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THE PREPARATION AND PROPERTIES OF NEUTRAL DIAMIDE IONOPHORES FOR GROUP IIA METAL CATIONS—II

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Abstract—The elaboration of a series of neutral ligands featuring vicinal ether and N,N-dialkylacetamido groups is described. Several of these ligands were previously described.† The ligands are moderate binders with $K_{app} = 10^3$–10^5 in methanol of the Group IIA cations for which they are sensitive. Binding constants by the Scatchard method are reported for a number of ligands mainly with Ca, Sr, Mn and Ba. The ligands in methylene chloride solution extract these cations *via* their picrate salts from water. The electrochemical K_{ij}^{pot} (selectivity) values for some of the ligands when they are incorporated into liquid membrane electrodes and tested with various cations as determined by Simon *et al.* (ETH Zurich) are reported. Selectivity ratios of over 100:1 for Na vs Ca were found for several piperidenyl amides of 1,2-phenylenedioxydiacetic acid. Incorporation of N-methylamino instead of ether oxygen groups into the basic structure gives a stronger cation binder which is still selective for Group IIA vs Group IA cations but with binding capacity for transition metal cations also. Limitations of the Scatchard plots for these ligands and the non-correspondance of electrochemical selectivities with the ordering of binding of cations in single liquid phase are discussed.

Several years ago we reported the synthesis of a series of neutral 3,6-dioxa-4,5-disubstitutedoctanedicarboxamides as well as some binding studies with Group IIA metal cations.[1,2] More recently, we reported structural studies on isolated crystalline complexes of Group IIA and transition element cations with several ligands, notably N,N,N′,N′-tetrakis-(n-propyl)-1,2-phenylenedioxydiacetamide (**1**).[3] This ligand exhibits binding selectivity in single-phase (MeOH): $Ca^{2+} > Sr^{2+} > Ba^{2+} > Mg^{2+} > Na^+$, K^+. The ligand system is a complicated one in that there is a tendency for 2:1 ligand/cation chelation (the stoichiometry of isolated complexes and interaction in concentrated solution) as well as 1:1 stoichiometry (in dilute solution). We now report the effects on the strength and selectivity of bindings of various cations caused by some structural changes in the ligand system.

RESULTS

New ligands were prepared either by reaction of the appropriate acid chloride with excess secondary amine plus triethylamine[1a,b] or by one-step alkylation of the appropriate polyhydroxy compound (phenol or alcohol) with N,N-dipropyl chloroacetamide.[1c] The syntheses of many of the ligands discussed here have been reported previously.[1,3a]

Complexation in methanol

As previously shown[1b,2a] the addition of concentrated solutions of metal cation bromides (and other salts) to a dilute solution of **1** causes changes in its UV absorption spectrum. These UV changes have been used to obtain the stoichiometry of complexation. The limiting value ΔA_M (the maximum absorbance change usually for the strongest absorbing peak) is obtained as the intercept of a plot of $1/\Delta A$ vs $1/[C_T]$ where ΔA is the observed change in UV absorption and $[C_T]$ is the total cation concentration. The "best fit" (highest correlation coefficient) is obtained from a graphic plot which shows which points are highly deviant and can be discarded plus a calculator-run linear-regression computation. Usually initial points have to be discarded and, in some cases, the final ones also. Alternatively, some of the reciprocal plots and the subsequent K_{app} calculations were done using the interactive MINITAB subroutines available to us on a PDP 11/70 computer utilizing the UNIX command language. The utilization of ΔA_M to determine K_{app} (apparent binding constant) was done by Scatchard plots as described previously.[2a] Stoichiometry (n) values were *ca* 1.0 if the initial and (sometimes) final ΔA values were dropped as described above. The ΔA_M values were also used to get mole-ratio plots[4] which confirmed the relative strength of binding of a given ligand with various cations.[1b] The results of the Scatchard plots are given in Tables 1 and 2.

The strength of binding with $CaBr_2$ is greater for the 2,6-dimethylpiperidinyl amide **3** than the piperidinyl amide **2** ($\cong$ **1**) which is greater than that for the tetramethylpiperidinyl amide **4**. The previously prepared phenylbenzylamide **5** is weaker than **4** and the weakest in the series is the cyclic dilactam **6**. The ordering of binding for **5** is $Ca^{2+} > Sr^{2+} > Ba^{2+}$ as for **1** but the individual binding constants are smaller and the relative ratios of K_{app} are smaller. The addition of a third chelation "arm" to give **7** results in a change of binding order: $Sr^{2+} > Ba^{2+} > Ca^{2+}$ and stronger binding for Sr^{2+} and Ba^{2+} than is found for **1**.

The *cis*-cyclopentane ligand **8** exhibits a binding order of $Ca^{2+} > Sr^{2+} > Ba^{2+}$ but is less selective for Ca^{2+} vs Sr^{2+}, Ba^{2+} than is **1** or **9**. The *trans*-ligand

†*Tetrahedron* **33**, 1697 (1977).

