species present was probably 1:1. The data was not good enough for estimation of association constants for several reasons including the lack of a single complex. It became obvious that the magnitude of the maximum shifts for a cation with a given proton type could not be used to estimate even relative binding strengths for different ligands. Thus different ligands, which were known to have different binding strengths by UV studies,[1,2] gave *ca* the same maximum downfield shift for the interaction of a Group II cation with the $OCH_2$ protons.[7] Other groups, such as the $NCH_2$ or aromatic protons, also went to maximum shifts, which didn't differ much for different ligands. The maximum shifts on any one ligand decreased with the distance of the group from the coordinating ether and amide oxygen sites. Further discussion will concentrate mainly on the shifts for the $OCH_2$ protons.



Scheme 1

For any one ligand, such as **2**, the amount of downfield $OCH_2$ shift caused by cation binding decreased in the order: $Ca^{2+}>Mg^{2+}>Sr^{2+}>Ba^{2+}$ (Fig. 1).

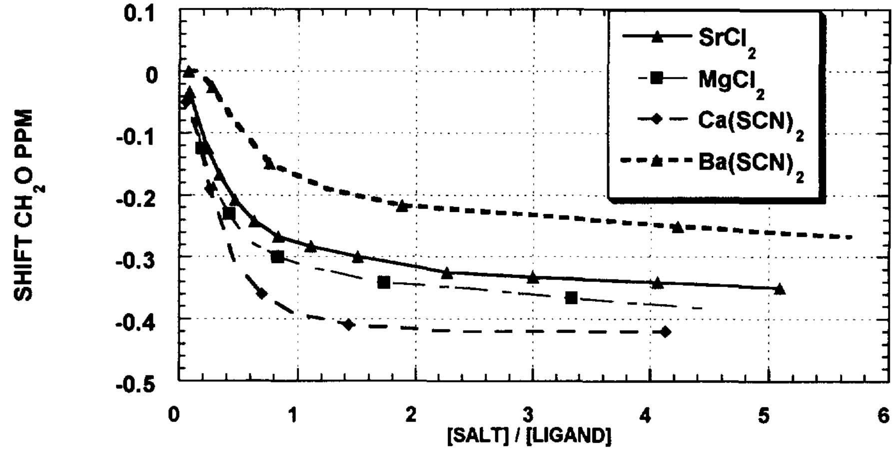


**Fig.1** Cation induced shifts for **2** in methanol-$d_4$ at 60 MHz.[7]

The original work was done with hydrated salts and different anions: $Ca(SCN)_2$ , $SrCl_2$, $Ba(SCN)_2$, $MgBr_2$.[7] However, our UV binding studies[1b] and the work of Chan[6] and others [9] indicated that the binding of cations by these ligands or by crown ethers was decreased by the presence of water. The lack of anion uniformity, the presence of hydrated cations, and the unexpectedly large shift caused by the weak chelator $MgBr_2$, caused us to delay publication of this study until more controlled work could be done. We now report the results of using anhydrous bromides of some Group II and some Group I cations with **1** as well as further $Mg^{2+}$ studies. Some of this work has been done recently at 200 or 400 MHz and 0.02M solutions which gave cleaner 1:1 stoichiometries than previously obtained by more concentrated solutions. We also acknowledge the recent NMR cation induced shift results of Raban *et al.*[10] on a related alicyclic dioxydiacetamide system. Their $^{13}C$ NMR studies gave CATIS curves, which looked similar to our $^{1}H$ NMR curves.

## RESULTS

The CATIS found for the $OCH_2$ hydrogens of **1** with several cation bromides and with various magnesium salts are shown in Tables I and II. .

Table I. CATIS for $OCH_2$ Hydrogens of **1** with Cation Bromides[a]

| Salt | Salt/Ligand | $\delta$ $OCH_2$ ppm | Induced Shift, ppm |
|---|---|---|---|
| none | | 4.96 | 0 |
| $CaBr_2$ | 3.07 | 5.39 | -0.43 |
| $BaBr_2$ | 3.23 | 5.19 | -0.23 |
| LiBr | 4.1 | 5.06 | -0.10 |
| NaBr | 4.2 | 5.01 | -0.05 |

[a] In methanol-$d_4$ at 60 MHz., 0.1M ligand.

Table II. CATIS for the $OCH_2$ Hydrogens of **1** with Various Salts[a]

| Salt | Salt/Ligand | $\delta$ $OCH_2$ ppm | Induced Shift, ppm |
|---|---|---|---|
| none | | 4.933 | |
| $CaCl_2$ | 4.05 | 5.334 | -0.401 |
| $Mg(ClO_4)_2$ | 4.07 | 5.212 | -0.279 |
| $MgCl_2$ | 3.94 | 5.247 | -0.314 |
| $MgBr_2$ | 2.45 | 5.250 | -0.317 |
| $MgI_2$ | 2.34 | 5.280 | -0.347 |

[a] In methanol-$d_4$ at 200 MHz, 0.022M ligand.

