lution of 0.20 mL (2.33 mmol) of isopropenyl bromide in 5 mL of ether was cooled to −78 °C, whereupon 2.25 mL of 2.0 M *tert*-butyllithium was added via syringe. After 1 h at −78 °C the solution of isopropenyllithium was transferred via cannula into a precooled (−78 °C) slurry of 218 mg (1.15 mmol) of copper(I) iodide in 5 mL of ether. The solution was warmed to −40 °C and 250 mg (1.03 mmol) of epoxy acetate **17b** in 5 mL of ether was slowly added. After stirring at −40 °C for 1 h the reaction mixture was quenched with 2 mL of saturated aqueous NH_4Cl. The separated organic layer was washed with three 10-mL portions of 10% aqueous NH_4OH followed by 10 mL of water and brine. Drying ($MgSO_4$) and removal of the solvent under reduced pressure gave 270 mg of a crude oil, which was purified via column chromatography on silica gel with 10% ethyl acetate–hexane to afford 35 mg (13%) of **26** and 120 mg (44%) of acetate **24b** contaminated with a small amount of epoxy acetate **17b**. **24b**: IR (film) 2900, 1780, 1740, 1380, 1250, 1020, cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.20 (dd, 1 H, J = 4.5, 7.8 Hz, CHOAc), 5.00–4.70 (m, 4 H, CH_2=C), 4.26 (q, 1 H, J = 6.0 Hz, lactone carbinyl), 3.00–2.20 (m, allylics), 2.08 (s, 3 H, CH_3CO_2), 1.79, 1.73 (2 br s, vinyl CH_3's); MS, calculated for $C_{15}H_{22}O_4$ m/e 266.1519, found m/e 266.1507.

***rel*-(3*R*,5*S*)-6-Methyl-5-hydroxy-3-[*rel*-(1*S*)-1-hydroxy-3-methyl-3-butenyl]-5-heptenoic Acid γ-Lactone Tetrahydropyranyl Ether (24d).** A solution of 5.0 mL of 0.5 M isopropenyllithium in ether was slowly added to a precooled (−78 °C) slurry of 225 mg (2.50 mmol) of copper(I) cyanide in 25 mL of ether. The reaction was warmed to −60 °C whereupon a solution of 95 mg (0.317 mmol) of epoxy ester **17d** in 5 mL of ether was added. The reaction mixture was stirred at −60 °C for 90 min, a solution of 5 mL of saturated aqueous NH_4Cl was added, and the reaction was allowed to reach room temperature. The separated organic layer was washed with three 10-mL volumes of 10% aqueous NH_4OH followed by 10 mL of water and brine. Drying ($MgSO_4$) and removal of the solvent under reduced pressure afforded 110 mg of crude product, which was chromatographed on silica gel with 15% ethyl acetate–hexane to furnish 60 mg (61%) of lactone **24d**: IR (film) 3050, 2900, 1780, 1630, 1460, 1380, 1030, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.89 (m, vinyl CH's), 4.30–3.20 (br m, carbinyl protons), 2.80–2.00 (m, allylics), 1.82, 1.78 (2 br s, vinyl CH·s), 1.80–1.00 (m, aliphatics).

