# Complete Conformational Switching in a Calcium Ionophore[11]

Morton Raban,* Darlene L. Burch,[2] Edwin R. Hortelano, and David Durocher

*Department of Chemistry, Wayne State University, Detroit, Michigan 48202*

Daniel Kost*

*Department of Chemistry, Ben Gurion University, Beer-Sheva, 84 105 Israel*

*Received July 29, 1993*•

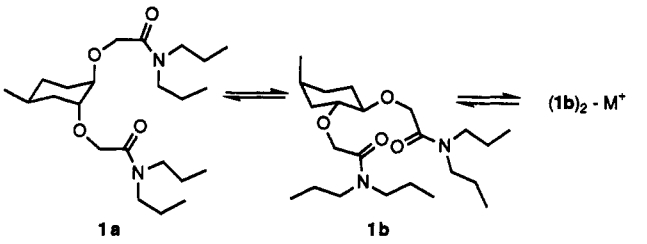
A new, conformationally mobile, ether–amide, calcium ionophore, 1(*S*,*R*),2(*S*,*R*),4(*R*,*S*)-4-Methyl-1,2-bis((*N*,*N*-dipropylcarbamyl)methoxy)cyclohexane, is described. The changes in the conformation of the ionophore were monitored by $^1H$ and $^{13}C$ NMR spectroscopy at room temperature and at low temperature (−90 °C). Examination of conformational effects on NMR spectra allowed a direct determination of 2:1 ionophore-to-cation stoichiometry and facilitated the measurement of the association constant. Conformational monitoring of the difference in complexing ability at room temperature and at −90 °C demonstrated that complexation was more pronounced at room temperature. Less effective complexation was demonstrated for magnesium and potassium ions.

## Introduction

Acyclic ionophores containing amide and ether functionalities have been extensively studied, especially in connection with complexation of alkaline earth cations.[3] Of special importance are the amide ether ionophores developed by Simon and his co-workers which have found important application in calcium-specific ion-selective electrodes.[4] We have shown that conformational biasing of acyclic polyethers offers a powerful tool for direct measurement of the association constants for complexation of metal ions[5] and now describe the application of this approach to the examination of a flipped-out calcium ionophore similar to those studied by the ETH[4] group. In addition, comparison of complexation studies at room temperature with those carried out at low temperature provides evidence about the importance of entropic factors in the complexing ability of this and related ionophores.

Flipped out ionophores such as 1 can exist in two conformations **1a** and **1b** which interconvert rapidly on the NMR time scale at room temperature by ring reversal of the cyclohexane ring (Scheme 1). The favored conformation is **1a** in which the methyl group adopts the equatorial orientation, while the two alkoxy groups are disposed axially. This is a consequence of the much smaller *A* values[6] of alkoxy groups, as compared with methyl, as well as the repulsive dipole–dipole interaction of two equatorial C–O bonds.[7] In this "flipped-out" conformation the two podand substituents are too far apart for the oxygen atoms to surround a metal ion, and as a consequence, this conformation does not exhibit ionophoric properties. In principle, twist conformations are also possible for 1 but should be much less stable in situations such as this when neither very large groups nor diaxial interactions are present. Although the conformation **1b** with equatorial podand groups is less stable than **1a** the energy difference is small and can be overcome by the energy of chelation of a metal ion even in a polar solvent such as methanol. Thus, the introduction of metal salt led to population of conformer **1b** as its metal ion complex. The conformational change is thus a direct consequence of complexation and can be used to monitor the extent of complexation. In this paper we show how NMR spectroscopy can be used to study complexation in these compounds. We describe the consequences of complexation on spectra taken at low temperature, where the interconversion of **1a** and **1b** is slow on the NMR time scale, as well as at room temperature, in which the effect of complexation is evidenced in the averaged spectrum of **1a** and **1b**. Comparison of the results obtained in the two temperature ranges provides information concerning the stoichiometry of complexation and the importance of entropic effects.