Table 1. Binding constants for **2** to **6** in methanol

Ligand	Salt[a]	K_{app}[b]	n[c]	R[d]
2	$CaBr_2$	7.0×10^4	0.97	0.99
	$SrBr_2$	1.4×10^4	1.0	1.00
	NaCl	6.6×10^2	1.0	0.95
3	$CaBr_2$	1.65×10^5	0.98	0.99
	$SrBr_2$	3.04×10^4	0.94	1.00
4[e]	$CaBr_2$[f]	5.71×10^3	0.99	1.00
5	$CaBr_2$[g]	4.95×10^3	0.97	0.99
	$SrBr_2$[f]	3.25×10^3	1.0	0.98
	$BaBr_2$[f]	1.20×10^3	1.0	1.00
6	$CaBr_2$[f]	8.69×10^2	1.06	0.997

[a] Usually 0.1 M. (Ligand) = 10^{-5} to 10^{-4} M.
[b] Units of K_{app} are M^{-1} for 1:1 complexation.
[c] Stoichiometry of binding: ligand/ salt.
[d] Correlation coefficient in linear regression analysis.
[e] Weak binding with NaBr.
[f] Job plot indicates 1:1 stoichiometry.
[g] Job plot indicates 2:1 stoichiometry. K_1 given.

Table 2. Binding constants for **7**, **8** in methanol[a]

Ligand	Salt	K_{app}	n	R
7	$CaBr_2$	5.30×10^4	0.96	0.97
	$SrBr_2$	1.48×10^5	0.93	0.96
	$BaBr_2$	1.31×10^4	1.00	0.97
8	$CaBr_2$	1.21×10^4	2.1[b]	0.96
	$MnBr_2$	3.90×10^3	3.0[b]	0.94
	$SrBr_2$	9.35×10^3	0.94	0.85
	$BaBr_2$	2.37×10^3	1.00	0.98

[a] See Table 1 for definitions.
[b] R/L *vs* R used instead of usual (for 1:1 stoichiometry) r/C *vs* r in Scatchard plots.[2a]

10 was previously measured in binding only with $CaBr_2$.[2a] Table 3 gives new binding data for **10**. The K_{app} values are all weaker than for the *cis*-ligand **9** and slightly less selective.

The binding of **1** with cations not previously reported[2a] is given in Table 3. K_{app} values for the series of rare earth chlorides decreases in the order: $LaCl_3 > NdCl_3 > GdCl_3 > YbCl_3$: differing by a factor of 2.1.

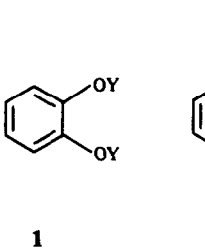
The substitution of N-Me groups for the ether oxygens gives **11**. For **11** the stoichiometry of binding varies with different cations (Table 4), making quantitative comparison of K_{app} values difficult. The data can be compared in a qualitative manner to give relative binding orders. Ligand **11** binds more strongly with Group IIA cations than do the ether O-containing ligands but it also binds with transition metal cations.

The S-containing ligands **12** and **13** showed no UV change with added $CaBr_2$. Furthermore **12** showed no UV change with $CoCl_2$ or $MnBr_2$ and gave no isolable complexes with AgSCN, $AgNO_3$, $CuBr_2$, $Co(SCN)_2$ or $MnBr_2$. No UV changes with $CaBr_2$ was found for **14–21**. No UV changes with Group IIA cations were found for **18** nor did **19** give UV changes with Na^+ or Li^+.

Table 3. Binding constants for **1**, **10** in methanol[a]

Ligand	Salt	K_{app}	n	R
1[b]	$CdBr_2$	1.45×10^3	1.02	0.93
	$LaCl_3$	1.13×10^5	1.09	0.96
	$NdCl_3$	8.40×10^4	0.96	0.91
	$GdCl_3$	6.68×10^4	0.96	0.99
	$YbCl_3$	5.40×10^4	0.96	0.97
10	$CaBr_2$	7.72×10^4	1.0[c]	c
	$SrBr_2$	5.14×10^3	1.02	0.99
	$MnBr_2$[c]	1.11×10^4	2.1	0.95
	$BaBr_2$	2.29×10^3	0.95	1.00

[a] See Table 1 for definitions.
[b] Weak binding with NaCl.
[c] R/L vs R used in Scatchard plots.[2a]



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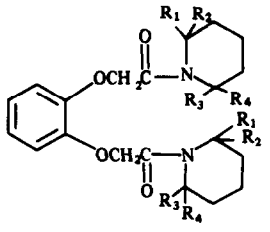
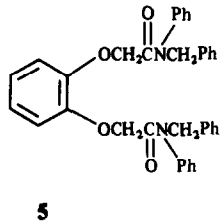


2 $R_1 = R_2 = R_3 = R_4 = H$
3 $R_1 = R_3 = CH_3$, $R_2 = R_4 = H$
4 $R_1 = R_2 = R_3 = R_4 = CH_3$ $Y = CH_2CN(C_3H_7)_2$



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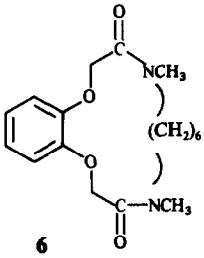