Methyl *rel*-(3*R*)-(5*E*)-3-[*rel*-(1*S*)-1,2-Epoxyethyl]-6,8-dimethyl-5,8-nonadienoate (25) and *rel*-(3*R*)-(5*E*)-3-[*rel*-(1*S*)-1-Hydroxy-3-methyl-3-butenyl]-6,8-dimethyl-5,8-nonadienoic Acid γ-Lactone (26). A solution of 0.55 mL (6.19 mmol) of isopropenyl bromide in 10 mL of ether was cooled to −78 °C, whereupon a solution of 5.0 mL of 2.5 M *tert*-butyllithium was added via syringe. After 1 h at −78 °C this yellow solution was transferred via cannula into a precooled (−78 °C) slurry of 556 mg (6.25 mmol) of copper(I) cyanide in 30 mL of ether and the reaction mixture was warmed to −40 °C. A solution of 200 mg (0.781 mmol) of acetate **17b** in 10 mL of ether was added and the reaction was stirred between −40 and −20 °C for 3 h. The solution was then warmed to 25 °C and quenched with 5 mL of saturated aqueous ammonium chloride. The separated organic layer was washed with three 10-mL portions of 10% aqueous NH_4OH followed by 10 mL of water and brine. Drying ($MgSO_4$) and removal of the solvent under reduced pressure afforded ca. 210 mg of crude product which was chromatographed on silica gel with 10% ethyl acetate–hexane to afford 130 mg (65%) of recovered **17b**, 47 mg (24%) of S_N2' product **25**, and 18.4 mg (10%) of bis adduct **26**. **25**: IR (film) 2900, 1740, 1640, 1440, 1380, 1260, 1200, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.20 (br t, 1 H, CH=C), 4.77 (m, 2 H, CH_2=C), 3.68 (s, 3 H, CH_3O), 3.00–2.00 (m, allylics and epoxide), 1.65, 1.60 (2 br s, vinyl CH_3's); *MS*, calculated for $C_{14}H_{22}O_3$ m/e 238.1570, found m/e 238.1558. **26**: IR (film) 2900, 1780, 1640, 1440, 1210, 1070, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.22 (m, 1 H, CH=C), 4.91–4.60 (m, 4 H, CH_2=C), 4.18 (br q, 1 H, lactone carbinyl), 2.80–2.00 (m, allylics), 1.81, 1.69, 1.60 (3 br s, vinyl CH_3's); MS, calculated for $C_{16}H_{24}O_2$ m/e 248.1777, found m/e 248.1760.

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Registry No. 1, 88376-85-6; **2**, 88376-86-7; **3**, 88376-87-8; **4**, 88376-88-9; **5**, 88376-89-0; **7**, 88376-90-3; **8**, 88376-91-4; **9**, 88376-92-5; **10**, 88376-93-6; **11**, 88376-94-7; **12**, 88376-95-8; **13**, 88376-96-9; **14**, 88376-97-0; **16b**, 88376-98-1; **16c**, 88376-99-2; **17a**, 88377-00-8; **17b**, 88377-01-9; **17c**, 88377-02-0; **17d**, 88377-03-1; **18**, 88377-04-2; **19**, 88377-05-3; **20**, 88377-06-4; **21**, 88424-24-2; **22**, 88424-25-3; **23**, 88377-07-5; **24a**, 88377-11-1; **24b**, 88377-08-6; **24d**, 88377-09-7; **25**, 88377-12-2; **26**, 88377-10-0; $(CH_2$=$C(CH_3))_2CuCNLi_2$, 87136-18-3; CH_2=$C(CH_3)CuCNLi$, 88391-95-1; $(CH_2$=$C(CH_3))_2CuLi$, 21329-14-6; CH_2=$C(CH_3)Br$, 557-93-7; propargyl bromide, 106-96-7; methacrolein, 78-85-3.

Synthesis of Lipophilic 18-Crown-6 Diacids for the Membrane Transport of Alkaline-Earth Cations

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The synthesis of three different types of lipophilic 18-crown-6 diacids is described. A didecyl crown ether 2,3-diacid (**1**) was prepared as a minor product from a diiodide precursor (**12**) and *threo*-11,12-docosanediol by thallous ethoxide cyclization. The major nonpolymeric products resulted from elimination followed by cyclization to give 15-crown-5 derivatives. A crown ether 11,12-diamide 2,3-diacid (**4**) was prepared by a similar route involving cyclization of a benzyl protected precursor (**26**) and *N,N,N′,N′*-tetramethyltartaramide (**9**). Isomeric syn and anti 2,11(12)-diamide 3,12(11)-diacid derivatives **6** and **7** were prepared from the known crown ether bisanhydride **8** and alkylamines. The product mixture was separated by chromatography, and the isomers were identified by comparison of acidity and stability constants for complexation with those of closely related syn/anti crown ether acids.

