

Thermodynamic Studies of Alkaline-Earth-Metal Cation Complexation by Lipophilic Dioxa, Trioxa, and Dithia Dicarboxylic Acids

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Abstract. Five new lipophilic dicarboxylic acids with systematic structural variation in the bridge which joins the two lipophilic carboxylic acid units have been synthesized. Potentiometric equilibrium measurements of hydrogen ion concentrations have been employed to determine the protonation constants for these lipophilic di-ionizable acyclic ligands in 90% methanol–10% water (v/v) at 25.0 °C and an ionic strength of 0.10 M and the stability constants for their complexes with Mg^{2+} , Ca^{2+} , and Sr^{2+} . Although all five ligands exhibit the highest stability constants for Ca^{2+} , the magnitude of the differences between the stability constants for complexation of Ca^{2+} versus Mg^{2+} or Sr^{2+} is found to vary widely depending upon the identity of the bridging unit which joins the two carboxylic acid end groups.

Key words: Stability constants, protonation constants, di-ionizable lipophilic podands.

1. Introduction

In 1974, Toei and coworkers reported that the chelate stability constant ordering for alkaline-earth-metal cation complexation by $HO_2CCH_2O(CH_2CH_2O)_nCH_2CO_2H$ in water varied with changes in the length of the polyether chain which joins the two carboxylic acid end groups [1]. This indicated that acyclic polyether dicarboxylic acids with appropriate lipophilicity might be useful agents for the separation of alkaline-earth-metal cations.

The potential of lipophilic acyclic polyether dicarboxylic acids for use in alkaline-earth-metal cation separations by solvent extraction and liquid membrane transport processes is being explored [2–6]. For solvent extraction, the di-ionizable nature of the ligand obviates the need for concomitant transfer of one or more

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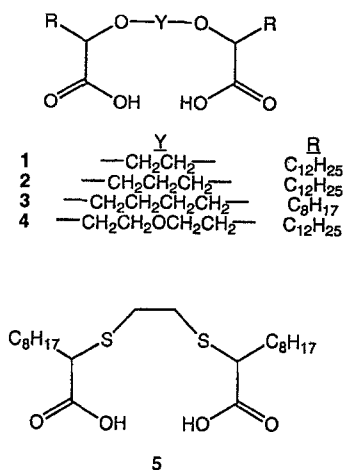


Fig. 1. Structures of lipophilic dicarboxylic acid ligands.

aqueous-phase anions into the organic phase when a divalent metal ion is extracted. This factor is of immense importance to potential practical applications in which hydrophilic anions, such as chloride, nitrate, and sulfate, would be involved. For transport of divalent metal ions from an aqueous source phase across an organic liquid membrane into an aqueous receiving phase, lipophilic acyclic polyether dicarboxylic acid carriers have an additional advantage that metal ion transport is coupled with the antiport of protons. Thus a pH gradient can be utilized to transport metal ions against their concentration gradients.

We now report the synthesis of a new series of lipophilic acyclic polyether dicarboxylic acids **1–5** (Figure 1) in which the structure of the bridging unit which joins two lipophilic carboxylic acid groups is systematically varied. Although these ligands are designed to have very low solubility in water, their alkaline-earth-metal ion complexation behavior has been assessed in 90% methanol–10% water.

2. Experimental

2.1. REAGENTS

Sources of reagents include: 2-bromodecanoic and 2-bromotetradecanoic acids, Aldrich Chemical Company; magnesium nitrate dihydrate, Junsei Chemical Company; calcium nitrate dihydrate, Kanto Chemical Company; strontium nitrate monohydrate, Shinyo Pure Chemical Company; and tetramethylammonium hydroxide, Fluka Chemical Corporation. The 2-bromodecanoic and 2-bromotetradecanoic acids were dried with benzene and a Dean–Stark trap. Other inorganic and organic compounds were reagent grade and were used as received from commercial suppliers. Deionized water was prepared by passing distilled water through OM-S cartridges.

2.2. PREPARATION OF 2,7-DI-(DODECYL)-3,6-DIOXADIOIC ACID (1)

Under nitrogen, NaH (60% dispersion in mineral oil, 9.08 g, 227 mmol) was washed with dry pentane (3 × 30 mL) to remove the protecting mineral oil and suspended in 100 mL of dry THF at 45 °C. Dry diethylene glycol (2.41 g, 39.0 mmol) in 75 mL of THF was added dropwise during a 1-h period and the mixture was stirred for an additional 2 h. A solution of 2-bromotetradecanoic acid (23.74 g, 78 mmol) in 100 mL of THF was added during a 2-h period and the mixture was stirred for an additional 8 h.

