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SYNTHESIS AND BINDING STUDIES OF NEUTRAL DIOXYDIAMIDE IONOPHORES - III

Grace B. Borowitz,* Irving J. Borowitz, Josephine D. Readio, Gabriel Rubinstein, Peter Nirchio, Matthew Rutten, Timothy Strohmeyer, David Brill, Jill Sparling, and Peter Connolly

Department of Chemistry, Ramapo College of New Jersey, Mahwah, NJ 07430
Department of Chemistry, Yeshiva University, New York, NY 10033

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Abstract : *The syntheses of several bis-(1,2-phenylenedioxydiacetamides) with eight binding sites (four ethers, four amides) are described. It had been anticipated that these bis-compounds would be much stronger binders for Group IIA cations than are members of our previously described 1,2-phenylenedioxydiacetamide system, e.g. 1-3, which give isolable complexes usually of 2:1 ligand/metal cation stoichiometry. Binding constants for the new diesters 4 and 5 were determined in methanol using UV absorption changes and the Scatchard method. The binding strength of 4 was concentration dependent and only moderately greater than that for 1 or for the more closely related 4-hydroxymethyl compound 3. Diester 5 was a weaker binder for Group IIA cations than was either 1 or 3.*

Cooperativity of the two sets of binding sites with either Sr^{2+} or Ba^{2+} was demonstrated for 4 but not for 5. Electrochemical selectivity values (K^{pot}_{ij}) as determined by Simon et al for 4, 5, and 6, in liquid membrane electrodes are reported for various cations. High ion selectivity for Na^+ vs either Ca^{2+} or K^+ were found, especially for 6.

Some years ago we reported the synthesis of a series of neutral dioxydiamides such as N,N,N',N'-tetrakis-(n-propyl)-1,2-phenylenedioxydiacetamide 1 and related aliphatic and alicyclic analogs as well as the evaluation of these compounds in the binding of metal cations.[1,2] Later we reported structural studies on isolated crystalline complexes of 1 and related compounds with various Group IIA and transition element cations.[3] An important finding in this work and in the single crystal X-ray analysis of several of our complexes by Dobler and Neupert-Laves[4] was the formation of eight-coordinate dodecahedral complexes featuring 2:1 ligand/cation stoichiometry. This was in contrast to the 1:1 stoichiometry of binding found in $<7\times10^{-4}$M methanol solutions. More recently, the effects on binding strength and cation selectivity in ion-selective electrodes caused by structural changes in the basic system were reported.[5] We now report the synthesis, binding studies in methanol, and the ion-selective electrode behavior (as determined by W. Simon et al, ETH Zurich) for several diesters featuring two sets of the 1,2-phenylenedioxydiacetamide moiety, *i.e.* featuring eight binding sites.[6]

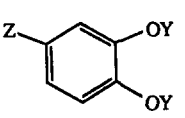
Results

Synthesis of the Ligands

Sodium borohydride reduction of N,N,N',N'-tetrakis-(*n*-propyl)-4-formyl-1,2-phenylenedioxydiacetamide, 2,[1c] in methanol gave the corresponding alcohol 3. Two equivalents of 3 were condensed with decanedioyl chloride in the presence of 4-dimethylaminopyridine (DMAP)

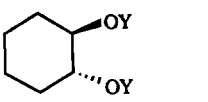
and triethylamine to give bis-[N,N,N',N'-tetrakis-(*n*-propyl)-4-methylene-1,2-phenylenedioxydiacetamido] decanedioate, **4**. Spectral and chromatographic data indicated that **4** had the desired structure. Combustion analysis of **4** indicated the presence of a mole of water which could not be removed readily.

Scheme I



1. Z = H
2. Z = C(H)=O
3. Z = CH_2OH

Y = $CH_2CN(C_3H_7)_2$ (=O)



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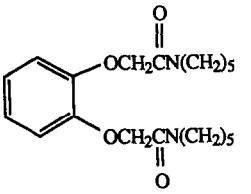

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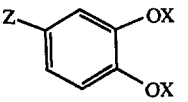
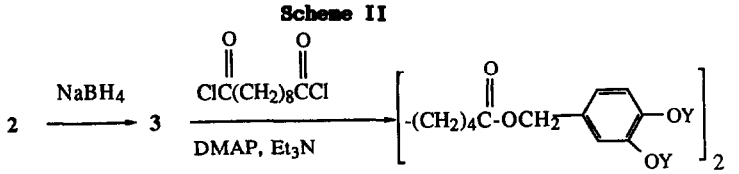


9. Z = H
10. Z = C(H)=O
11. Z = CH_2OH

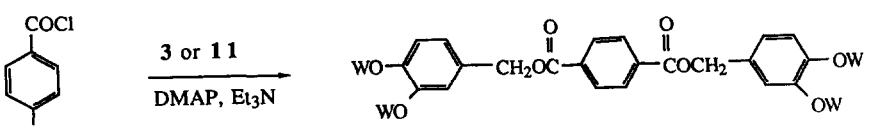
X = $CH_2CN(C_6H_{11})_2$ (=O)

Reaction of terephthaloyl chloride with two equivalents of **3** in the presence of DMAP and triethylamine gave bis-[N,N,N',N'-(*n*-propyl)-4-methylene-1,2-phenylenedioxydiacetamido] 1,4-phthalate, **5**, as a crystalline solid. Neither **4** nor **5** have given isolable complexes with $CaBr_2$, $SrBr_2$, $BaBr_2$, or $MnBr_2$ to date, in contrast to **1** and related ligands. The N,N-dicyclohexyl analog of **5**, namely **6**, was prepared by our one-step synthesis[1c] starting with N,N-dicyclohexylchloroacetamide.