The transport of ionic species through membranes is of central importance in biological systems and has an increasing role in the development of practical separation schemes. Several transport mechanisms have been proposed and demonstrated in natural and artificial systems. Of these, coupled transport mediated by mobile carriers (ionophores) presents one of the simplest mechanisms for the selective removal of a specific ion from a dilute solu-

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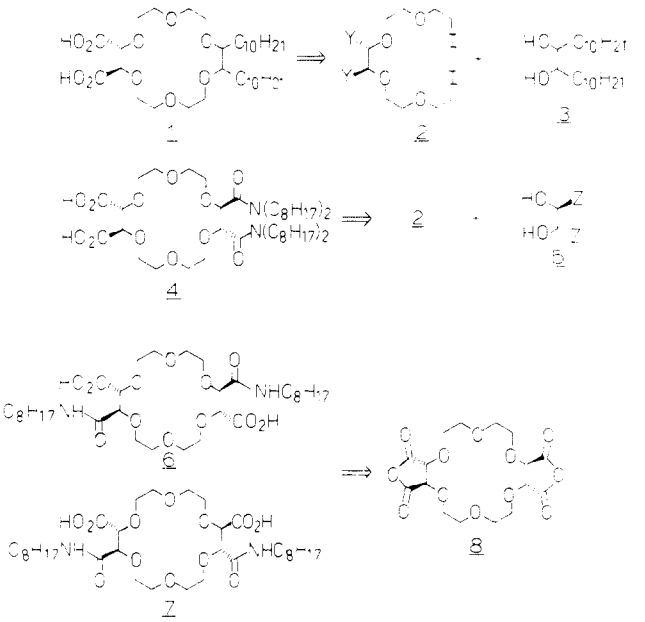
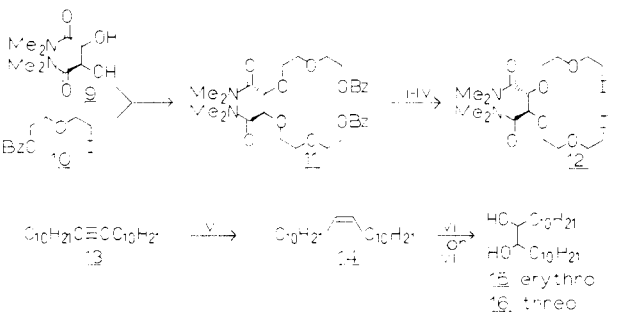
tion.[1] Such a system utilizes the flux of one ion moving down its concentration gradient to drive the transport of the desired ion up its concentration gradient. Typically the "driving" gradient is due to protons: cations move by *countertransport* from basic to acidic solution, while anions move by *cotransport* from acidic to basic solution. Cation–proton-coupled countertransport has been demonstrated by using many of the carboxylate ionophore antibiotics[2] in natural and artificial systems. Thus, sodium is pumped from basic to acidic solution through a supported octanol membrane containing the sodium specific antibiotic monensin.[3] Similarly calcium is transported by lascalocid (X 537-A) and calcimycin (A 23187) across bulk liquid membranes and from vesicles.[4-7] With such systems as models, we have prepared synthetic crown ether carboxylic acids that have been shown to act in an entirely analogous fashion for the transport of alkali-metal cations.[8,9] The synthetic system moreover allows control of carrier specificity, lipophilicity, and shape through directed synthesis and has permitted a detailed examination of the extraction and transport process.[10]