The reaction mixture was allowed to cool to room temperature and was poured into cold 6N HCl (120 mL) in a large beaker (**caution—frothing**). The organic layer was separated from the acidic aqueous layer and concentrated *in vacuo*. The residue was dissolved in benzene followed by azeotropic distillation with a Dean–Stark apparatus to remove the water. The dried organic solution was filtered and cooled to 0 °C for 48 h. Filtration gave 14.10 g (80%) of **1** as a white solid; mp 109–112 °C. IR (Nujol): 3377–2280 (OH); 1720, 1706 (C=O); 1119 (CO) cm^{-1} . $^1\text{H-NMR}$ ($\text{CDCl}_3/\text{DMSO-}d_6$, ca. 10 : 1) δ 0.88 (t, 6 H), 1.10–1.57 (m, 40 H), 1.57–1.90 (m, 4 H), 3.49–3.68 (m, 2 H), 3.68–3.97 (m, 2 H). $^{13}\text{C-NMR}$ ($\text{CDCl}_3/\text{DMSO-}d_6$, ca. 10 : 1) δ 13.34, 21.80, 24.37, 24.49, 28.47, 28.65, 28.78, 31.02, 31.99, 32.15, 68.40, 69.00, 78.17, 78.42, 173.93, 174.13. *Anal. Calcd.* for $\text{C}_{30}\text{H}_{58}\text{O}_6$: C, 69.99; H, 11.36. *Found*: 70.28; H, 11.47.

2.3. PREPARATION OF 2,9-DIOCTYL-3,7-DIOXANONANEDIOIC ACID (2)

The procedure given for the preparation of **1** was followed with NaH (60% dispersion in mineral oil, 4.00 g, 100 mmol) in THF (250 mL), dry 1,3-propanediol (1.28 g, 16.8 mmol) in 20 mL of THF, and 2-bromotetradecanoic acid (10.27 g, 33.4 mmol) in 30 mL of THF. After workup, 6.83 g (77%) of crude product was obtained which was recrystallized from a small amount of hexane to give **2** as a white solid; mp 65 °C. IR (deposit from CDCl_3 solution on a NaCl plate): 3500–2500 (OH), 1714 (C=O), 1115 (CO) cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): δ 0.88 (t, 6 H), 1.18–1.55 (m, 40 H), 1.68–1.88 (m, 4H), 1.88–2.00 (m, 2H), 3.52–3.67 (m, 2 H), 3.67–3.81 (m, 2 H), 3.88 (t, 2 H), 8.0–8.5 (br s, 2 H). $^{13}\text{C-NMR}$ (CDCl_3): δ 14.02, 22.67, 25.13, 25.18, 29.29, 29.34, 29.42, 29.58, 29.63, 29.79, 31.90, 32.50, 32.71, 67.36, 68.26, 78.91, 79.00, 177.48, 177.57. *Anal. Calcd.* for $\text{C}_{31}\text{H}_{60}\text{O}_6$: C, 70.41; H, 11.44. *Found*: C, 70.43; H, 11.37.

2.4. PREPARATION OF 2,9-DIOCTYL-3,8-DIOXADECANEDIOIC ACID (3)

The procedure given for the preparation of **1** was followed with NaH (60% dispersion in mineral oil, 6.56 g, 164 mmol) in 250 mL of THF, dry 1,4-butanediol (2.46 g, 27.3 mmol) in 100 mL of THF, and 2-bromodecanoic acid (13.67 g, 54.5 mmol) in 50 mL of THF. After workup, 9.37 g (80%) of **3** was obtained as a white wax. IR (neat): 3300–2500 (OH), 1702 (C=O), 1131 (C—O) cm^{-1} . $^1\text{H-NMR}$ (CDCl_3):

δ 0.88 (t, 6 H), 1.10–1.60 (m, 24 H), 1.60–1.92 (m, 4 H), 3.38–3.54 (m, 2 H), 3.54–3.77 (m, 2 H), 3.86 (t, 2 H), 9.3–9.9 (br s, 2 H). *Anal. Calcd.* for $C_{24}H_{46}O_6$: C, 66.94; H, 10.76. *Found*: C, 67.19; H, 10.69.