Scheme II



4. Y = $CH_2CN(C_3H_7)_2$ (=O)



5. W = Y
6. W = $CH_2CN(C_6H_{11})_2$ (=O)

Complexation in Methanol

As previously shown[1b,2a,5] the addition of concentrated solutions of anhydrous metal cation bromides and other salts to the dilute solutions of **4** in 2-5 x 10^{-5}M methanol causes changes in the 275-285 nm region. These UV changes have been used to obtain the binding stoichiometry and apparent binding constants for various cations with our previously described ligands *via* Scatchard plots.[2a,5]

Table I. Binding Constants for **4** (2.0 x 10^{-5}M) in Methanol at 285 nm

Salt[a]	K_{app}[b]	n[c]	R[d]	ΔA_{max}
CaBr2	1.74 x 10^5	0.80	0.995	0.38
SrBr2 [e]	1.23 x 10^5	0.95	0.99	0.28-0.47[e]
BaBr2	1.89 x 10^5	0.85	0.99	0.26
MnBr2	3.42 x 10^5	0.93	0.99	0.24
CdCl2	2.8 x 10^4	1.99[f]	0.89[f]	0.14
ZnBr2	9.0 x 10^4	1.25[g]	0.98	0.02[h]
NaBr	1.0 x 10^2	0.96[i]	0.99	0.02[h]
KBr	5.6 x 10^3	0.97[j]	0.98	0.02[h]

[a] Usually between 0.03-0.06M. [b] Units of K_{app} are M^{-1} for 1:1 complexes. The K values are "apparent" since activity coefficients of the salts are unknown in methanol. The mean of several runs is given. The reproducibility is ± 10%. Scatchard plots of r/C *vs* r were usually used. (r = [bound cation/total ligand] ; c = [free cation]). [c] Stoichiometry of binding= cation/ligand. [d] Correlation coefficient in linear regression analysis. [e] Based on the linear, latter part of the total curve. Many runs were done and the curvature is reproducible. [f] Here the alternate equation using R/L *vs* R (see ref. 2a) was needed since n = 1 (Scatchard Plot) but it did not correlate well. [g] Using R/L *vs* R since n = 1, where in these cases n=ligand/cation. [h] The observed ΔA_{max} values are not considered as reliable as the larger values for other cations and calculated values are considered approximate. [i] Based on points 7-13. The early points (1-6) gave an apparently larger, reproducible K_{app} of *ca.* 10^4. [j] Based on a small number of points in the linear part of an otherwise non-linear Scatchard plot.

The results of Scatchard plot analysis for **4** are given in Tables I and II. At the lower concentration of 2.0 x 10^{-5}M the ligand has somewhat higher K_{app} values (Table I) than at 4.98 x 10^{-5}M (Table II). The selectivity of binding of Group IIA cations is better at the higher concentration. Binding constants for **3** with Group IIA cations are given in Table III, as are comparison values for **4** and **1**. The binding constants for **5** are given in Table IV. The K_{app} values for **4** and **5** may be less accurate than those previously

Table II. Binding Constants for **4** (4.98 x 10^{-5}M) in Methanol at 285 nm

Salt[a]	K_{app}[b]	n[c]	R[d]	ΔA_{max}
CaBr2	9.19 x 10^4	0.90	0.99	0.855
SrBr2	1.55 x 10^4	0.80	0.98	0.95
BaBr2	1.97 x 10^5	0.93	0.98	0.38
MnBr2	5.56 x 10^4	2.0[e]	0.96[e]	0.075[e]
NaBr	3.5 x 10^3	0.95	0.79	0.15
KBr	1.99 x 10^4	0.95	0.81	0.15

[a] Usually 0.1M. [b] A typical run is given. Usually several runs were done. [c,d] See Table I for definitions. [e] R/L *vs* R, in which n=ligand/cation, was used since r/c *vs* r does not apply. See ref. 2a.

reported[2a,5] for 1 and its analogs since maximal UV changes upon binding of 4 and 5 are smaller. While Beer's Law is obeyed for 1, 4, and 5 at λ_{max} for concentrations less than 10^{-3}M, it may be less perfectly obeyed for the complexes at the wavelengths of change (280, 285 nm) which are used to determine the binding of 4 or 5 with cations.

Table III. Comparison of Binding Constants (K_{app}) of 3 vs 4 or 1

Salt[a]	K_{app} [b,c]	n[d]	R[e]	$K_{app\ 4}/K_{app\ 3}$ [f]	$K_{app\ 1}$ [g]
$CaBr_2$	4.05×10^4	0.97	0.98	4.3	7.33×10^4
$SrBr_2$	1.24×10^4	0.91	0.99	10	1.23×10^4
$BaBr_2$	6.49×10^3	0.96	0.99	29	4.42×10^3

[a] Usually 0.1M. [b] See Table II for definitions. [c] Conc.= 5.0×10^{-5}M in methanol (276 nm). [d,e] See Table I for Definitions. [f] Using data for 4 from Table I. [g] See ref. 2a. Conc. of 1 = 1.13×10^{-5}M.