We are interested in extending the cation–proton countertransport strategy to separations of divalent ions, and as a first step, we chose to examine the transport of alkaline-earth cations. Crown ether derivatives are known to complex and extract divalent metal ions into organic solvents[11] and have been shown to mediate the anion-dependent passive (down a concentration gradient) transport of divalent ions across artificial membranes.[12,13] Cation–proton countertransport of alkaline-earth cations has been examined in a variety of systems. Solvent polymeric membranes incorporating lipophilic diamides and weak acids transport divalent ions under the influence of a pH gradient.[14] Synthetic acyclic ionophores modeled on lascalocid and calcimycin also transport calcium across bulk liquid membranes[15] as do diazacrown ether carboxylates.[16] All these systems utilize mono basic carriers. Both the passive and coupled countertransport of Zn^{2+} and Cu^{2+} utilizing a range of common cation complexones and surfactants as carriers have been reported.[17-21] All systems studied to date involve the formation of 2:1 complexes within the membrane phase.

Scheme I



Scheme II. Synthesis of Precursors of 1[a]



[a] Reagents: i, TlOEt/DMF; ii, H_2/10% Pd-C; iii, PBr_3; iv, NaI/acetone; v, H_2/Lindlar catalyst; vi, (1) KIO_3/I_2/acetic acid, (2) KOH/CH_3OH; vii, (1) H_2O_2/HCO_2H, (2) KOH/CH_3OH.

Our synthetic goal was to design and prepare crown ether derivatives that would be capable of binding divalent (alkaline earth) cations and that could form monomeric, neutral lipophilic complexes for the transport of divalent ions, utilizing two-proton exchange to drive the process. Candidate carriers bearing two carboxylic acid groups on the crown ether periphery were therefore considered. Previous studies suggested that ion extraction could occur with as little as one octyl group per charge to provide liposolubility[9] although additional, or longer alkyl groups, would be expected to enhance extraction. In order to achieve simple syntheses from materials of known configuration, the structures **1**, **4**, **6**, and **7** (Scheme I) were selected as targets. Each carrier, as the dianion, was expected to form neutral salt complexes with divalent cations. Structural permutations within the group include the relative dispositions of the carboxylates, increasing lipophilicity, and overall shape. Ultimately all chiral centers except those of **3** could be derived from tartaric acid derivatives **5**, **2**, and the known anhydride **8**.[22] Se-

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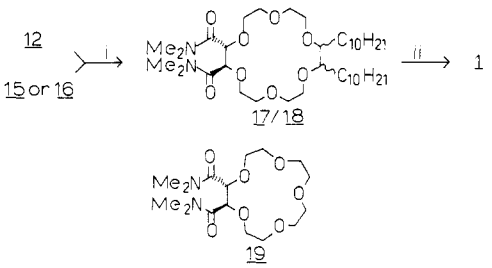
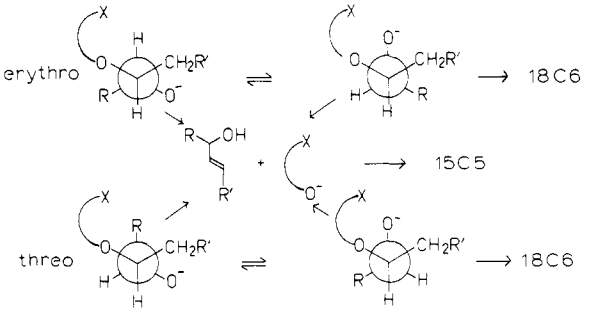
Scheme III. Synthesis of 1[a]



[a] Reagents: i, TlOEt/DMF; ii, 1 M HCl/dioxane.