2.5. PREPARATION OF 2,10-DI-(DOEDCYL)-3,6,9-TRIOXAUNDECANEDIOIC ACID (4)

The procedure given for the preparation of **1** was followed with NaH (60% dispersion in mineral oil, 14.0 g, 350 mmol) in 100 mL of THF, dry diethylene glycol (7.43 g, 70 mmol) in 150 mL of THF, and 2-bromotetradecanoic acid (43.02, 140 mmol) in 150 mL of THF. After workup, the crude product was dissolved in dichloromethane. The dichloromethane solution was refluxed with decolorizing carbon for 3 h, dried over magnesium sulfate and evaporated *in vacuo* to provide 31.0 g (82%) of **4** as a white solid; mp 43–45 °C. IR (melt): 3500–2500 (OH), 1750–1721 (C=O), 1131 (C—O) cm^{-1} . 1H -NMR ($CDCl_3$): δ 0.88 (t, 6 H), 1.11–1.57 (m, 40 H), 1.60–1.93 (m, 4 H), 3.60–3.82 (br s, 8 H), 3.87–4.00 (m, 2 H), 10.2 (br s, 2 H). ^{13}C -NMR ($CDCl_3$): δ 14.07, 22.64, 25.15, 29.25, 29.32, 29.42, 29.57, 29.61, 29.64, 31.88, 32.69, 70.24, 70.34, 79.63, 79.72, 176.11, 176.33. *Anal. Calcd.* for $C_{32}H_{62}O_7$: C, 68.78; H, 11.18. *Found*: C, 68.91; H, 11.22.

2.6. PREPARATION OF 3,6-DITHIA-2,7-DIOCTYL-1,8-OCTANEDIOIC ACID (5)

To a solution of 1,2-ethanedithiol (0.75 g, 8.0 mmol) and sodium methoxide (0.86 g, 21.0 mmol) in 50 mL of THF was added slowly a solution of 2-bromodecanoic acid (4.00 g, 16.0 mmol) and sodium methoxide (0.86 g, 21.0 mmol) in 50 mL of THF and the mixture was stirred at reflux for 8 h. The solvent was evaporated *in vacuo* and 50 mL of 3 N HCl was added to the residue. The mixture was extracted with dichloromethane (3 \times 30 mL). The combined extracts were dried over magnesium sulfate and evaporated *in vacuo*. A by-product was removed by distillation of the contaminant from the crude product at 120 °C/0.2 Torr. The desired product (2.05 g, 60%) was obtained as a colorless oily residue in the distillation flask. IR (neat): 1698 (C=O), 705 (C—S) cm^{-1} . 1H -NMR ($CDCl_3$): δ 0.88 (t, 6 H), 1.21–1.50 (br s, 24 H), 1.51–2.00 (m, 4 H), 2.8–3.10 (m, 4 H), 3.31 (t, 2 H), 11.61 (br s, 2 H). ^{13}C -NMR ($CDCl_3$): δ 14.07, 22.63, 27.24, 29.17, 29.28, 30.92, 31.12, 31.78, 46.30, 46.71, 179.54, 179.61. *Anal. Calcd.* for $C_{22}H_{42}O_4S_2$: C, 60.78; H, 9.74. *Found*: 60.83; H, 9.78.

2.7. EQUILIBRIUM CONSTANT DETERMINATIONS

Measurements of pH were made with an Orion Model 701A pH meter which could be read to 0.001 pH unit. The pH meter was standardized against oxalate buffer solution before each titration. For the sample solution, the ionic strength was adjusted to 0.10 M with tetramethylammonium chloride and the temperature was kept at 25.0 ± 0.1 °C.

TABLE I. Protonation constants for iminodiacetic acid.

Protonation constant	This work*	Literature value [7b]
Log K_{H1}	9.40	9.34
Log K_{H2}	2.51	2.55

*An aqueous solution prepared by combining 20.00 mL of 0.01234 M iminodiacetic acid, 5.00 mL of 1.00 M potassium chloride, and 25.00 mL of water was titrated with an aqueous 0.1024 M solution of potassium hydroxide.

Into a thermostated titration vessel equipped with a magnetic stirring bar, a glass combination electrode, and a microburet with 5.0 mL capacity, 50 mL of a 1.00×10^{-3} M solution of the ligand in 90% methanol–10% water (by volume) was introduced. The tetramethylammonium hydroxide titrant concentration was 2.03×10^{-2} M. A nitrogen atmosphere was maintained over the solution during the titration. Titrations were conducted in triplicate and values were reproducible within ± 0.01 pH units. Protonation and stability constants were calculated by the program Best [7a, 8].

3. Results and Discussion

3.1. LIGAND SYNTHESIS

The new lipophilic dicarboxylic acids **1–4** were prepared in 77–82% yields by reaction of the appropriate diols with sodium hydride in tetrahydrofuran followed by the addition of 2-bromodecanoic acid or 2-bromotetradecanoic acid. Lipophilic dithia dicarboxylic acid **5** was synthesized in 60% yield by reaction of 1,2-ethanedithiol with sodium methoxide and 2-bromodecanoic acid in tetrahydrofuran. Structures of ligands **1–5** were verified by ^1H - and ^{13}C -NMR spectra and IR spectra and by combustion analysis. Ligands **1–5** contain two chiral carbon atoms each. No attempt was made to separate the diastereomeric forms of these lipophilic dicarboxylic acids.