Table IV. Binding Constants for 5 (1.0×10^{-5}M) in Methanol at 285 nm

Salt[a]	K_{app} [b]	n[c]	R[d]	ΔA_{max}
$CaBr_2$	3.18×10^4	0.99	0.985	0.20
$SrBr_2$	2.92×10^4	1.01	0.975	0.11
$BaBr_2$	7.35×10^4	1.05	0.975	0.08
$MnBr_2$	2.5×10^3	0.79	0.92	0.31
NaBr	negligible			
KBr	negligible			

[a] 0.1M except $[Mn^{2+}]$=0.03M. [b] Mean value for several runs except for $MnBr_2$. [c,d] See Table I for definitions.

Scatchard plots of bound/free (B/F) *vs* bound (B) ligand, done as described previously,[5] for the interaction of 4 with Sr^{2+} or Ba^{2+} gave curves suggestive of cooperativity[7a,8] instead of straight lines.

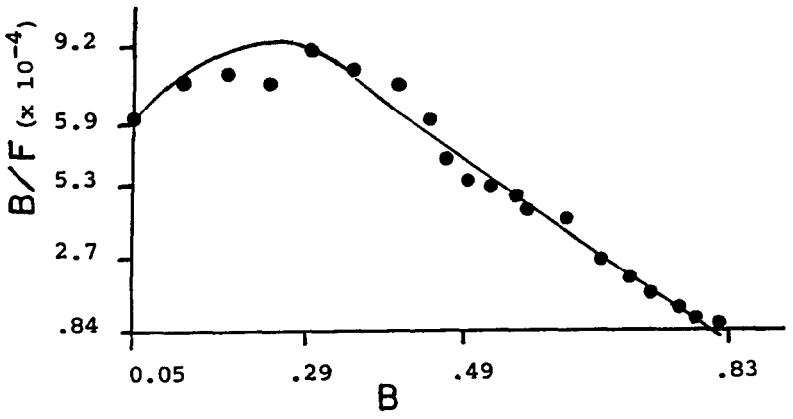


Figure 1. Scatchard Plot of 4 (2×10^{-5}M) with $BaBr_2$.

In order to test for the presence of positive cooperativity in the two sets of dioxydiamide ligands in 4 and 5 *vs* 1 as a control, where cooperativity is not possible, the data was treated in several alternate methods to the Scatchard plot. Thus, the plot of B^2/F *vs*

B and the double reciprocal plot, 1/B *vs* 1/F, also suggested that **4** is showing cooperativity in its binding of Sr^{2+} and Ba^{2+}, in contrast to **1** and **5** which showed no cooperativity. These alternate plots were graphed with PROSTAT.[9]

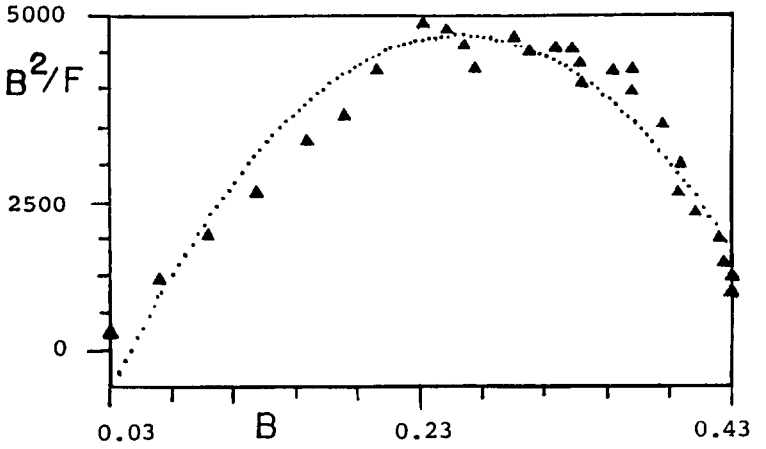


Figure 2. B^2/F *vs* B for **4** (2×10^{-5}M) with $SrBr_2$.

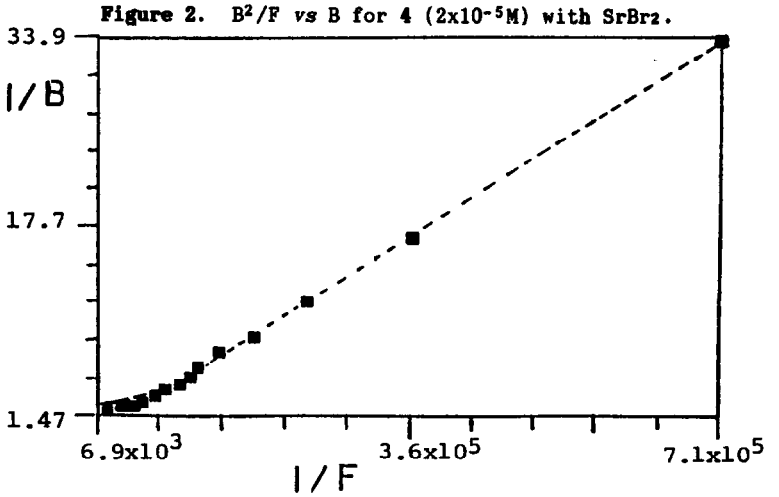


Figure 3. Double Reciprocal Plot for **4** (2×10^{-5}M) with $SrBr_2$.