**Scheme 1. Interconversion of Noncomplexing Conformer 1a and Complexing Conformer 1b**



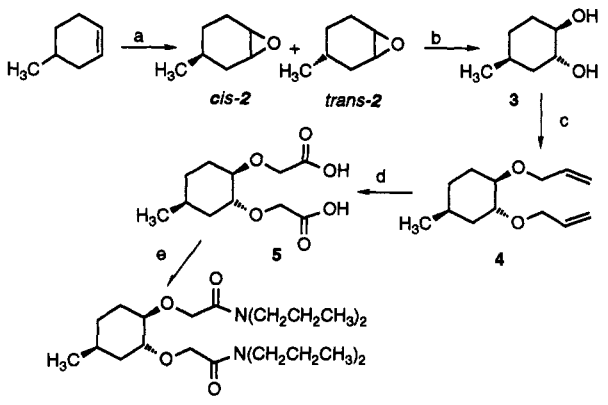

## Results and Discussion

Compound 1 was prepared as illustrated in Scheme 2. The epoxidation of 4-methylcyclohexane appeared to be completely nonstereospecific and led to an equal mixture of the epoxides *cis*-2 and *trans*-2. However, the opening of epoxide under either acidic or basic conditions is stereoconvergent leading to a single isomer for diol 3. The stereoconvergence of the epoxide opening depends on the ability of the methyl substituent to hold each of the

• Abstract published in *Advance ACS Abstracts*, December 15, 1993.
(1) (a) Supported in part by the National Institutes of Health under Grant No. RR08167 and the United States–Israel Binational Science Foundation. (b) This work was abstracted in part from the M.S. Thesis of D.L.B. and the Ph.D. Dissertation of E.R.H.
(2) MARC Graduate Fellow.
(3) (a) Morf W. E.; Ammann, D.; Bissig, R.; Pretsch, E.; Simon, W. In *Progress in Macrocyclic Chemistry*; Izatt, R. M., Christensen, J. J., Eds.; J. Wiley & Sons: New York, 1979; Vol. 1, p 1. (b) Simon, W.; Morf, W. E.; Meier, P. C. *Struct. Bonding* **1973**, *16*, 113.
(4) (a) Ammann, D.; Morf, W. E.; Anker, P.; Meier, P. C.; Pretsch, E.; Simon, W. *Ion-Sel. Electrode Rev.* **1983**, *5*, 3. (b) Anker, P.; Wieland, E.; Ammann, D.; Dohner, R. E.; Asper, R.; Simon, W. *Anal. Chem.* **1981**, *53*, 1970.
(5) (a) Raban, M.; Hortelano, E.; Quin, J., III; King, N.; Koch, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1557. (b) Raban, M.; Quin, J., III; Belguise, A. *Tetrahedron Lett.*, **1991**, *32*, 35.
(6) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*. 199.
(7) Zefirov, N. S.; Gurvich, L.; Shashkov, A. S.; Krimer, M. Z.; Vorobrieva, E. A. *Tetrahedron.* **1976**, *32*, 1211.

0022-3263/94/1959-1283$04.50/0 

**Scheme 2. Preparation of 1(*S,R*),2(*S,R*),4(*R,S*)-4-Methyl-1,2-bis(*N,N*-dipropylcarbamyl)methoxy)cyclohexane**




diastereomeric epoxides, *cis*-**2** and *trans*-**2**, in a single conformation in which the methyl substituent is in a pseudoequatorial orientation. Then the preference for axial attack by nucleophile assures that *cis*-**2** is attacked at C-2, while *trans*-**2** suffers attack at C-1. When the epoxide was opened in acetic acid the intermediate acetoxy alchol was a mixture of constitutional isomers resulting from attack at different carbon atoms in the two diastereomers, but upon basic hydrolysis only a single diastereomer could be detected in the isolated diol.

The diacid was obtained by treatment of the dianion of **3** with allyl bromide affording the bis(allyl ether), which was subjected to ruthenium tetraoxide catalyzed oxidation according to the method of Sharpless and co-workers.[8] Finally, the conversion to the bis(*n*-propyl amide) was accomplished *via* the bis(acid chloride).