Scheme IV. Conformations of Half-Reacted 12



lective opening of 8 with amines to give syn (6) and anti (7) isomers has been reported for related compounds and product stereochemistry has been described.[23,24]

Results and Discussion

Synthesis of Carrier 1. The synthesis of 1 as given in Scheme I requires the closure of precursor 2 and the diol 3 to form the crown ether. We anticipated utilizing the dithallium salt of the diol and a diiodide as in previous and related cases.[8,22] A compound of type 2, i.e., 12 (Scheme II), has been prepared by Lehn and co-workers from tartaramide (1 equiv) and diethylene glycol diiodide (2 equiv) as a mixture with monoalkylated product.[22] Our directed synthesis of this same precursor is outlined in Scheme II. Diethylene glycol was monoprotected with benzyl bromide and the remaining hydroxyl was converted to the chloride and thence to the iodide 10. The dithallium salt of *N,N,N′,N′*-tetramethyltartaramide (9) was prepared as a slurry in DMF and treated with 10 to give, on simple extractive workup, the bis(benzyl ether) 11 in 50% yield. Experience showed that extensive chromatography at this and subsequent stages could be avoided provided the extractions were closely controlled. This is due to the convient hydrophilic/hydrophobic balance of 11, 12, and related compounds. Hydrogenolysis of the benzyl ethers and bromination with PBr_3 gave a readily characterized dibromide, which was converted to 12 by halide exchange. The overall yield of 35% (based on 9) compares with the reported yield of 29% (also based on 9) reported by Lehn and co-workers. The present method is somewhat more easily controlled on a large scale and avoids extensive chromatography.

The other half of the desired crown ether was prepared from 11-docosyne (13) (ultimately from decyl bromide and acetylene) via catalytic semihydrogenation to a 90:10 mixture of (*Z*)- and (*E*)-11-docosenes (14). The mixture was oxidized under two sets of conditions: I_2, IO_3^-, acetic acid[25] to give predominantly the *erythro*-diol 15 by net syn addition and performic acid epoxidation and hydrolysis[26] to give predominantly the threo diol 16 by net anti addition. Diastereomers 15 and 16 were readily separated by fractional crystallization.

As outlined in Scheme III, the cyclization of 12 with 15/16 gave the desired crown ethers 17/18, albeit with some unexpected complications. Cyclizations with erythro diol 15 gave only the 15-crown-5 derivative 19.[8] Examination of all other fractions failed to provide evidence for any of the desired crown ether although half-cyclized products and short polymers were indicated by NMR and MS. Among the products bearing decyl groups were small amounts of 15 and 16 and a large amount of an allylic alcohol, probably docos-12-en-11-ol (MS, NMR). Acidic treatments of some residues liberated a ketone, probably 11-docosanone (MS, IR, NMR). The "cyclization with contraction" is apparently general: a mixture of 15, thallous ethoxide, and DMF will cyclize pentaethylene glycol diiodide to form the parent 15-crown-5 and tetraethylene glycol diiodide to form the parent 12-crown-4 with formation of the same allylic alcohol. These results may be rationalized as shown in Scheme IV by consideration of the conformations of the half-cyclized diol. For erythro diol 15, conformations with the alkyl groups gauche or eclipsed are required for closure to 18-crown-6 derivatives. The more energetically favorable conformation has the alkyl groups anti and cannot give cyclized product. According to the commonly observed template effect,[22,27] we anticipated that coordination of the thallium ion would shift this unfavorable equilibrium. Apparently this has not occurred or the competing elimination (from either conformation) occurs readily to give the allylic alcohol plus an ω-iodo alkoxide that cyclizes to the 15-crown-5 derivative observed. As a result we have not succeeded in preparing isomers of 1 with syn disposed alkyl groups from the *erythro*-diol 15.

The case of the threo diol 16 is similar with the major products being 19, allylic alcohol, and uncyclized material. However, among the minor products were the two isomeric crown ethers 17 and 18 (differing at C11,12 either *R,R* or *S,S*). Extensive chromatography on a variety of supports allowed isolation of 17 and 18 as a coeluting 1:1 mixture. The conformations in the threo case are shown in Scheme IV for comparison. In this case the energetically favored conformer can lead to 18-crown-6, but either conformer can eliminate. Since we observe cyclization with 16 but not with 15, this suggests a relatively minor role for the thallium ion in templating the reaction. To complete the synthesis, the 17/18 mixture was hydrolyzed in aqueous acid to 1 as a mixture of 11*R*,12*R* and 11*S*,12*S* isomers.