In order to confirm our assumption that the ester groups in the diesters are not involved in cation binding, the IR spectrum of **4** in methanol was compared before and after addition of excess $Ca(SCN)_2$. The ester carbonyls do not shift from 1720 cm^{-1} but the amide carbonyls shift from 1660 to 1620 cm^{-1}.

Ion Selectivities of Ligands in Liquid Membrane Electrodes

Electrochemical data for **4** to **6** is shown in Figures 4 and 5. The determination of the data and its presentation is by W. Simon *et al.*[10] Selectivity constants K^{pot}_{ij} are given relative to Na^+. Thus **6** has a selectivity of Na^+/Ca^{2+} = 100 and Na^+/K^+ = 71.

Discussion

Although dilute solutions of ligands such as **1-3** or **7** bind metal cations in 1:1 stoichiometry, these ligands form isolable complexes that usually have 2:1 ligand/cation

stoichiometry featuring eight-coordinate dodecahedral symmetry.[3,4] Therefore, it was anticipated that a ligand such as **4** might be a stronger binder since it contains <u>two</u> sets of four-coordination sites. CPK models of **4** indicate that the two sets of binding sites can fit around a cation with the dodecahedral geometry found for the $MnBr_2$ or $CaBr_2$ complex of **1**.[3b,4] It was realized that in order for this cooperation to occur, a large unfavorable entropy factor involved in the two ends of a 10-carbon chain coming together would have to be overcome. Shorter chains do not allow the proper dodecahedral "fit" to occur in CPK models. In comparing the binding constant data for **4** (Table II) with that for **3** (Table III) or for **1** (previously reported[2a] and reproduced in table III), it is found that **4** is a stronger binder but by factors not as large as anticipated. Thus, the largest increase is for the binding of Ba^{2+}, wherein **4** binds 43 times more than **1** does and 29 times more than **3** does. The selectivity in single-phase binding for **4** is much less than that for either **1** or **3**. Part of the decrease in selectivity, as shown by the fact that **3** is less selective than is **1** (Ca^{2+}/Ba^{2+} = 6.2:1 *vs* Ca^{2+}/Ba^{2+} = 16.7:1), may be due to the electron-withdrawing effect of the C-4 aromatic OCH_2 groups. Simon has recently discussed the conditions under which higher coordination number ligands do not necessarily show greater ion selectivity than than do related ligands with a lower coordination number.[11] It is felt that data gathered at the lower concentration is better used in comparison to either **1** or **3**. The latter compounds showed little concentration dependency for K_{app}.

Another reason for the decrease in selectivity of binding of cations by **4** may be due to the flexibility bestowed upon the system by the two binding "arms." Ligand **4** shows complicated binding behavior in several ways. There is a concentration dependence for K_{app}, *i.e.* greater values at a lower concentration (2 x 10^{-5}M, Table I) than at a higher concentration (4.98 x 10^{-5}M, Table II). This effect, although reproduced for **4**, was not found for **1**, **7** or other four-coordinate dioxydiacetamide ligands.[2a,5] Ligand **4** (4.98 x 10^{-5}M) binds the Group IIA cations in the unusual order: $Ba^{2+}>Ca^{2+}>Sr^{2+}$. Most of our previously tested ligands exhibit the binding order: $Ca^{2+}>Sr^{2+}>Ba^{2+}>Mg^{2+}$. This frequently found order has been rationalized by others using "radius ratio" and "field" effects.[2a,3c] Ligand **4** also binds K^+ and Na^+ in 5.7:1 ratio with reasonable K_{app} values. Thus it is the only 1,2-phenylenedioxydiacetamide ligand to date to exhibit even moderate Group 1A cation binding in methanol solution. Even though CPK models of **5** suggest that its two "arms" should fit Ca^{2+} very neatly, the K_{app} value was disappointingly similar to and lower than those for **3** or **1**, as compared on Tables III and IV. The binding of Sr^{2+} by **5** was 2.4 times greater than by **1** or **3** while Ba^{2+} was bound only 1.6 times more by **5** than by **1**. Ligand **5** binds $Ca^{2+}\tilde{=}Sr^{2+}>Ba^{2+}$ with a smaller spread of K_{app} values than the previously described dioxydiacetamides including **1**, **3**, and **7**.

The criticism of the Scatchard plot method by I. Klotz[12] states that the determination of n (stoichiometry) from data that does not approach anywhere near the "saturation" of the substrate (ligand) with the binding compound (cation) can be erroneous. We analyzed some of our data using his method of plotting the fraction of bound cation *vs* log C_t, where C_t = total cation concentration. In most of the cases the desired "S" shaped curves were obtained, confirming that we were looking at binding that went to 80-90% of full

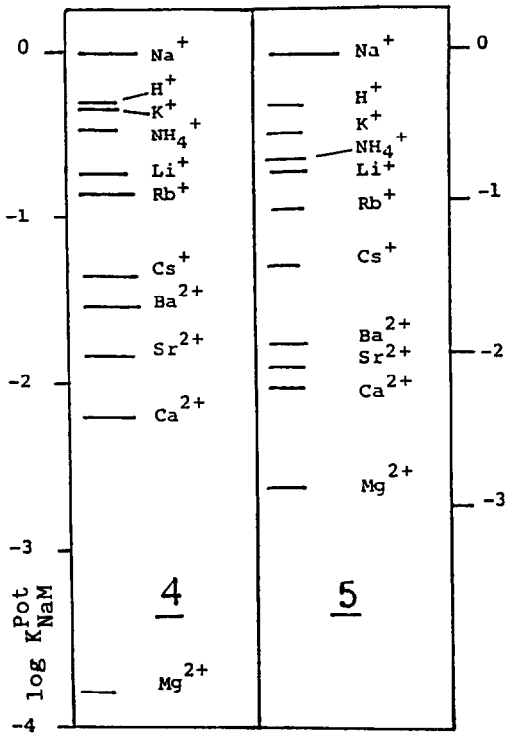


Figure 4 Cation Selectivities Relative to Sodium for **4** and **5** (1% w/w) both in *Bis*-(1-butylpentyl) adipate (BBPA) (66%)/PVC (33%).