In the lipophilic diether dicarboxylic acid series **1–3**, the principal structural variation is increasing the number of methylene groups in the bridge between the two ether oxygens from two to three to four, respectively. In ligand **4**, the bridge has been extended to include five atoms, one of which is an ether oxygen. The lipophilic dithia dicarboxylic acid **5** is structurally related to dioxa dicarboxylic acid **1** by replacement of the two ether oxygens in the former by two sulfide sulfurs in the latter. For the series of new di-ionizable ligands, the change from dodecyl lipophilic groups in compounds **1**, **2**, and **4** to octyl groups in compounds **3** and **5** is deemed to be a minor structural variation.

TABLE II. Protonation constants for lipophilic dicarboxylic acids 1–5 in 90% methanol–10% water at 25.0 °C and $\mu = 0.10$ M.

Protonation Constant*	Ligand 1	Ligand 2	Ligand 3	Ligand 4	Ligand 5
$\log K_{H1}$	6.98 ± 0.12	7.20 ± 0.01	7.26 ± 0.01	7.21 ± 0.01	7.32 ± 0.02
$\log K_{H2}$	6.01 ± 0.11	6.28 ± 0.01	6.28 ± 0.01	6.06 ± 0.02	6.20 ± 0.03

* $\log K_{H1}$ is for the equilibrium $L^{2-} + H^+ \rightleftharpoons HL^-$ and $\log K_{H2}$ is for the equilibrium $HL^- + H^+ \rightleftharpoons H_2L$.

TABLE III. Stability constants for complexation of Mg^{2+} , Ca^{2+} , and Sr^{2+} by lipophilic dicarboxylic acid ligands 1–5 in 90% methanol–10% water at 25.0 °C and $\mu = 0.10$ M.

M	$\log K_{ML}$ *				
	Ligand 1	Ligand 2	Ligand 3	Ligand 4	Ligand 5
Mg^{2+}	3.60 ± 0.03	3.50 ± 0.03	3.14 ± 0.03	3.56 ± 0.05	3.27 ± 0.02
Ca^{2+}	6.39 ± 0.08	4.74 ± 0.18	3.39 ± 0.04	6.21 ± 0.04	3.66 ± 0.03
Sr^{2+}	5.26 ± 0.12	3.51 ± 0.01	3.02 ± 0.04	5.57 ± 0.05	3.16 ± 0.06

* $\log K_{ML}$ is for $M^{2+} + L^{2-} \rightleftharpoons ML$.