Figure 2 illustrates the titration of **1** (0.02M) with incremental amounts of anhydrous $CaBr_2$ in methanol-$d_4$ at 400 MHz. The general shape of the curve is similar to the CATIS curves done previously at 60 MHz for **1-3** and related ligands with $Ca(SCN)_2 \cdot 3H_2O$ as in Figure 1[7]. The leveling off of the line is now clearly at 1:1 salt/ligand, confirming the previous finding of 1:1 stoichiometry of binding for these ligands in dilute solution.[1b,2a] The limiting shift is -0.43 ppm, compared to -0.4 ppm found for $Ca(SCN)_2 \cdot 3 H_2O$ (Figure 1).

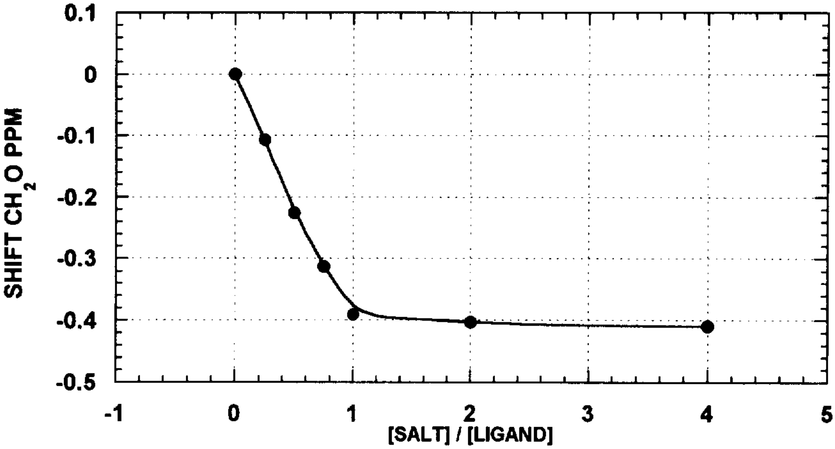


FIG. 2 $CaBr_2$ induced shifts for **1** in methanol-$d_4$ at 400 MHz

## DISCUSSION

The data in Table I suggests that at least for $Ca^{2+}$ and $Ba^{2+}$ the CATIS found with **1** or **2** is almost independent of the nature of the anion, and the presence of water of hydration in the salts. Thus anhydrous $CaBr_2$ and anhydrous $BaBr_2$ give *ca* the same maximum induced shifts (-0.43, - 0.23 ppm) as do $Ca(SCN)_2 \cdot 3 H_2O$ (-0.4 ppm) or $Ba(SCN)_2$ 3 $H_2O$ (-0.23 ppm). The small shifts given by the very weak binders, $Na^+$ and $Li^+$ enforce the general expectation that non- or weak binders should not cause chemical shift changes. It is noteworthy that the intensely charged $Li^+$ cation does not exhibit any "special effect."

The data in Table II, done at 200 MHz and 0.022M ligand solutions, gives -0.40 ppm as the limiting shift for **1** with $CaCl_2$. This is comparable to -0.43 ppm for $CaBr_2$ (Table I, at 60 MHz, 0.1 M ligand). The limiting shifts for various $Mg^{2+}$ salts slightly increase in the order: $ClO_4^- > Cl^- > Br^- > I^-$. Thus even for $MgClO_4$, where there is no covalent bonding between the ions, the cation induced shift remains unexpectedly large. Since the differences in limiting shifts between the $Mg^{2+}$ compounds are small, any covalency in the $MgX_2$ compounds would seem to play a minor role. Perhaps $Mg^{2+}$ is strongly coordinated with methanol in all of the compounds and the resulting solvated ion as well as some covalent $MgX_2$, for the halides, causes the observed chemical shifts. It would be most useful to have data on an isolable complex of $Mg^{2+}$ with **1** or a related ligand. Attempts to prepare such a complex have failed in the past but will be redone.

In summary, the CATIS caused by the interaction of Group I and II metal cations with the protons of 1 and related ligands can be used to estimate the stoichiometry of cation/ligand binding and the probable binding sites within a given ligand. In some cases, the relative strength of binding of the cations can be estimated. $Mg^{2+}$ appears to be an exception to the latter statement.

## EXPERIMENTAL

$^1H$ NMR spectra at 60 MHz were recorded on Varian A-60 (YU) and EM 360 (RCNJ) spectrometers. The 200 and 400 MHz spectra were recorded on Varian spectrometers at Columbia University. All spectra were done with TMS as an internal standard. Inorganic salts were purchased from Aldrich and Alfa Chemical Companies and earlier from ROC/RIC. The organic solutions were prepared in anhydrous methanol-$d_4$ in stoppered 1 mL volumetric test tubes. In the 60 MHz runs, and many of the 200 and 400 MHz runs, the salts were added as solids to the organic solutions to minimize concentration changes. The test tubes were then shaken for several minutes to ensure complete solution of the salts. In some of the 200 and 400 MHz runs, including the titration illustrated in Figure 2, 1.0 M solutions of the salts, in methanol-$d_4$ were added in 5-40 μL increments to the test tubes using Eppendorf pipettes. The total volume added was never more than 80 μL.

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