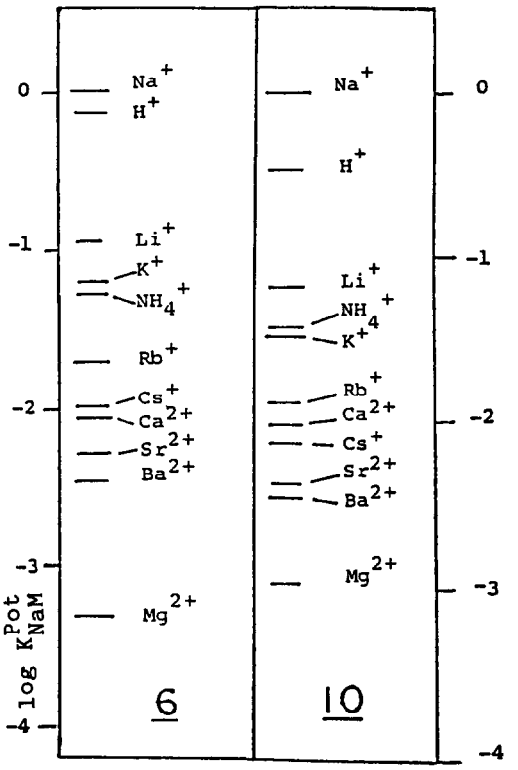


Figure 5 Cation Selectivities Relative to Sodium for **6** and **10**(1% w/w)

Carbon 13 NMR spectra were recorded on the Lederle GE-Nicolet spectrometer. Infrared spectra were recorded on Beckman IR 33 and Perkin-Elmer 1420 spectrophotometers at Ramapo College and on a GE-Nicolet FT-IR spectrophotometer at Lederle. Mass spectra were done by Dr. M. Siegel at American Cyanamid's Medical Research Division, Lederle Laboratories, using a Kratos MS-50 using FAB (fast atom bombardment) techniques, xenon, and sulfolane solutions as well as with a VG Analytical ZAB-SE mass spectrometer with a matrix of threitol/erythritol (5:1). Ultraviolet spectra and single phase binding studies in methanol were done on a Varian Spectroscan 3 spectrophotometer. Thin layer chromatography was done on Eastman Kodak, E. Merck, Whatman, or Analtech silica gel sheets or plates mainly using the following solvents: A toluene-diethyl ether-dichloromethane-methanol (ratios: 180:90:17:9), B toluene-diethyl ether-glacial acetic acid-methanol (ratios: 180:90:17:9), C 85% ethanol-ethyl acetate (ratio: 4:1), and D $CHCl_3$-methanol (ratio: *ca.* 98.5:1.5 or 1-2 %) . Elemental Analyses were done by Lederle Laboratories, American Cyanamid, Pearl River, NY.

N,N,N',N'-Tetrakis-(*n*-propyl)-4-hydroxymethyl-1,2-phenylenedioxydiacetamide (3). To a solution of **2**[1c] (5.0 g, 0.012 mol) in anhydrous methanol (150 mL) was added sodium borohydride (2.5 g, 0.067 mol) in increments, with stirring, at room temperature. After 30 min at 25 °C and 1 min of warming the mixture was evaporated *in vacuo* to yield a residue which was dissolved in dichloromethane (100 mL), washed with 1 N HCl (2 x 50 mL), water (3 x 100 mL), saturated NaCl (100 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give a golden oil (4.89 g, 0.022 mol, 98%): IR (NaCl) 3370, 1660 cm^{-1}; 300 MHz PMR $CDCl_3$) δ 7.318, 6.977, 6.861 (s, 3, aryl), 5.302 (s, 1, OH, exchangeable with D_2O), 4.721, 4.682 (s, 2, $OCH_2C{=}O$), 4.560, 4.541 (s, 2, CH_2-aryl), 3.311 (t, 4, CH_2N, "inner"), 3.253 (t, 4, CH_2N, "outer"), 1.620 (t,4, $NCH_2\mathbf{CH_2}$, "inner"), 1.543 (t, 4, $NCH_2\mathbf{CH_2}$, "outer"), 0.918 (t, 6, CH_3,

"inner") 0.868 (t, 6, CH_3, "outer"); ^{13}C NMR ($CDCl_3$) δ 167.49 (amide C=O), 148.19, 147.39. (C_1 and C_2 aryl), 135.63 (C_4 aryl), 120.52 (C_3 aryl), 115.14, 113.83 ($C_{5,6}$ aryl), 68.48, 68.11 (OCH_2C=O), 64.53 ($HOCH_2$), 49.52, 48.43, (NCH_2), 22.11, 20.67 (CH_2CH_3), 11.34, 11.20 (CH_2CH_3); TLC solvent **A**, one spot (R_f=0.37), solvent **B**, one spot (R_f=0.25); mass spectrum (75 eV) m/e 422 (M^+). Anal. Calcd for $C_{23}H_{38}N_2O_5$: C, 65.38; H, 9.06; N, 6.63. Found: C, 65.14; H, 9.09; N, 6.44.