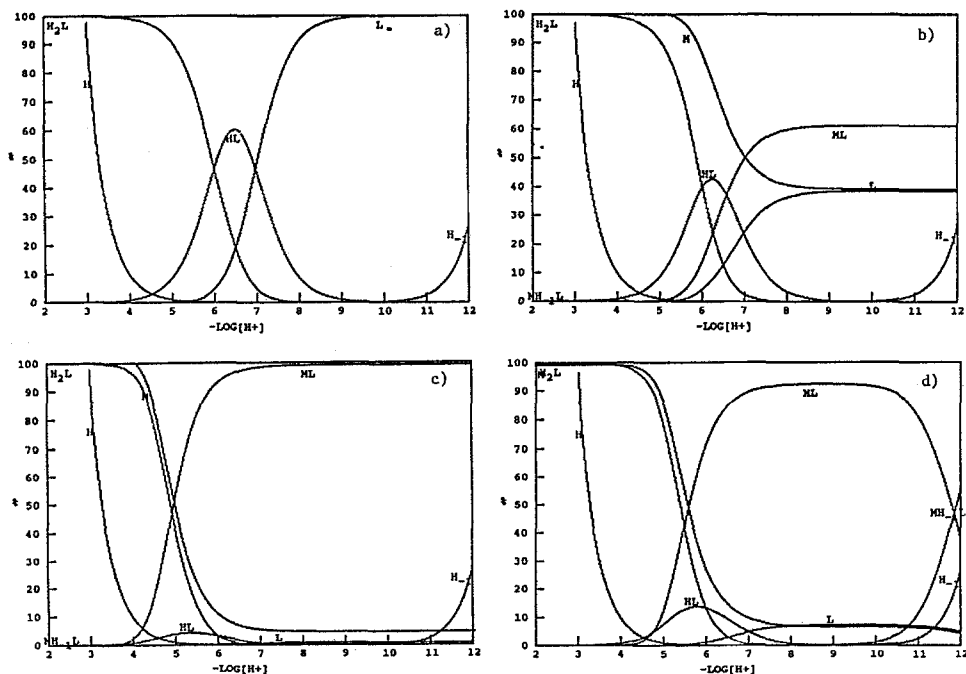


Fig. 2. Distribution of species as a function of $-\log [H^+]$ in systems containing ligand 1 and alkaline-earth-metal cation complexes of ligand 1 at 25 °C and $\mu = 0.10$ M: (a) ligand only; (b) ligand and Mg^{2+} ; (c) ligand and Ca^{2+} ; and (d) ligand and Sr^{2+} .

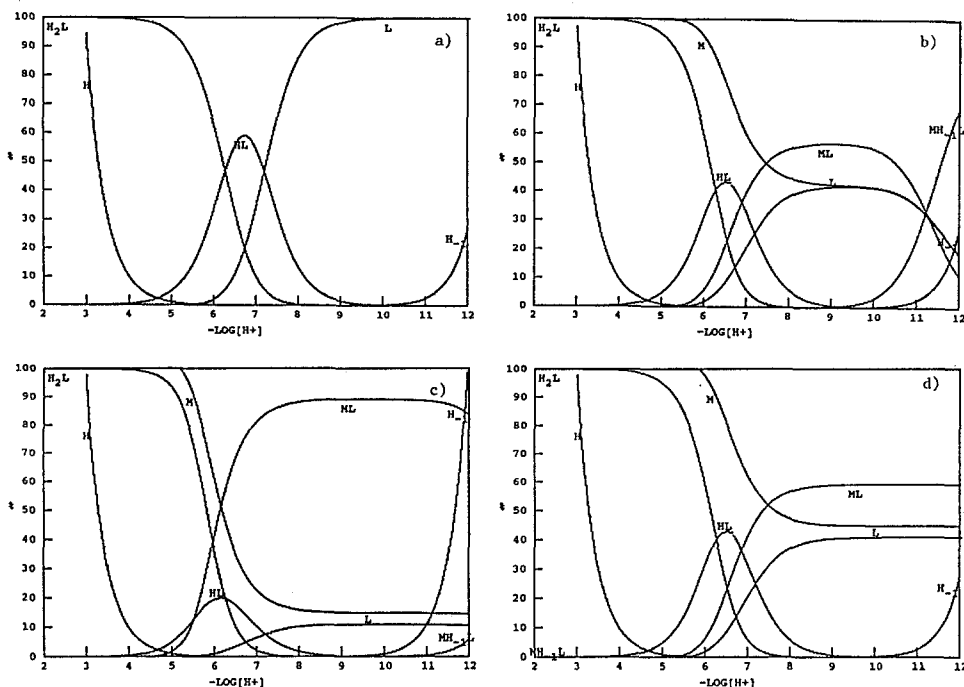


Fig. 3. Distribution of species as a function of $-\log [H^+]$ in systems containing ligand **2** and alkaline-earth-metal cation complexes of ligand **2** at 25 °C and $\mu = 0.10$ M: (a) ligand only; (b) ligand and Mg^{2+} ; (c) ligand and Ca^{2+} ; and (d) ligand and Sr^{2+} .

3.2. PROTONATION CONSTANTS

To establish the accuracy of the potentiometric titration method [7a], protonation constants of iminodiacetic acid in aqueous solution [7b] were determined at 25.0 °C (Table I). The protonation constant values obtained of iminodiacetic acid agree well with the published values [7b].

Due to their high lipophilicity, acyclic dicarboxylic acids **1–5** will have very low solubility in water. Therefore the protonation constants for lipophilic acyclic dicarboxylic acids **1–5** were determined in 90% methanol–10% water (by volume) at 25 °C with $\mu = 0.10$ M. The results presented in Table II reveal that the protonation constants are very similar for the series of compounds **1–5**. Thus variation of the bridging unit which joins the two ether oxygens in dicarboxylic acids **1–3** and the two outer ether oxygens in dicarboxylic acid **4** does not significantly affect the acidity. Also replacement of the two ether oxygens in lipophilic diether dicarboxylic acid **1** with sulfur atoms in ligand **5** has essentially no effect on the protonation constants.

The first protonation constants for the dicarboxylates are about one log unit higher than those for the second protonation steps. This is consistent with reported first and second protonation constants for succinate and malate in water [9].