Examination of the room-temperature $^1$H NMR spectrum (300 MHz) indicates that this molecule exists predominantly in conformation **1a**. The coupling patterns of the ring methine protons on the carbon atoms bearing the podand side chains are very characteristic of the conformation (Figure 1). In the flipped-out conformation, **1a**, these hydrogens are in an equatorial orientation and are each coupled to three other hydrogens with *gauche* coupling constants. By contrast, in the flipped-in conformation, **1b**, they are axial and are each coupled to two hydrogens with an *anti* coupling constant and one hydrogen with a *gauche* coupling constant. In the room-temperature $^1$H NMR spectrum (Figure 1a) they appear as two quartets at $\delta$ 3.54 and $\delta$ 3.63 with small coupling constants characteristic of equatorial hydrogens ($J$ = 4 Hz). In this flipped-out conformation complexation of calcium ion is not possible since the two ether oxygens lie on opposite sides of the average plane of the cyclohexane ring.

Upon the addition of excess calcium ion, the spectrum changes dramatically. Of particular interest is the portion of the spectrum deriving from the ring methine hydrogens which undergo a change in chemical shift (to resonances centered at $\delta$ 3.85 and $\delta$ 3.63). More informatively, they also suffer a change in the coupling pattern approximated by a triplet of doublets (Figure 1b). The triplet character of the multiplets is evidence for a change in conformation to one in which the two hydrogens are axial. This behavior is in accord with the conclusion that only **1b** can complex

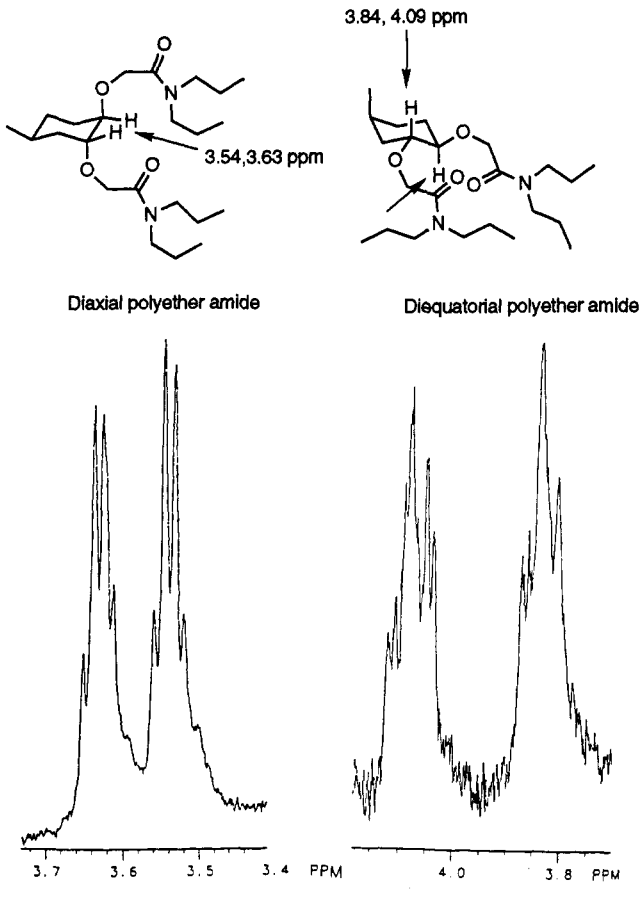



**Figure 1.** Portions of the room-temperature $^1$H NMR spectra of **1**. Left: absence of metal ion (conformation **1a**). Right: after addition of excesCa(SCN)$_2$ (conformation **1b**).

with calcium ion and that addition of metal ion displaces the equilibrium from **1a**, the predominant form in the absence of metal ion, toward **1b**·$M^+$. The change in the appearance of the two multiplets provides good evidence for a conformational change involving two chair forms rather than one involving boat or twist-boat conformers. The large upfield shift in the $^{13}$C spectrum described below provides additional evidence for a chair conformation with an axial methyl group in the presence of excess calcium ion. These results are not surprising since the twist form should be high enough in energy as to be undetectable in these NMR spectra.