Synthesis of Carrier 4. The synthesis of 4, as sketched in Scheme I, requires two different protecting groups for the carboxylates. We initially envisaged 2 (where Y = ester) coupling with 5 (where Z = amide) to give a precursor to 4 with differentiated protected carboxylic acids. The shortcoming of this approach is that each homologue of 4 would require a unique cyclization step. Additional shortcomings were readily apparent as indicated in Scheme V. The alkylation of diethyl tartrate dithallium salt gave variable mixtures of di-O-alkylated product 20 together with C-alkylated materials such as 21 and 22. The isolation of 20 from these mixtures was tedious and conditions to

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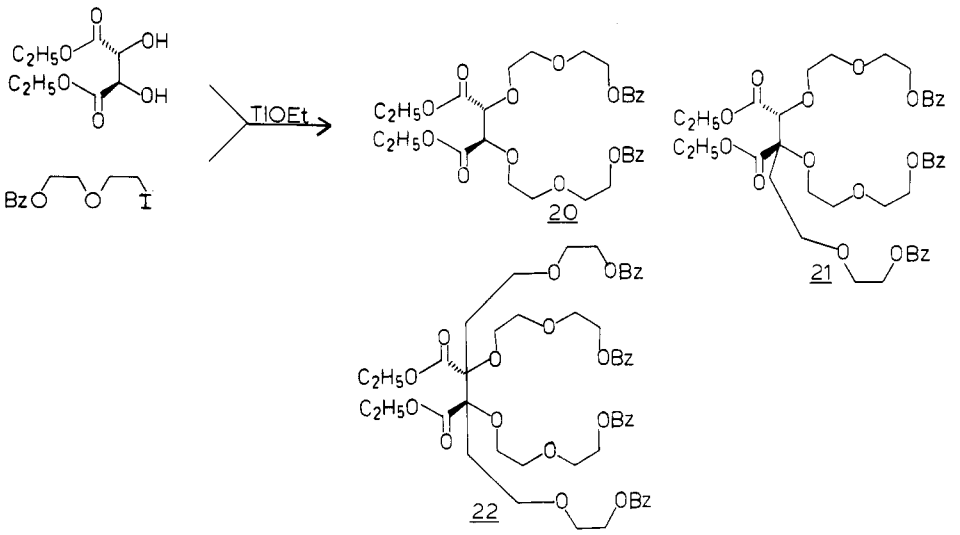
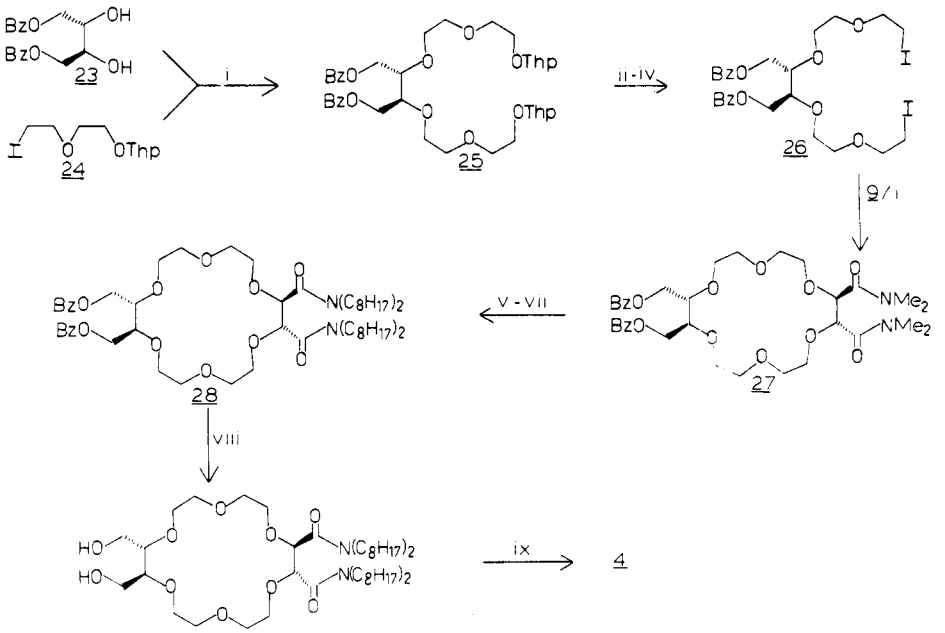
Scheme V. Attempted Coupling with Diethyl Tartrate