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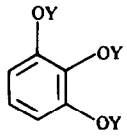

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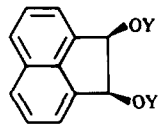

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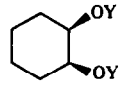

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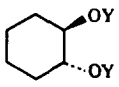

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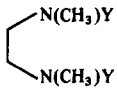

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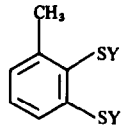

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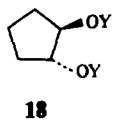
13

$[XOCH_2C(=O)\overset{Z}{N}CH_2]_2$

14 X = C_6H_{11}, Z = H
15 X = C_6H_{11}, Z = CH_3
16 X = Ph, Z = H
17 X = Ph, Z = CH_3



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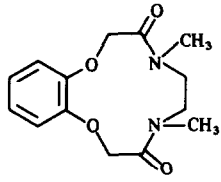

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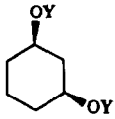

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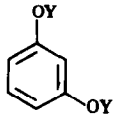

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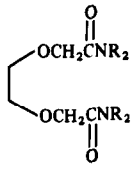

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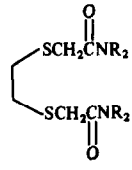

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Table 4. Binding constants for **11** in methanol[a]

Ligand	Salt	K_{app}	n	R
11[b]	$CaBr_2$	4.40×10^5	3.0	c
	$SrBr_2$	1.30×10^5	0.95	0.99
	$BaBr_2$	1.44×10^4	0.92	0.99
	$Co(SCN)_2$	1.99×10^5	0.95	0.98
	$CuBr_2$	3.22×10^5	1.07	0.99
	$ZnCl_2$	1.15×10^5	0.86	0.92

[a] See Table 1 for definitions.
[b] Strong binding with $CdBr_2$, moderate binding with $FeCl_3$, no binding with KBr (not definite stoichiometry with $CdBr_2$ or $FeCl_3$).
[c] Stoichiometry= 3 for salt/ligand= 0.1 to 0.47. Above 0.5 data is non-linear.

Table 5. Cation picrate extraction by ligands[a]

Ligand[b]	Fraction of cation extracted					
	Ca^{2+}	Sr^{2+}	Ba^{2+}	Mg^{2+}	Mn^{2+}	picric acid[c]
1	0.06	0.11	0.12	0.04	0.05	0.05
6	0.07	0.11	0.16	0.04	0.04	0.04
7	0.14	0.37	0.35	0.06	0.06	0.07
8	0.13	0.10	0.11	0.08	0.08	0.08
9	0.84	0.43	0.50	0.15	0.50	0.14
20	0.08	0.05	0.05	0.05	0.05	0.05

[a] See ref. 1b. Done between equal volumes (1.5 mL) of water and CH_2Cl_2 at 25°. Ligand = 7.0×10^{-4} M, picric acid = 6.86×10^{-5} M, cation = 1.0×10^{-2} M using MCl_2. The error limit is estimated to be less than 0.01 for extraction performed in triplicate.

[b] Ligand 11 extracts picric acid in the absence of cations; 0.90 picric acid extracted even at pH = 9.5.

[c] Fraction extracted = 0.04 without ligand. Done on a Varian Spectroscan-3 spectrophotometer.

Cation picrate extraction

As reported previously,[1b] the extraction of metal cation picrate (**5**) from water into an organic phase (methylene chloride) by a ligand is a convenient method for rapid screening of the ability of ligands to complex cations. It relates to the "intake" part of transport through membranes or other three-phase systems. Table 5 gives the relative extractability of cations by several of the new ligands relative to standard compounds **1** and **9**. Notably, **8** is slightly better than **1** but much less effective than **9** (or **10**[1b]). Ligand **7** extracts $Ba^{2+} > Sr^{2+} > Ca^{2+}$, in contrast to **9** or **10**. It behaves similarly to **1** and other aromatic-ring containing ligands in this series but is more selective in extracting Ba^{2+}, Sr^{2+} vs Ca^{2+}, Mg^{2+}, Mn^{2+}. Note the different ordering for **7** in single-phase binding: $Ca^{2+} > Sr^{2+} > Ba^{2+}$ vs its extraction behaviour. This difference exists for all of the aromatic ring-containing ligands.[1b]

Ion selectivities of ligands in liquid membrane electrodes

Electrochemical data for **2** to **4** is shown in Fig. 1. The determination of the data and its presentation is by Simon *et al.*[5]† Selectivity constants K_{ij}^{pot} are given relative to Na. Thus **2** has a selectivity of $Na^+/Ca^{2+} = 93$.[6] Data for **8** and **18**, relative to Ca^{2+} (Fig. 2), and for **7**, relative to Ba^{2+} (Fig. 3), are also presented. No electrochemical ion selectivity was found for **21**. Slight water solubility prevented the study of **11**.