The change in conformation can be followed quantitatively using $^1$H NMR spectra measured at low temperature (−90 °C). At this temperature the rate of ring reversal which interconverts conformations **1a** and **1b** is slow on the NMR time scale, while the association/dissociation equilibrium which interconverts **1b** and **1b**·$M^+$ is rapid on the NMR time scale. At this temperature conformation **1a** gives rise to one set of resonances, and another set of resonances is observed for the other conformer **1b** in rapid equilibrium with its metal ion complex (**1b** ⇄ **1b**·$M^+$). In principal, integration of corresponding signals in the low-temperature NMR spectra taken in the absence of metal ion can be used to determine the equilibrium constant $K_{eq}$ which relates the two conformations **1a** and **1b**. As salt is added, the equilibrium is displaced toward the flipped-in conformation as the complex **1b**·$M^+$ is formed by complexation of **1b** with metal ion. Since the ratio of uncomplexed **1a**/**1b** remains constant, the increase in the concentration of the seconc conformation must be entirely due metal ion complex **1b**·$M^+$. The equilibrium constant

(8) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. D. *J. Org. Chem.* 1981, *46*, 3936.

for the complexation of metal ion **1b** ⇄ **1b**·$M^+$ can be obtained from the dependence of integrated intensities upon the amount of added metal ion using eq 1. Here, $K_a$

$$K_a = \frac{(R - K_{eq})(1 + R)}{K_{eq}[M_T(R + 1) - I_T(R - K_{eq})]} \quad (1)$$

represents the association constant for a 1:1 complex, $R$ is the ratio of intensities of signals (**1b**/**1a**) corresponding to the two conformations, $K_{eq}$ is the conformational equilibrium constant (i.e., the ratio, $R$, in the absence of metal ion), $I_T$ is the total concentration of substrate, and $M_T$ is the total concentration of metal ion.

If $K_{eq}$ is greater than ca. 20 it may not be possible to detect the NMR resonances of the minor isomer especially if there is extensive signal broadening at low temperature. In such situations another association constant $K_a' = (K_aK_{eq})$ which is associated with the equilibrium **1a** ⇄ **1b** can be determined. Rearranging and simplifying eq 1 leads to eq 2.

$$K_a' = K_aK_{eq} = \frac{R}{[M_T - (R\,I_T/(1 + R))]} \quad (2)$$

Similar equations can be derived for other stoichiometries. In the present case we evaluated data for the complexation of calcium ion by 1 both in terms of 1:1 and 2:1 ionophore to metal ion stoichiometries. For the 2:1 stoichiometries eq 3 and 4 take the place of eqs 1 and 2.

$$K_a(2{:}1) = \frac{R(R + 1)^2}{K_{eq}{}^2 I_T[2M_T(R + 1) - I_T R]} \quad (3)$$

$$K_a'(2{:}1) = K_aK_{eq}{}^2 = \frac{R(R + 1)^2}{I_T[2M_T(1 + R) - I_T R]} \quad (4)$$

The ring methine protons, which signal the conformational change in the room-temperature $^1$H NMR spectra, provide the most useful probe for quantitative analysis of metal ion complexation in the low-temperature (−90 °C) spectra (Figure 2). In the absence of metal ion two singlets are observed at $\delta$ 3.58 and $\delta$ 3.62 which correspond to conformation **1a**. (The broadening at low temperature prevents the observation of the characteristic vicinal coupling observed at room temperature.) Addition of metal ion results in the decline of these resonances and appearance of two new peaks at $\delta$ 3.66 and $\delta$ 3.92 which are considerably broader because of the greater coupling constant characteristic of axial hydrogens. When intermediate amounts of metal ion are added we observe two broad peaks, a single broad peak which includes both of the equatorial methine hydrogens in **1a** and one of the methine hydrogens in **1b**, and a second less intense peak corresponding to the other methine hydrogen of **1b**. It is difficult to tell exactly when the conformational change becomes complete, but it is clear that some **1a** remains in the spectrum corresponding to 0.64 mol of $Ca(SCN)_2$. The change in conformation does appear to have become essentially complete before 1 mol of $Ca(SCN)_2$ has been added for each mole of ionophore present. Examination of the spectra also indicates a change in the chemical shift of the down field methine signal arising from **1b**. Initially this resonance appears at $\delta$ 3.6 but after about 0.6 mol of salt have been added begins to shift further downfield to $\delta$ 3.9.