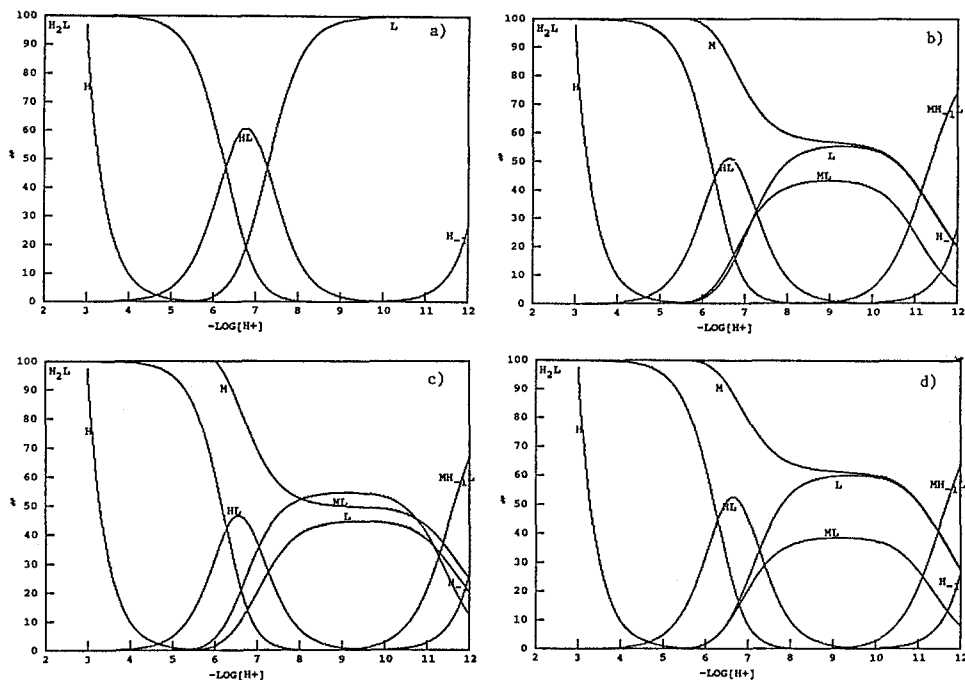


Fig. 4. Distribution of species as a function of $-\log [H^+]$ in systems containing ligand **3** and alkaline-earth-metal cation complexes of ligand **3** at 25 °C and $\mu = 0.10$ M: (a) ligand only; (b) ligand and Mg^{2+} ; (c) ligand and Ca^{2+} ; and (d) ligand and Sr^{2+} .

3.3. STABILITY CONSTANTS

Potentiometric titrations were conducted in 90% methanol–10% water (by volume) at 25 °C and $\mu = 0.10$ M to determine stability constants for the complexation of Mg^{2+} , Ca^{2+} , and Sr^{2+} by the lipophilic dicarboxylic acids **1–5**. The stability constants which are presented in Table III were calculated from the collected data by the program Best [7a, 8].

For lipophilic dioxa dicarboxylic acids **1–3**, the number of methylene carbons which join the two lipophilic carboxylic acid units is systematically varied from two to three to four, respectively. As can be seen from the data in Table III, elongation of the bridging unit which connects the two lipophilic carboxylic acid groups causes a diminution in the stability constants for binding each of the alkaline-earth-metal ion species. The magnitude of this variation is found to be dependent upon the identity of the alkaline-earth-metal cation and decreases in the order $Ca^{2+} > Sr^{2+} > Mg^{2+}$. For lipophilic dioxa dicarboxylic acids **1** and **2**, the stability constants decrease in the order $Ca^{2+} > Sr^{2+} > Mg^{2+}$; whereas with **3**, which has the longest spacer unit, the order is $Ca^{2+} \sim Sr^{2+} > Mg^{2+}$. Clearly, lipophilic dioxa dicarboxylic acid **1** in which the two ether oxygens are connected with an ethylene unit gives the greatest selectivity and strongest binding of Ca^{2+} . Examination of a CPK (Corey–