Bis-[N,N,N',N'-tetrakis-(*n*-propyl)-4-methylene-1,2-phenylenedioxydiacetamido] 1,10-decanedioate (4). To a solution of **3** (4.0 g, 0.0095 mol) 4-N,N-dimethylaminopyridine (0.232 g, 0.0019 mol) and triethylamine (1.4 mL, 1.02 g, 0.010 mol) in dichloromethane (100 mL) under nitrogen, decandioyl chloride (1.0 mL, 1.12 g, 0.0047 mol) was added dropwise from a syringe over a 30 min period. The reaction was stirred for an additional 60 min. Ethyl acetate (200 mL) was added and the mixture was filtered *in vacuo* and the filtrate was evaporated *in vacuo* to give an oil. The oil was redissolved in dichloromethane (100 mL), washed with 5% $NaHCO_3$, water, dried, filtered, and evaporated *in vacuo* to give the product as a golden oil (4.47 g, 0.0044 mol, 93% if pure). The oil was redissolved in a minimum volume of dichlormethane and flash chromatographed[11] on silica gel using ethyl acetate-methanol-dichloro-methane (4:4:1) as the eluting solvent. Fractions of 15 mL were collected. Fraction two contained some starting material but fractions three through nine showed essentially pure product, **4** (TLC solvent **A**). Further purification by preparative HPLC (silica gel column) using ethyl acetate-hexane-triethylamine (12:8:1) removed a trace amount of starting **3** but did not change the analysis. IR (NaCl) 1740, 1660 cm^{-1}; TLC solvent **A**, one spot (R_f=0.4), solvent **B**, one spot (R_f=0.21); 300 MHz PMR ($CDCl_3$) δ 7.22 (s) and 6.92 (d) (6, aryl), 4.96 (s, 4, OCH_2-aryl, 4.70 (s, 8, OCH_2C=O), 3.33, 3.18 (each t, 16, NCH_2), 2.25 (t, 4, CH_2C=O) 1.50, 1.52 (m, 16, NCH_2CH_2 + 2H, $CH_2CH_2(C$=O)O), 1.22 (m, 8, CH_2), 0.85, 0.78 (each t, 24, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.40 (ester C=O), 167.30, 167.24 (amide C+O), 148.23, 148.14, 130.84, 122.27, 122.22, 115.52, 115.10 (aryl), 68.43, 65.65 (OCH_2C=O, OCH_2aryl), 48.82, 47.49 (NCH_2), 34.19, 33.89, 28.97, 28.92, 28.83 (CH_2), 24.78, 24.70 ($CH_2(C$=O)OCH_2), 22.06, 21.60 (CH_2CH_3), 11.24, 11.12 (CH_2CH_3); mass spectrum (FAB + sodium) 1033 $(M+Na)^+$, 1011 $(M+H)^+$, 527 $(M/2+Na)^+$. Anal. Calcd for $C_{56}H_{90}N_4O_{12}.H_2O$: C, 65.34; H, 9.01; N, 5.44. Found: C, 65.38; H, 9.18; N, 5.07.

Bis-[N,N,N'N'-tetrakis-(*n*-propyl)-4-methylene-1,2-phenylenedioxydiacetamido] 1,4-phthalate (5). Reaction of **3** (4.0 g, 0.0095 mol) with terephthaloyl chloride (1.12 g, 0.0055 mol) in the manner described for **4** above, but with a longer reaction time of several days, gave **5** as a thick yellow oil (4.1 g). The oil was solidified by trituration with anhydrous diethyl ether to a white solid (2.8 g. 0.0029 mol, 59%), mp 63-65 °C) which was recrystallized from diethyl ether to a white solid: mp 78-81.5 °C; IR (NaCl) 1725, 1660 cm^{-1}; 100 MHz PMR ($CDCl_3$) δ 8.2 (s, 4, terephthaloyl aromatic H), 6.8-7.2 (m, 6, aryl), 5.35 (s, 4, OCH_2aryl), 4.75 (s, 8, (C=O)CH_2O), 3.25 (t, 16, NCH_2), 1.57 (m, 16, (CH_2CH_3), 0.85 (t, 24, CH_2CH_3); TLC Solvent **C**, one spot (R_f=0.8); ^{13}C NMR ($CDCl_3$) featuring the attached proton test,[19] in which 1 or 3 protons/C cause ^{13}C peak to invert* while 0 or 2 protons do not cause inversion of the peak, δ 166.86, 165.13, (amide C=O), 148.13, 147.2 ($C_{1,2}$ of aryldioxy), 133.42 (C_1', C_4' of terephthaloyl), 130.6* (C_2', C_3', C_5', C_6' of terephthaloyl), 129.08 (C_4 of aryldioxy), 122.10* (C_5 of aryldioxy), 115.26*, 114,6* ($C_{3,6}$ of aryldioxy), 67.02, 66.52, (OCH_2C=O), 47.10, 48.47 (NCH_2), 20.35, 21.81 (CH_2CH_3), 10.01* (CH_2CH_3). The spectrum was not taken to the range for esters (*ca.* 173 ppm). Anal. Calcd for $C_{54}H_{78}O_{12}N_4$: C, 66.50; H, 8.06; N, 5.75. Found. C, 66.37; H, 7.85; Nm 5.65.