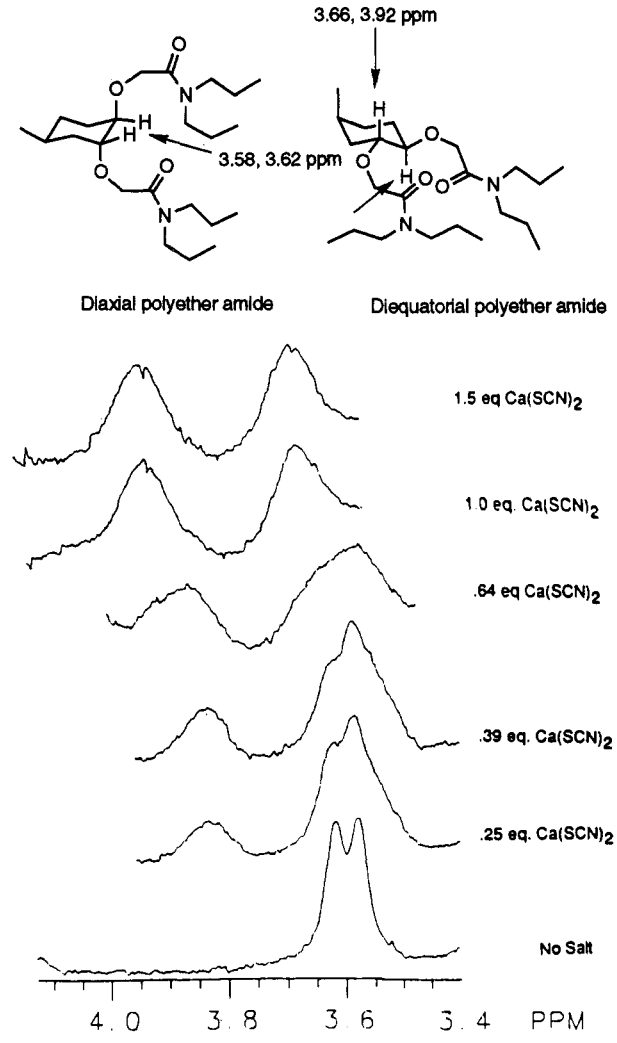



**Figure 2.** Low-temperature NMR spectra of 1 in the presence of varying amounts of $Ca(SCN)_2$.

These observations are best interpreted in terms of the initial formation of a 2:1 ionophore to metal ion complex. Definitive evidence for this stoichiometry is obtained from room-temperature $^{13}$C NMR data which are discussed below. The 2:1 stoichiometry has also been observed in the solid state for closely related amide ether calcium ionophores.[9] Apparently, the downfield resonance in the 2:1 complex appears at $\delta$ 3.6, and then as the metal ion concentration is increased the peak shifts as a 1:1 complex is formed. By the time 1.0 equiv of metal ion is present this chemical shift change is complete and we attribute the peak at $\delta$ 3.9 to the 1:1 complex.

Integration of a series of spectra of 1 in the presence of increasing amounts of metal ion was performed. Two separate experiments each with spectra taken at five different metal ion concentrations were carried out. The data were analyzed using the appropriate equation for 2:1 stoichiometry (eq 4) and furnished an association constant of $K_a(2{:}1) = 3 \times 10^3$ (experiment 1, $K_a = 3.1 \times 10^3$ mol$^{-2}$; experiment 2, $K_a = 2.7 \times 10^3$ mol$^{-2}$). A similar experiment with magnesium chloride showed that this ion is much less effectively bound by 1. Even after 2 mol of magnesium ion per mol of ionophore had been added more than two-thirds of the ionophore was still in the flipped out

(9) (a) Dobler, M. *Ionophores and their Structures*; J. Wiley & Sons: New York, 1981. (b) Neuper-Laves, K.; Dobler, M. *Helv. Chim. Acta* **1977**, *60*, 1861.