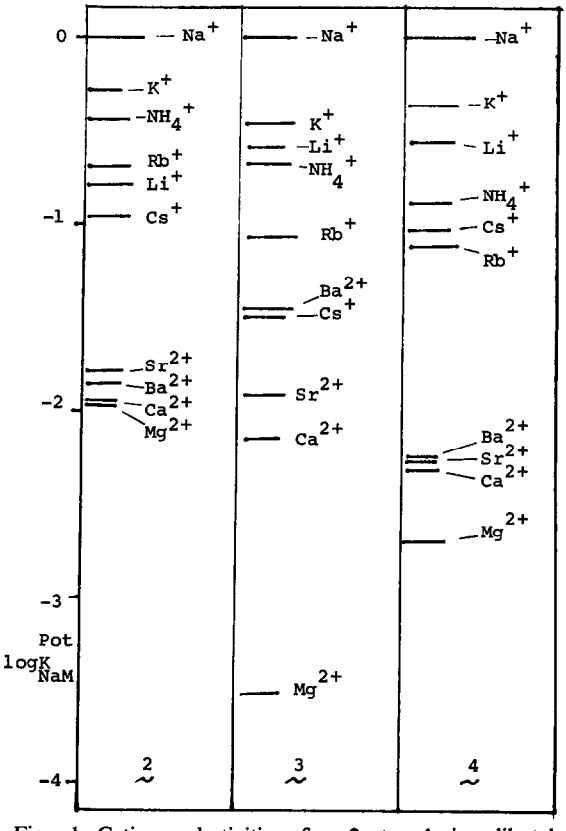

Fig. 1. Cation selectivities for **2** to **4** in dibutyl sebacate/PVC (1 wt.% ligand) relative to sodium.

DISCUSSION

It was found for many of the cases that the best correlation for K_{app} and stoichiometry values (ligand:cation binding) closest to 1.0 were obtained when the first few and (usually) the last few data points, out of a set of 12–20 data points, were omitted. These points usually showed large deviations from the rest of the data set: especially the early points. These points are expected to indicate ligand/salt stoichiometries greater than 1:1 since the experimental method involves the addition of small amounts of salt to excess ligand. Very late points may be inaccurate due to the high absorbance of UV energy involved. The finding that the "best data" consists of intermediate points is in agreement with the theoretical analysis of Deranleau[7] which concluded that the limits for accurate simultaneous determination of K and stoichiometry are *ca* $0.2 \leqslant S \leqslant 0.8$ where S = "saturation factor" $\cong A/A_{max}$. It is understood that the binding of

†Done by W. Simon *et al.* ETH Zurich.

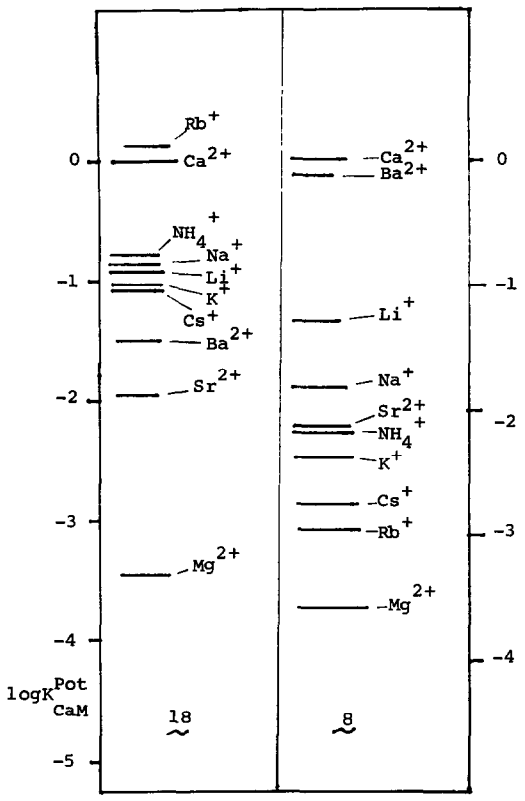

Fig. 2. Cation selectivities for **18** and **8** (1 wt.%) in o-nitrophenyl octyl ether (66 wt.%): PVC (33 wt.%) relative to calcium. Metal chlorides 0.1 M.

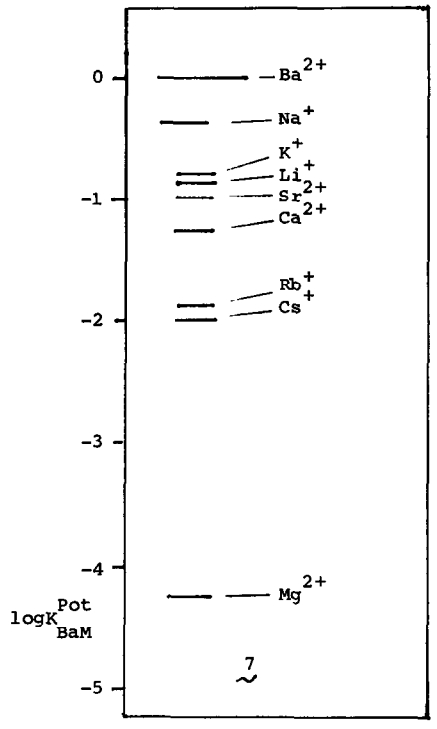

Fig. 3. Cation selectivities for **7** (1 wt.%) in o-nitrophenyl octyl ether (66 wt.%): PVC (33 wt.%) relative to barium. Metal chlorides 0.1 M.