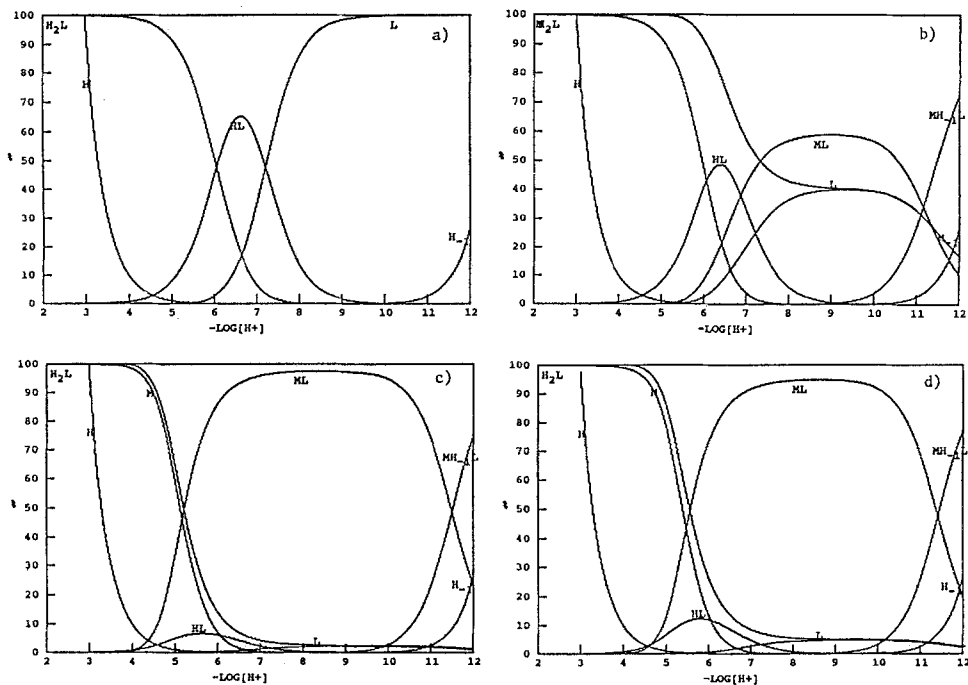


Fig. 5. Distribution of species as a function of $-\log[H^+]$ in systems containing ligand **4** and alkaline-earth-metal cation complexes of ligand **4** at 25 °C and $\mu = 0.10$ M: (a) ligand only; (b) ligand and Mg^{2+} ; (c) ligand and Ca^{2+} ; and (d) ligand and Sr^{2+} .

Pauling–Kortun) space-filling model of **1** reveals that both etheral oxygens as well as one oxygen of each carboxylate group can simultaneously coordinate with Ca^{2+} when the $—OCH_2CH_2O—$ linkage is arranged in a *gauche* conformation. This conformation allows for attractive *gauche* interactions between the two ether oxygens [10].

Lipophilic trioxa dicarboxylic acid **4** has five atoms in the bridging unit which connects the outer ether oxygens. Based upon the results obtained with ligands **1–3**, a five-atom bridging unit would be expected to produce stability constants for alkaline-earth-metal ion complexation even lower than those observed for compound **3**, which has a four-atom bridge. Instead, the stability constants found for ligand **4** are very similar in magnitude to those noted for lipophilic dioxo dicarboxylic acid **1**. (However the Ca^{2+} selectivity for **1** is slightly higher than that of **4**.) Thus the presence of the ether oxygen in the bridging unit of **4** markedly enhances the strength of alkaline-earth-metal ion complexation over that which would be anticipated for an analogous compound with only carbon atoms in the spacer. Two potential explanations for the observed enhancement in metal ion complexation upon incorporation of an ether oxygen as the central atom of a five-carbon bridging unit are apparent. One is increased flexibility of the bridging unit and the second is additional coordination of the metal ion. Examination of a CPK