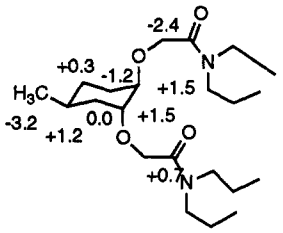



**Figure 3.** $^{13}C$ chemical shift changes upon addition of excess calcium ion.

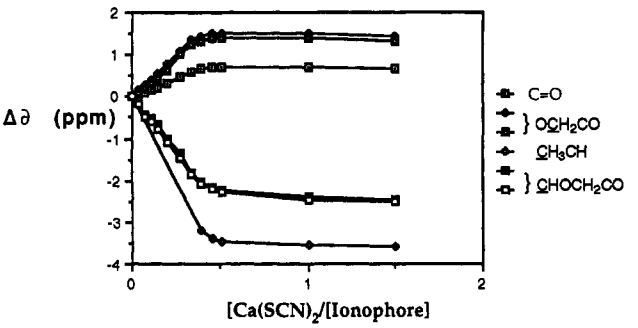



**Figure 4.** $^{13}C$ chemical shift changes vs metal ion concentration.

conformation. Application of eq 4 indicated that the equilibrium constant was smaller than that for calcium by nearly two powers of 10 ($K_s(2:1) = 9 \times 10^1$).

The extent of complexation can also be effectively monitored using room-temperature $^{13}C$ NMR spectroscopy. Addition of calcium thiocyanate results in chemical shift changes for a number of carbon atoms. The chemical shift changes resulting from the addition of excess calcium ion are summarized in Figure 3. It is noteworthy that significant shifts are observed for the carbons of the cyclohexane ring although they are remote from the site of complexation. Indeed, the largest shifts are the upfield shifts observed for the methyl substituent and the methylene group to which it bears a $\gamma$ relationship. It is clear that these shifts are best interpreted in terms of the conformational change which results from complexation rather than from any direct electronic effect of the calcium ion. In the flipped out form of the ionophore the equatorial methyl group is in an *anti* relationship with the ring methylene carbon. When complexation occurs the methyl group becomes axial and has a $\gamma$-*gauche* relation to the methylene group. Such upfield shifts attributed to $\gamma$-*gauche* effects are quite well known. Since the methyl group is so remote from the site of complexation and the shift seems solely due to the conformational change, we are justified in assuming that the chemical shift change upon complexation should be independent of the identity of the metal ion. Thus, complete complexation by other metal ions should result in essentially the same shift. Not surprisingly, the shifts observed for addition of calcium chloride were identical to those resulting from addition of an equivalent amount of calcium thiocyanate. On the other hand addition of KSCN resulted in much smaller shifts; 1.5 mol of KSCN resulted in a shift of the axial methyl group of only 0.5 ppm assuming that this shift is entirely the result of complexation it corresponds to only 15% of the effect seen with 0.5 mol of calcium ion.

Plots of the chemical shift changes for the most sensitive carbon atoms as a function of added salt (Figure 4) all feature end points at the addition of 0.5 mol of added $Ca(SCN)_2$. This provides convincing evidence for the existence in solution of the 2:1 stoichiometry which has been observed in the solid state for calcium complexes of similar ligands.[10] The very small upfield shifts that are observed after the conformational change is complete provide an indication that medium and dielectric constant effects from the added salt are not of great importance. It is also clear from these results that the change from 2:1 to 1:1 complexation which we may infer at higher salt concentrations has a negligible effect when compared with the effect of the conformational change.

These plots also indicate that the formation of the complex is essentially quantitative at room temperature although more metal ion is required to complete the conformational change at low temperature. The greater complexing power of **1** at room temperature is due to a positive entropy for complexation. This phenomenon which has been termed the "chelate effect" can be ascribed to the greater translational entropy of the solvating methanol molecules which are displaced by the ligand.[11]

## Experimental Section

Room-temperature $^1H$ NMR spectra were measured at 300 MHz and $^{13}C$ NMR spectra were measured at 75.48 MHz on a GE QE-300 spectrometer in $CDCl_3$. $^1H$ chemical shifts are expressed in $\delta$ (ppm)referenced to internal tetramethylsilane. $^{13}C$ chemical shifts are reported in $\delta$ (ppm) measured relative to the center resonance of $^{13}CDCl_3$ resonance at 77.000 ppm. Variable-temperature $^1H$ NMR spectra were measured at 300 MHz on a GE NT-300 spectrometer in $CD_3OD$ solvent. $^{13}C$ NMR peak assignments were supported by DEPT and/or APT spectra. Melting points were measured on a Thomas Hoover Unimelt capillary melting point apparatus and are uncorrected. Elemental analysis was performed by Midwest Microlab.