N,N-Bis-(cyclohexyl)chloroacetamide. Chloroacetyl chloride (16.95 g, 0.15 mol) was added dropwise over a period of 30 min with stirring to a solution of N,N-dicyclohexylamine (54.3 g, 0.30 mol) in dichloromethane (400 mL), cooled in a NaCl-ice bath to -5°. The resultant reaction mixture was stirred at 25 °C for *ca.* 12 h, vacuum filtered over a bed of Celite-charcoal, and the solvent was evaporated *in vacuo* to give a dark thick liquid. This crude product was chromatographed on silica gel (35-70 mesh) using dichloromethane and the fractions containing the product as determined by TLC (solvent **A**) were combined and evaporated *in vacuo* to give material which when recrystallized from ethyl acetate was a yellow solid (23.5 g, 0.091 sol, 61%): mp 110-111 °C; IR (KBr) 1640 cm^{-1} (amide); 300 MHz PMR ($CDCl_3$) δ 4.02 (s, 2, CH_2Cl), 3.45 (broad t, 1, NCH), 3.0 (m, 1), 2.4 (m, 2), 1.2, 1.5, 1.8 ppm (m, 8, CH_2); 75 MHz ^{13}C NMR ($CDCl_3$) δ 165.24 (C=O), 56.295, 58.824 (C_1, C_1' amide), 43.37 (CH_2Cl), 29.12, 29.41, 31.13 (C_2, C_6 and C_2' , C_6'), 25.12, 25.74, 26.38 ppm (C_3-C_5, C_3' - C_5'). The product may be heat sensitive. Anal. Calcd for $C_{14}H_{24}NOCl$: C, 65.20; H, 9.38; N, 5.43; Cl, 13.75. Found: C, 65.28; H, 9.32; N, 5.34; Cl, 13.76.

N,N,N',N'-Tetrakis-(cyclohexyl)-4-formyl-1,2-phenylenedioxydiacetamide (10) A solution of N,N-bis-(cyclohexyl)chloroacetamide (12.5 g, 0.049 mol) in anhydrous acetone (175 mL) was added dropwise over 60 min with stirring under nitrogen to a mixture of 3,4-dihydroxybenzaldehyde (3.35 g, 0.024 mol), anhydrous K_2CO_3 (6.9 g, 0.05 mol), and KI (0.5 g, 0.003 mol) in anhydrous, freshly distilled acetone (200 mL). The resultant mixture was stirred at gentle reflux for 40 h and the precipitate, mostly inorganic salts, was removed by vacuum filtration, washed with a small volume of dry acetone, and the combined acetone solutions were evaporated *in vacuo* to give the crude product as a thick yellow oil. This oil was dissolved in dichloromethane (*ca.* 100 mL), washed with portions (*ca.* 50 mL) in turn of aqueous K_2CO_3, 10% HCl, water, and saturated NaCl, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to give a thick orange-tan oil (14.8 g). The oil was crystallized by solution in a minimal volume of hot ethyl acetate to which petroleum ether (bp 60 - 90 °C) was added. This gave an orange solid (8.82 g, 0.015 mol, 63%): mp 175 - 185 °C. A small amount of this product was recrystallized from diethyl ether-petroleum ether (60-90 °C) to give a white solid: mp 198-200 °C. IR (KBr) 1690 (formyl), 1658 (amide I), 1590 cm^{-1} (amide II); 300 MHz PMR ($CDCl_3$) δ 9.82 (s, 1, HC=O), 7.42- 7.45 (2d), 7.27 - 7.35 (t), 7.04 (d) (total 3, aryl-H), 4.78, 4.71 (2s, 4, OCH_2) 3.57, 3.45 (broad t, 2, NCH) 2.95 (m, 2, NCH), 2.45 (m, 4, NCCH) 1.2 - 1.9 ppm (broad m, 36, CH_2); ^{13}C NMR ($CDCl_3$) δ 190.5 (formyl C), 165.86, 165.62 (amide C=O), 153.0 (aryl-C_2), 148.1 (aryl-C_1), 130.4 (aryl-C_4), 126.6 (aryl-C_5), 112.7 (aryl-C_5), 111.7 (aryl-C_6), 77.4, 77.0, 76.58 (t, 1 $CDCl_3$), 69.44, 68.64 (OCH_2O) 57.80, 57.55, 56.30 (NCH), 31.56, 31.35, 29.60, 29.12, 26.44, 25.72, 25.14, 24.71 ppm (cyclohexyl Carbons); TLC one spot R_f = 0.6 (Solvent A); mass spectrum: *m/e* (relative intensity) (CI, CH_4, GC column temp 74 °C) 581 (100) [M+H⁺], 400 (12), [-N(C_6H_{11})$_2$], 372 (8), [-(C=O)-N(C_6H_{11})$_2$], 360 (90), 222 (32), [CH_2-(C=O)N(C_6H_{11})$_2$], 180 (32), [$NC_{12}H_{22}$], 89 (56). Anal. Calcd for $C_{35}H_{52}N_2O_5$: C, 72.38; H, 9.02; N, 4.82. Found: C, 72.02; H, 9.14; N, 4.99.