Scheme VI. Synthesis of 4[a]



[a] Reagents: i, TlOEt/DMF; ii, HCl (aq)/CH_3OH; iii, $SOCl_2$/pyridine/benzene; iv, NaI/acetone; v, 25% HCl/H_2O; vi, $SOCl_2$; vii, $(C_8H_{17})_2NH$/THF; viii, H_2/10% Pd-C; ix, Jones reagent/acetone.

suppress C-alkylation eluded us. Since the projected final cyclization again involves thallous ethoxide, the yield at that step would also be impaired. Apart from yield, the chiral integrity of the centers α to ester is lost; hence isomeric mixtures must result. This dismal analysis was indeed correct: a small sample of purified **20** was carried to the final cyclization, but the yield of the desired crown ether was very low and accompanied by C-alkylation to give polymeric material.

A more reliable set of differentiated protected carboxylates utilizes the reduced acid groups protected as benzyl ethers. This would permit selective cleavage of an amide (from **5**) on the formed crown ether and hence would lead more simply to a set of homologues. The sequence chosen is outlined in Scheme VI. 1,4-Dibenzyl-L-threitol (**23**) was prepared by literature methods[28-30] and the iodide **24** was prepared from the known chloride.[31] Initial attempts to couple **23** and **24** using alkali-metal bases (NaH, Na metal, *n*-butyllithium) were unwidely due to the gelatinous nature of the disalt of **23**. In contrast, the dithallium salt of **23** in DMF was easily alkylated to give the bis(tetrahydropyranyl ether) **25**. Hydrolysis, conversion to the dichloride, and halide exchange proceeded without incident to give **26**. Thallous ethoxide cyclization of **9** and **26** gave the protected crown ether **27** in 18% yield, which was readily purified by chromatography. Acidic hydrolysis gave a diacid that was converted to a diacid chloride with thionyl chloride and treated with dioctylamine to give **28**. The diamide **28** and all subsequent products are extremely surface active, and initially, losses on chromatography exceeded 80%. Consequently the final few steps were optimized to yield **4** without chromatography. Small samples of purified **28** were hydrogenated and oxidized to

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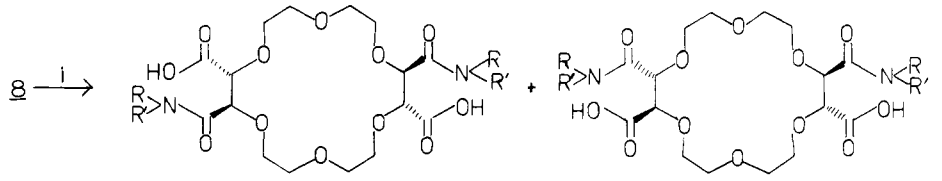
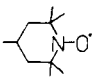
Scheme VII. Syntheses of Diamide/Diacid Crown Ethers[a]



6 R = C_8H_{17} R' = H 7

29 R = R' = C_8H_{17} 30

31 R =  R' = H 32

[a] Reagents: i, RR'NH with or without Et_3N/CH_2Cl_2.

give **4** of sufficient purity (>97%) for transport studies. Analytically pure **4** can be obtained by chromatography of the calcium salt on a reverse-phase support. The free acid is regenerated by repeated washing of a methylene chloride solution of **4** with dilute HCl.