**4-Methyl-1,2-cyclohexene oxide, 2.** A mixture of 4-methylcyclohexene (39.4 g, 0.41 mol) and trichloroacetonitrile (94.2 g, 0.65 mol) in 500 mL of methylene chloride was stirred and cooled to 0 °C. Hydrogen peroxide (30%, 74.2 g, 0.65 mol), which had been adjusted to pH 7.0 with $K_2HPO_4$, was added dropwise over a period of 45 min, and the mixture was stirred at 0 °C for 3 h. Pentane (1 L) was added and the white precipitate filtered. The filtrate was cooled to −20 °C and filtered again. The pentane was evaporated and replaced with 75 mL of methylene chloride. The yellow solution was extracted with aqueous $Na_2SO_3$, washed with saturated aqueous NaCl, and dried over $MgSO_4$ and the solvent removed by rotary film evaporation. Vacuum distillation (20 °C, 2.5 mmHg) afforded a colorless oil (45.9 g, 62%) which was shown to be a 1:1 mixture of stereoisomers by NMR spectroscopy: $^1H$ NMR ($CDCl_3$) $\delta$ (ppm) 0.85, 0.86 (d, $CH_3$, $J$ = 7.5 Hz), 1.2–2.0 (m, 14H, cyclohexane ring), 3.12, 3.15 (s, 2H, CHO); $^{13}C$ NMR ($CDCl_3$) $\delta$ (ppm) 53.3, 52.3, 51.9, 51.5 (CO), 33.6, 32.6, 29.0, 27.7, 26.5, 25.3, 24.3, 23.4, 22.0, 21.7.

**1(*R,S*),2(*R,S*),4(*S,R*)-4-Methyl-1,2-cyclohexanediol, 3.** The mixture of diastereomeric epoxides **2** (28.0 g, 0.25 mol) was dissolved in 200 mL of glacial acetic acid containing sodium acetate (160 g, 1.18 mol) and allowed to reflux for 72 h. The reaction mixture was added to 200 mL of distilled water and extracted three times with 75 mL of methylene chloride. The combined organic extracts were washed with 10% $NaHCO_3$ and saturate aqueous NaCl, and dried over $MgSO_4$ and the solvent removed by rotary film evaporation. The crude acetoxyalcohol (a mixture of constitutional isomers) was converted to the diol with no further purification. The crude oil was dissolved in 150 mL of 3:1 ethanol/water containing potassium hydroxide (43 g) and the reaction mixture allowed to reflux for 3.5 h. After the mixture was cooled, 100 mL of saturated NaCl was added, and the mixture was extracted seven times with $CH_2Cl_2$. The

(10) (a) Schefer, U.; Ammann, Pretsch, E.; Oesch, U.; Simon, W. *Anal. Chem.* **1986**, *58*, 2282. (b) Neuper-Laves, K.; Dobler, M. *Helv. Chim. Acta* **1977**, *60*, 1861.

(11) Martell, A. E. The Chelate Effect. In *Advances in Chemistry Series*; American Chemical Society: Washington, DC, 1967; p 272.

combined organic extracts were dried over sodium sulfate and the solvent removed by rotary film evaporation yielding a crude oil. The oil was dissolved in hot ethyl acetate, and hexane was added until cloudy. The diol which crystallized upon standing was recrystallized from ethyl acetate/hexane yielding pure **3**, mp 65–66 °C. Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.29; H, 11.10.

**1(*R,S*),2(*R,S*),4(*S,R*)-4-Methyl-1,2-bis(allyloxy)cyclohexane, 4.** Sodium hydride (6.0 g, 0.25 mol) was added slowly at 0 °C to a solution of diol **3** (5.00 g, 0.039 mol) and allyl bromide (22.8 g, 0.19 mol) in 80 mL of dry dimethylformamide. The reaction mixture was allowed to stir for 3 h as it came to room temperature. The reaction mixture was then allowed to reflux for 1 h. After the reaction mixture was cooled to room temperature, 80 mL of water was added and the mixture extracted with two 25-mL portions of ether. Vacuum distillation (68–72 °C, 0.3 mmHg) yielded the product in 84.3% yield: $^{13}$C NMR ($CDCl_3$) δ (ppm) 21.69, 25.2, 26.2, 28.6, 34.4, 69.7, 75.3, 75.6, 116.1, 135.5; $^1$H NMR ($CDCl_3$) δ (ppm) 0.89 (d, $J$ = 7.0 Hz, 3H), 1.33 (m, 1H), 1.40 (m, 2H), 1.76 (m, 4H), 3.45 (q, $J$ = 5.0 Hz, 1H) 3.65 (q, $J$ = 5.5 Hz, 1H), 4.08 (m, 4H), 5.25 (d, 10.0 Hz, 2H), 5.29 (dd, $J$ = 2.5 Hz, $J$ = 18.5 Hz, 2H), 5.9 (m, 2 H).