N,N,N',N'-Tetrakis-(cyclohexyl)-4-hydroxymethyl-1,2-phenylenedioxydiacetamide (11) $NaBH_4$ (2.0 g, 0.054 mol, 7.7 eq) was added in increments, with stirring, at room temperature to a slurry of **9**, (4.0 g, 0.0069 mol) in anhydrous methanol (300 mL). The slurry dissolved and the reaction mixture warmed somewhat as the reaction proceeded. After *ca.* 45 min the solvent was evaporated *in vacuo* to leave a solid residue which was dissolved in dichloromethane (100 mL),to give a solution which was washed with water (3 x 100 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give a white foam which solidified (3.31 g, 0.0057 mol, 82%): mp *ca.* 145 °C dec; TLC one spot in various solvents (inc. 4:1:1 EtOAc-MeOH-toluene, wherein R_f = 0.54 while the 4-formyl compound **10** has R_f=0.7); IR (KBr) 3400 (OH), 1660 (amide) cm^{-1}; 300 MHz PMR ($CDCl_3$) δ 6.93- 7.26 (m, 3, aryl-H), 5.29 (d, 1, OH ?), 4.65 (d, 4, OCH_2C=O), 3.30 (s, 2, CH_2-Aryl), 3.6, 2.9, 2.5 (broad m, 4, NCH), 1.2 - 1.9 ppm (broad m, 40, CH_2); ^{13}C NMR ($CDCl_3$) δ 166.70, 166.35 (amide C=O), 147.7, 147.4, 131.41, 119.73, 113.09, 111.66 (6 aryl C), 102.87 (CH_2OH ?), 77.42, 77.00, 76.58, (t, 1, $CDCl_3$), 69.83, 69.32 (OCH_2C=O), 57.68, 57.63, 56.08, 52.65 (NCH), 31.27, 29.53, 26.42, 25.88, 25.66, 25.11 ppm (other cyclohexyl C's). Anal. Calcd for $C_{35}H_{54}N_2O_5.H_2O$: C,69.97; H, 9.39; N, 4.66. Found: C, 69.67; H, 9.21; N, 4.37.

Bis-[N,N,N',N'-Tetrakis-(cyclohexyl)-4-methylene-1,2-phenylenedioxydiacetamido]-1,4-phthalate (6) Terephthaloyl chloride (0.55 g, 0.0027 mol) and **11**, (2.61 g, 0.0045 mol) were reacted in the same manner as that used to prepare **4** and **5** to give a white solid (2.39 g, 0.0018 mol if pure **6**, 82%): mp 110-113 °C; TLC several spots. The product **6** was purified by methods including flash chromatography and HPLC until the detection of only one spot on Whatman TLC plates and consistent spectral data were obtained. Mp 113-115 °C; IR (KBr) 1710 (ester), 1640 (amide) cm^{-1}; 300 MHz PMR ($CDCl_3$) δ 8.095 (s, 4, phthalate-H), 6.86 - 6.99 (m, 6, aryl-H), 5.246 (s, 4, OCH_2-aryl), 4.679, 4.648 (d, 8, OCH_2), 3.473 - 3.540 (m, 5, NCH and NCCH or error 1 H), 2.907 (m, NCH, 4), 2.410 (m, 8.5, NCCH), 1.92 (s, 14, H_2O), 1.13 - 1.75 (3m, 79 (poss. high), cyclohexyl-CH_2); ^{13}C NMR ($CDCl_3$): solubility too low for satisfactory spectrum; mass spectrum (FAB) *m/e* (rel intensity) 1319 (25) [MNa⁺], 1296.1 (100) [M⁺], 627.6 (20), 309.1 (42), 264.3 (20), 222.2 (25) [CH_2(C=O)N(C_6H_{11})$_2$], 180.2 (20) [N(C_6H_{11})$_2$], 164 (10) [$O_2CC_6H_4CO_2$], 155 (100) [(O=C)C_6H_4(C=O)Na], 135 (55), 118.9 (100) [$C_6H_4CO_2$]. Anal. Calcd for $C_{78}H_{110}N_4O_{12}.4H_2O$: C, 68.50; H, 8.70; N, 4.10. Found: C, 68.76; H, 8.17; N, 3.78.

Preparation of Complexes of 3. The addition of $CaBr_2$ (0.24 g, 1.2 x 10^{-3} mol) to a solution of **3** (0.050 g, 1.2 x 10^{-3} mol) in dry methanol (20 mL) containing 2,2-dimethoxypropane (1 mL) as a drying agent under conditions as previously reported for other

complexes[3a] (heating, stirring for 30 min) led to a solid which was crystallized from $CHCl_3$ to give a white solid: mp 185 °C dec; IR (KBr) 3410-3220, 1645 cm^{-1}. Anal. Calcd for $C_{23}H_{38}N_2O_8 \cdot H_2O \cdot CaBr_2$: C, 43.13; H, 6.30; Ca, 6.26. Found: C, 43.13; H, 6.70; Ca, 6.07. Similar treatment of **3** with $SrBr_2$, $MnBr_2$, and $BaBr_2$ gave solids whose analyses are not yet satisfactory. Similar treatment of **4** with the above salts did not lead to isolable, crystalline complexes.

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