various cations for a given ligand can be compared quantitatively only for the same stoichiometry. For **8**, and to a lesser extend **11**, the stoichiometry of binding was not constant for the cations tested. The relative strength of binding was not constant for the cations tested. The relative strength of binding could still be determined by mole-ratio plots[4] and/or the qualitative comparison of Scatchard plot data.[8]

The 3,6-dioxaoctanedicarboxamide ligands coordinate with Group IIA cations[3] at both ether and amide oxygen sites.[3b,9] Insoluble complexes have had mainly 2:1 ligand/cation stoichiometry.[3a] In dilute solution (*ca* 10^{-5} M) K_{app} binding constants for 1:1 stoichiometry can be obtained. Several conclusions can be made.

Reversing the sequence of groups to give 1,2-diamido structures (**14–17**) results in a non-chelating system. This is indirect evidence for cation binding by amide oxygen (which here would have to occur *via* unfavourable large-membered rings) rather than nitrogen (which could bind *via* 5-membered rings but does not). Constraining the diamide system into a 16-membered ring (**6**) lowers K_{app} for $CaBr_2$ binding by *ca* 100 fold.[10]

Steric and electronic effects on K_{app} values and on Ca^{2+}/Na^+ binding ratios can be compared within the series **2** to **5**. The ordering of K_{app} is proportional to the electron-donating ability of the amide group with the exception of **4** which should be first. It is assumed that crowding around the amide group lowers the K_{app} for **4** while electron-withdrawing and bulky phenyl and benzyl groups in 5 lower its K_{app} (Table 1). The more sterically hindered and "bulky" and amide group, the larger the Na^+/Ca^{2+} K_{ij}^{pot} selectivity constant (Fig. 1), i.e. the order: **5** > **4** > **3** > **2** ≅ **1**. Analytically useful ratios for Na^+/Ca^{2+} of 100 or more are obtained. Similar effects of increasing M^+/M^{2+} selectivities with increased substitution by "bulky" groups for cations of the same ionic radius are found in [2.2.2] cryptands and 18-crown-6 ethers.[11] Thus when substituted by benzene rings, K^+ vs Ba^{2+} (*ca* the same ionic radius) selectivity increases in these cryptands or crown ethers. The effect of benzene rings could be either steric or electronic (electron-withdrawing) or both. In the **2** to **4** series, steric factors would seem to control the observed Na^+/Ca^{2+} selectivities. It has been suggested that increased ligand bulk increases the isolation of the cation from the solvent. This disallows the recouping of energy expended in desolviating the cation upon complexation. Desolvation energy is greater for M^{2+} than for M^+ [12] so that complexes of M^{2+} are destabilized more than those of M^+. This effect may lead to the observed increased Na^+/Ca^{2+} or K^+/Ba^{2+} selectivities for "bulky" ligands.[3c,11]

It is of interest that all of the benzene ring-containing ligands in the dioxydiacetamide series show large Na^+/Ca^{2+} selectivities when incorporated into liquid membrane electrodes by Simon while non-aromatic ligands (**9**, **10**, Simon's **22**) show small to moderate Ca^{2+}/Na^+ selectivities. The ligands **1–10**, **22** all bind Ca^{2+} more than Na^+ in methanol. Ligands **1**, **9**, and **10** extract Ca^{2+} in preference to Na^+ as the picrates.[1b] The non-correspondence of K_{ij}^{pot} and K_{app} orderings is probably due to different binding stoichiometries.[6] The benzene ring in **1** is *not* involved in complexation. Single crystal X-ray analysis of the

$MnBr_2$ complexes of **1** and **10** reveal both to be $(Lig_2Mn)^{2+}$ $(MnBr_4)^{2-}$ structures of similar geometry.[9]

The addition of a third set of oxyacetamido coordination sites to give **7** increases K_{app} for Sr^{2+} and Ba^{2+} relative to **1**, possibly because of the "larger cavity" now present. The relative binding ratios for **7** are: Sr^{2+} (11.3) > Ca^{2+} (4.1) > Ba^{2+} (1) as compared to those for **1**: Ca^{2+} (16.8) > Sr^{2+} (2.8) > Ba^{2+} (1). Thus **7** is the only ligand in this series to bind Sr^{2+} more than other Group IIA cations (Table 2). In a liquid membrane, however, **7** exhibits a 10-fold selectivity for Ba^{2+} vs Sr^{2+} and *ca* 20-fold vs Ca^{2+} (Fig. 3).†

The N-methylamino-containing **11** is a stronger ligand than the ether oxygen-containing diamides. It binds Ca^{2+}, Sr^{2+} and Ba^{2+} more strongly than does **9** by factors of 5, 5.8 and 1.3* and more so than does **1** by factors of 6, 10.6 and 3.3. It is more selective for Ca^{2+} vs Sr^{2+} or Ba^{2+} with K^{app} ratios of 30.6:9.0:1. The presence of N-methylamino groups also increases the binding of transition metal cations, notably Co^{2+}, Cu^{2+} and Zn^{2+} (Table 4). These cations are not strongly bound by **1**.