**1(*R,S*),2(*R,S*),4(*S,R*)-4-Methyl-1,2-bis(carboxymethoxy)-cyclohexane, 5.** Diallyl ether **4** (2.14 g, 0.010 mol) and sodium periodate (17.9 g, 0.84 mol) were dissolved in a mixture of 40 mL of carbon tetrachloride, 40 mL of acetonitrile, and 60 mL of water. The mixture was stirred vigorously, and a catalytic amount of $RuCl_3 \cdot 3H_2O$ (0.28 g, 0.001 mol, 2 mol %) was added. The reaction mixture was allowed to stir for 16 h, and then 10 mL of methylene chloride was added. The organic layer was separated, and the aqueous layer was extracted three more times with methylene chloride. The combined organic extracts were dried over magnesium sulfate and the solvent removed by rotary film evaporation. The residue was dissolved in ether and filtered through a Celite pad. The ether was removed by rotary film evaporation and the oily residue taken up in aqueous sodium bicarbonate. After the residue was washed with chloroform the aqueous extract was acidified with concd hydrochloric acid and extracted with ether. The oil product (1.9 g, 30.5%) was recrystallized from chloroform (mp 139–140 °C): $^1$H NMR ($CDCl_3$) δ units 0.99 (d, $J$ = 7.4 Hz), 1.4–2.0 (m, 7H), 3.54 (m, 2H, CHO), 4.2 (overlapping AB quartets, 4H, $OCH_2COOH$, $J_{AB}$ = 17.2 Hz), 7.41 (broad, 2H); $^{13}$C NMR ($CDCl_3$) δ units 14.56, 19.41, 42.27, 26.16, 28.21, 34.19, 65.4, 65.91, 76.37, 77.73, 79.49, 173.40, 173.43; exact mass calcd for M − $H_2O$ 228.0998, found (EI) 228.099.

**1(*S,R*),2(*S,R*),4(*R,S*)-4-Methyl-1,2-bis(N,N-dipropylcarbamyl)methoxy)cyclohexane, 1.** The diacid **5** (2.5 g, 0.010 mol) was added to a solution of thionyl chloride (11.3 g) in 100 mL of dry methylene chloride and the solution stirred for 8 h. The solvent was removed by rotary film evaporation. Three 100-mL portions of dry benzene were added and removed under reduced pressure to remove any remaining thionyl chloride. The crude acid chloride was taken up in dry methylene chlorde, and dipropylamine (8.8 g, 0.62 mol) was added and allowed to react at room temperature for 18 h. The reaction mixture was extracted three times with 1 N HCl, three times with saturated sodium bicarbonate, and one time with brine. The organic layer was dried over sodium sulfate and then allowed to stand for 24 h over 3-Å molecular sieves before the solvent was removed by rotary film evaporation yielding diamide **1** (50%): $^1$H NMR δ (ppm) 0.90 (m, 9H), 1.59 (m, 10H), 1.77 (m, 5H), 3.35 (m, $NCH_2$–, 8H), 3.57 (m, $OCH_2$–, 1H), 3.66 (m, OCH, 1H), 4.21 (overlapping AB quartets, $OCH_2$–, 4H); $^{13}$C NMR δ (ppm) 11.12, 11.28, 20.57, 21.53, 21.96, 24.96, 26.11, 28.52, 34. 10, 47.25, 48.58, 68.39, 68.50, 76.62, 76.84, 168.99; exact mass calcd for **1** 412.33011, found 412.3298.