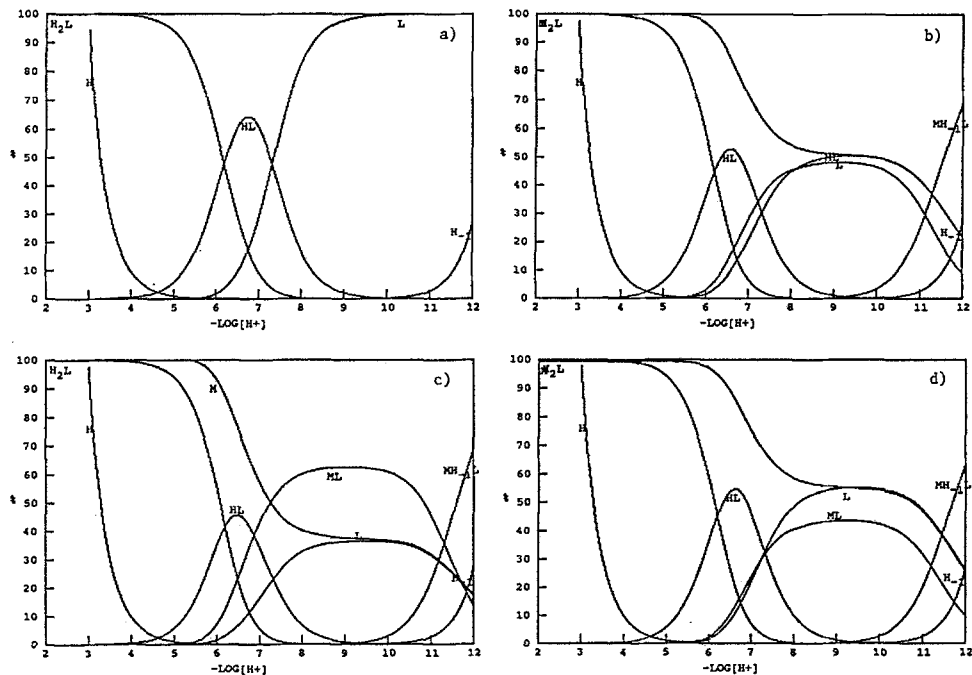


Fig. 6. Distribution of species as a function of $-\log [H^+]$ in systems containing ligand **5** and alkaline-earth-metal cation complexes of ligand **5** at 25 °C and $\mu = 0.10$ M: (a) ligand only; (b) ligand and Mg^{2+} ; (c) ligand and Ca^{2+} ; and (d) ligand and Sr^{2+} .

space-filling model of **4** suggests that the former is more important. When the $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{O}-$ bridging unit adopts a conformation with each pair of terminal and central ether oxygens in a favorable *gauche* arrangement [10], the overall spatial relationship for the two outer ether oxygens and one oxygen of each carboxylate group in **4** is very similar to that found in the dioxa dicarboxylic acid **1**. From the model, it appears that when Ca^{2+} is complexed by these four oxygen atoms the distance from the central oxygen in the bridging unit to the metal ion is significantly greater than those for the four coordinating oxygen atoms.

The primary structural difference between lipophilic dicarboxylic acids **1** and **5** is the replacement of two ether oxygens in the former by two sulfide sulfur atoms in the latter. This structural variation has a pronounced influence upon the alkaline earth-metal cation complexing properties of the two ligands. Thus the strong and rather selective complexation of Ca^{2+} by dioxa dicarboxylic acid **1** changes to much weaker and much less selective complexation of this alkaline-earth-metal cation by dithia dicarboxylic acid **5**. An *anti* conformation is expected for the $-\text{SCH}_2\text{CH}_2\text{S}-$ bridging unit in **5** [10]. In this conformation simultaneous complexation of the metal ion by both carboxylate groups would be impossible. The low stability constant values and the comparatively unselective complexation of the three alkaline earth-metal cations by dithia dicarboxylic acid **5** are very similar

to those noted for dioxa dicarboxylic acid **3**, which has a four-carbon bridging unit. This similarity suggests that the elongated carbon chain bridging unit in **3** makes it very difficult for both carboxylate groups to coordinate with a divalent metal ion at the same time.

3.4. DISTRIBUTION OF SPECIES

From the constants for monoprotonation and diprotonation of the lipophilic dioxa dicarboxylate derived from ligand **1** in 90% methanol–10% water, the distribution of species may be calculated as a function of $-\log [H^+]$. A plot of the distribution of neutral (H_2L), monoionized (HL), and di-ionized (L) ligand as a function of acidity is presented in Figure 2. In this graph, H_{-1} is the percentage of hydroxide ion. By use of both the protonation constants for the dicarboxylate form of **1** and the stability constants for complexation of the alkaline-earth-metal cations by **1**, the distribution of neutral (H_2L), monoionized (HL), and di-ionized (L) ligand and uncomplexed (M) and ligand-complexed (ML) metal cations as a function of $-\log [H^+]$ may be calculated for 1 : 1 solutions of the alkaline earth-metal cation and ligand. Three plots for the distribution of species as a function of acidity for lipophilic dioxa dicarboxylic acid **1** and Mg^{2+} , Ca^{2+} , and Sr^{2+} are also shown in Figure 2. In these graphs, $MH_{-1}L$ is the percentage of $MLOH$ species. When the pH is in the region of 2–4, H_2L is the dominant ligand species in solution. The pH at which ML becomes the dominant ligand species in solution depends upon the identity of the alkaline earth-metal cation and increases in the order: Ca^{2+} (5.1) < Sr^{2+} (5.7) < Mg^{2+} (7.2).

Figures 3–6 contain plots which are calculated from the protonation constants in 90% methanol–10% water for the dicarboxylates derived from ligands **2–5**, respectively, and the stability constants for the complexation of Mg^{2+} , Ca^{2+} , and Sr^{2+} by these lipophilic dicarboxylic acid ligands. The pH ranges over which H_2L and ML are the dominant ligand species in solution are noted to depend upon the identity of both the alkaline earth-metal cation and the ligand.

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