The 16-membered dilactam (**6**) is slightly more effective at extracting cation picrates from water than is **1** even though its binding constant with $CaBr_2$ (in methanol) is smaller. Possibly more lipophilic complexes are formed by **6**. The rigid *cis*-geometry of the binding groups in **8** has been expected to make it a very strong chelator. However, the electron-withdrawing effect of the naphthalene moiety opposes any such beneficial steric effect and **8** is a weaker chelator for Group IIA cations‡ than is **9** or **10**.

There is a direct correlation between the order of the cation crystal radius (in Å) and the order of the binding of MCl_3 for **1** plus the rare earths: La^{3+} (1.15) > Nd^{3+} (1.04) > Gd^{3+} 0.97) > Yb^{3+} (0.80), i.e. the largest cation (La^{3+}) binds the strongest (Table 3). The binding of La^{3+} is 1.54 that of Ca^{2+} for **1**, presumably due to the greater cationic charge.

The incorporation of S atoms instead of ether O atoms gave **12** which did not seem to be a useful cation binder, possibly because of the larger S atoms which crowd the chelating area. We note, however, that Simon has prepared **23** which shows selectivities (K_{ij}^{pot}) not that different from the dioxa analogue **22**.[13]

Compounds **18–21** show little or no binding of $CaBr_2$ in methanol, as expected. Each of these compounds has an unfavorable structure for chelation: the *trans*-geometry of the groups in **18**, small ring size in **19**[14], and groups too far apart in **20** and **21**. Ligand **20** shows weak ability to extract calcium picrate from water (Table 5) but not other cations. Compound **8** exhibits some electrochemical selectivity for Ca^{2+} (Fig. 2). Its behavior is inbetween aromatic ring-containing ligands such as **2–4** which have Na^+/Ca^{2+} K_{ij}^{pot} values > 1 (Fig. 1) and fully alicyclic ligands which sense Ca^{2+} vs Na^+, Ba^{2+} by factors of 44, 1587 (for **9**) or 17, 1100 (for **10**). The *trans*-ligand **18** shows unexpected Ca^{2+} selectivity vs Ba^{2+}, Na^+, K^+ (*ca* 10-fold) and Sr^{2+} (*ca* 37-fold, Fig. 2) considering its poor binding power in methanol. The selectivities are not as good as those for **22** or similar ligands[14] but definitely better than those for the solvent (*o*-nitrophenyl octyl ether) background[14] ($K^+ > Ba^{2+}$, $Na^+ > Ca^{2+}$, Mg^{2+} (10-fold spread) $\gg Sr^{2+}$).

In summary, this report extends the chemistry of the 3,6-dioxaoctanediamides substituted at the 4,5-positions. These ligands bind Group IIA cations in preference to Group IA cations in solution. The relative ordering of binding of Group IIA cations for many of the ligands is: $Ca^{2+} > Sr^{2+} > Ba^{2+} \gg Mg^{2+}$ which is the same order as found for many proteins including troponin (see discussion in Ref. 1[b]). This ordering is for very dilute single-phase solutions wherein the stoichiometry of ligand/cation binding is, or approaches 1.0. Under other conditions (more concentrated solutions, isolable complexes, incorporation in liquid membrane electrodes and extraction of cation picrates from water) the ligands exhibit higher ligand/cation stoichiometries. Fortunately, K_2, when determined,[6] is much smaller than K_1 ($= K_{app}$) so we can compare K_{app} values meaningfully. The ligands are moderate binders and not much weaker than the crown ethers which are, however, binders of both Group IA and IIA cations.[11a] The system represented by **1–4**, **9**, **10**, gives a "best fit" with cations of 2 Å diameter (*via* CPK models), i.e. Ca^{2+} or Na^+. 18-Crown-6 "best fits" the larger cations K^+, Ba^{2+}.

EXPERIMENTAL

Solvents used were dried by distillation over molecular sieves, CaH_2 or LAH. Organic solns were dried over $MgSO_4$. ^1H NMR spectra were recorded on a Varian A-60A spectrometer at 60 MHz, using TMS as an internal standard. Mass spectra were taken on a DuPont CEC 21-492 (electron impact mode) or (at Columbia University Dept. of Chemistry) on a Finnegan Quadrupole 3300 (chemical ionization mode) spectrometer. IR spectra were recorded on Perkin–Elmer 300 or 467 spectrophotometers. UV spectra were recorded on Perkin–Elmer 402 and Varian Spectroscan-3 spectrophotometers. Other techniques have been documented previously.[1b,3a] Ligands **1**, **5**, **7–11** have been synthesized before.[1,3a]

N,N,N′,N′ - *Bis(piperidinyl)* - 1,2 - *phenylenedioxy* - *diacetamide* **2** was obtained in 84% yield from 1,2-phenylenedioxydiacetyl chloride[1a] in reaction with piperidine (two equivs) and Et_3N (four equivs) in CH_2Cl_2 as previously described for other amines[1b] and purified by column chromatography: m.p. 97–98°; IR (KBr) 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.56 (m, 12, CH_2), 3.47 (m, 4, NCH_2), 4.65 (s, 4, OCH_2), 6.82 (s, 4, aryl). (Found: C, 66.67; H, 7.80; N, 7.47. Calc for $C_{20}H_{28}O_4N_2$: C, 66.64; H. 7.83; N, 7.77%).

The 2,6-dimethylpiperidinyl amide **3** was obtained in 49% yield as above: m.p. 104–106°; IR (KBr) 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (d, 12, CH_3), 1.63 (m, 12, CH_2), 4.42 (m, 4, NCH), 4.7 (s, 4, OCH_2), 6.05 (m, 4, aryl). (Found: C, 69.20; H, 8.91; N, 6.51. Calc for $C_{24}H_{36}O_4N_2$: C, 69.20; H, 8.71; N, 6.72%).

The 2,2,6,6-tetramethylpiperidinyl amide **4** was obtained in 39% yield as above: m.p. 151–152°; IR (KBr) 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.45 (s, 24, CH_3), 1.72 (s, 12, CH_2). (Found: 71.03; H, 9.44; N, 5.74. Calc for $C_{28}H_{44}O_4N_2$: C, 71.15; H, 9.38; N, 5.93%).

5,6 - *Benzo* - 1,10 - *dimethyl* - 4,7 - *dioxa* - 1,10 - *diazacyclohexadecane* - 2,9 - *dione* **6** (27%) was obtained as an oil from the reaction of 1,2-phenylenedioxydiacetyl chloride[1a] with N,N′-dimethyl-1,6-hexanediamine in CH_2Cl_2

†We believe that three-phase transport may more closely compare with K_{ij}^{pot} selectivities than do single-phase or two-phase (extraction) studies and have initiated such studies.

‡Comparison of K_{app} for **11** + $CaBr_2$ or **8** + $CaBr_2$, $MnBr_2$ with other K values must be qualitative because of non 1:1 stoichiometry for these cases.

under high dilution conditions; chromatographed on silica gel 60 and eluted with $CHCl_3$–EtOH (9:1); IR and NMR as for **2–4**; TLC R_f 0.6 (9:1 $CHCl_3$–EtOH); MS (20 eV) *m/e* 334 (10), 111 (100). (Found m.w. 293–340 (osmometry). Calc for $C_{18}H_{26}O_4N_2$: *m/e* 334).

N,N,N',N' - *Tetrakis* - (*n* - *propyl*) - 4 - *methyl* - 1,2 - *diphenylenedithiadiacetamide* **12** (53% chromatographed yield) was obtained as a yellow oil by the one-step alkylation[1c] of 4-methyl-1,2-benzenedithiol with N,N-dipropyl chloroacetamide: IR (neat) 1640 cm^{-1}; NMR ($CDCl_3$) δ0.83 (s, 3, CH_3-aryl), 3.18 (t, 8, NCH_2), 3.65 (d, 4, sCH_2–C(=O)), 6.71–7.34 (m, 3, aryl). (Found: C, 62.86; H, 8.72; N, 6.11. Calc for $C_{23}H_{38}O_2N_2S_2$: C, 62.97; H, 8.73; N, 6.38%).

1,1,11,11 *Tetrakis* - (*n* - *propyl*) - 1,11 - *diaza* - 2,10 - *dioxa* - 4,8 - *dithiaundecane* **13** (1100% crude yield), a yellow oil by the one-step alkylation[1c] of 1,3-propanedithiol with N,N-dipropyl chloroacetamide: IR (neat) 1640 cm^{-1}; NMR($CDCl_3$) δ0.86 (t, 12, CH_3CH_2), 1.2–2.16 (m, 10, CH_2), 2.68 (t, 4, CH_2S), 3.2 (s, 4, $SCH_2C(=O)$), 3.2 (t, 8, NCH_2). Purified by chromatography. (Found: C, 58.64; H, 9.93. Calc for $C_{19}H_{36}O_2N_2S_2$: C, 58.41; H, 9.29%).

1,10-*diphenyl*-1,10-*dioxa*-4,7-*diazadecane*-3,8-*didione* **16** (77%) was obtained from the reaction of phenoxyacetyl chloride (2 equivs) witn 1,2-ethylenediamine (1 equiv) and Et_3N (4 equivs) in CH_2Cl_2 at 25° overnight. Workup as before[1b] gave a solid: m.p. 154–156° (recryst. from EtOH). (Found: C, 65.74; H, 6.04; N, 8.61. Calc for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53%).

The N,N'-dimethyl compound **17** was obtained in similar manner from N,N'-dimethylaminoethane: m.p. 123–125°. (Found: C, 67.05; H, 6.81; N, 8.01. Calc for $C_{20}H_{24}O_4N_2$: C, 67.40; H, 6.79; N, 7.86%).

The dicyclohexyloxy compound **14** (58%) was similarly obtained from cyclohexyloxyacetyl chloride and 1,2-ethylenediamine: m.p. 116–118°. (Found: C, 63.61; H, 9.39; N, 8.41. Calc for $C_{18}H_{32}O_4N_2$: C, 63.50; H, 9.47; N, 8.23%).

trans - N,N,N',N' - *Tetrakis* - (*n* - *propyl*) - 1,2 - *cyclopentanedioxydiacetamide* **18**. Epoxycyclopentane in tetrahydrofuran was converted to the *trans*-1,2-diol in poor yield (20–25%) with formic acid or 60% perchloric acid–water–THF. The diol was alkyated with ethyl diazoacetate and BF_3. Et_2O[1a] to give trans-*diethyl*-1,2-*cyclopentanedioxydiacetate* (60%): b.p. 122–128° (0.17 mm); consistant NMR. The diester was hydrolyzed with KOH–water–C_2H_5OH at reflux for 4 hr to give the *diacid* (61%) which was converted to the diacid chloride (b.p. 123–126° (0.17 mm)) with $SOCl_2$ and then to **18** (100% crude) with dipropylamine: b.p. 155° (0.05 mm). (Found: C, 65.49; H, 10.39; N, 7.44. Calc for $C_{21}H_{40}O_4N_2$: C, 65.59; H, 10.48; N, 7.29%).

5,6 - *Benzo* - 1,10 - *dimethyl* - 4,7 - *dioxa* - 1,10 - *diazacycloundecane* - 2,9 - *dione* **19** (12%) was prepared by the simultaneous addition of 1,2-phenylenedioxydiacetyl chloride[1a] and N,N'-dimethyl-1,2-ethanediamine (1.0 equiv) over 90 min to a stirred soln of Et_3N (2.6 equivs) in CH_2Cl_2 under high dilution conditions. The resultant mixture was stirred at 25° for 18 hr; washed with water, dried and evaporated *in vacuo* to give a yellow gum which was chromatographed on silica gel 60. Elution with 1:1 $CHCl_3$–EtOH gave a residue which was recrystallized from EtOAc (twice): m.p. 183–184°: TLC R_f 0.3 (1:1 $CHCl_3$–EtOH); NMR ($CDCl_3$) δ3.1 (d), (3.3) (s) (6, CH_3), 4.05, 4.3, 4.7, 4.75, 4.85, 4.9, 5.15 (all s, 8, CH_2), 6.8–7.3 (m, 4, aryl); MS (CI) *m/e* 279 (M + I ≡ 278 mw). Calc mw 278. (Found: C, 60.21; H, 6.50; N, 10.04. Calc for $C_{14}H_{18}O_4N_2$: C, 60.42; H, 6.52; N, 10.07%).

N,N,N',N' - *Tetrakis* - (*n* - *propyl*) - 1,3 - *phenylene dioxydiacetamide* (**21**) was prepared from the alkylation of resorcinol with chloroacetic acid in NaOH–water. The resultant diacid was treated with $SOCl_2$ to give the acid chloride (brown oil) which was then treated with dipropylamine (2.0 equivs) and Et_3N (3.0 equivs) in CH_2Cl_2 to give a brown oil upon workup with 10% HCl. The crude product was chromatographed on silica gel in benzene (caution: now use toulene!) and eluted with 9:1 benzene-Et_3N to give 21 as an oil: 86%; IR 1650 cm^{-1}; NMR (CCl_4) δ0.9 (t, 12, CH_3), 1.5 (m, 8, CH_2), 3.2 (t, 8, CH_2N), 4.5 (s, 4, OCH_2), 7.1–7.5 (m, 4, aryl); TLC R_f 0.4 (1:1:1 diethyl ether–toluene–Et_3N). (Found: C, 67.21; H, 9.25; N, 7.03. Calc for $C_{22}H_{36}N_2O_4$: C, 67.32; H, 9.24; N, 7.14%).

cis - N,N,N',N' - *Tetrakis* - (*n* - *propyl*) - 1,3 - *phenylenedioxydiacetamide* **20**. Hydrogenation of 1,3-phenylendioxydiacetic acid (prepared above) with H_2/Rh–Al_2O_3 gave *cis*-1,3-cyclohexanediacetic acid (as previously shown for the hydrogenation of 1,2-phenylenedioxydiacetic acid to *cis*-1,2-cyclohexanedioxydiacetic acid which was converted to **9**[1a]). The diacid was treated with $SOCl_2$ at reflux under N_2 to give 100% (crude yield) of the acid chloride (IR (neat) 1800 cm^{-1}) which was then converted to **20** by the above procedure (for **21**) to give a yellow liquid (74% after chromatography): IR (neat) 1640 cm^{-1}; NMR ($CDCl_3$) δ0.9 (t, 12, CH_3), 1.1–1.9 (m, 16, CH_2), 3–3.5 (t, 10, CH_2N, OCH), 4.17 (s, 4, CH_2O). Found: C, 66.17; H, 10.58; N, 6.93. Calc for $C_{22}H_{42}O_4N_2$: C, 66.30; H, 10.62; N, 7.03%).

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