Synthesis of Carriers 6 and 7. In contrast to the lengthy syntheses described above, carriers **6** and **7** were readily prepared as outlined in Scheme VII. The known bisanhydride **8** was prepared following procedures developed by Lehn and co-workers.[22] Previous reports of the reaction of **8** with amines have focused on two sets of conditions:[23,24] stoichiometric amine in excess triethylamine or excess amine. The former set of conditions gave only the syn isomer (e.g., **31**), while the latter gave mixtures of syn and anti isomers as deduced by X-ray crystallography[23] or by observation of spin–spin exchange by ESR spectroscopy.[24] In our case, utilizing octylamine, either set of conditions gave mixtures of isomers of **6** and **7** (ca. 1:1). Separation of the isomers was most easily accomplished by chromatography of the calcium or strontium salts on a reverse-phase support. Similarly dioctylamine gave mixtures of **29** and **30** which somewhat less readily separated as strontium salts. The contrast between our nonselective synthesis and the stereoselective cases previously reported may simply reflect the greater flexibility and lower steric demands of our alkylamines compared with aromatic and cyclic amines. In any case, the postulated blocking of one face of the macrocycle[23] fails to provide sufficient control in our case.

The separated isomers were identified as syn (**6**) or anti (**7**) by several lines of evidence. Isomer I is higher melting (mp 180–183), has a higher R_f for TLC on silica in several solvent systems, and has a lower average chemical shift for the methine protons (4.43, 4.27 = 4.35 av) than isomer II (mp 74–78 °C, 4.44, 4.42 = 4.43 av). By comparison with dianilide syn and anti isomers,[23] these observations suggest that isomer I is anti (i.e., **7**) and isomer II is syn (**6**). More quantitative comparisons are presented in Table I, which compares the acidity and stability constants for complexation of isomers I and II and authentic di-spin-labeled crown ether diacids **31** and **33**. The sample of **31** exhibited the reported spin-spin exchange[24] and had the larger difference between pK_1 and pK_2 indicative of a stronger electrostatic interaction between the two carboxylates.[32,33] Quantitative and qualitative comparison of **31**/**32** with isomers I and II for all items in Table I leads to the conclusion stated above: isomer I is anti (**7**), while isomer II is syn (**6**). Assignments for the other derivative prepared (**29**/**30**) followed directly from NMR comparisons and pK_a determination. In general, the syn isomer is characterized by the larger difference between pK_1 and pK_2 and the more closely spaced, downfield set of methine proton resonances in the ^1H NMR.

Table I. Acidity and Stability Constants for Complexation of Potassium[a]

constant	31	32	isomer II (6)	isomer I (7)
pK_1	8.05	7.02	7.38	7.04
pK_2[b]	5.67	6.09	5.32	6.26
pK_1-pK_2	2.38	0.98	2.06	0.78
log K (110)[c]	5.4	6.8	5.4	6.4
log K (111)[b,c]	4.4	5.1	3.6	4.7
log K (120)[c]	8.4	d)	8.1	d)

[a] 10^{-3} M solutions, 25 °C, 0.1 M Me_4NCl, CH_3OH/H_2O (90:10), determined as described previously.[8] [b] Cumulative stability constant corrected to show apparent stepwise association constant.[8] [c] Number indicates the number of ligands (dianion), number of potassium ions, and number of protons in the complex considered, i.e., 110 = L^{-2}/K^+. [d] No complex of this stoichiometry was detected under the experimental conditions.

By way of conclusion we note that as with previously prepared carriers,[8] the carriers synthesized in this study are soluble in all organic solvents but virtually insoluble in water. All two-phase extraction equilibria strongly favor the carrier and its complexes partitioned to the organic phase. The calcium, strontium, and barium salts may be simply prepared by gently stirring dichloromethane solutions of the carriers with metal ion containing basic buffer solutions. Salt solutions prepared by this method contain substantial quantities of water as detected by ^1H NMR. Salt containing less water may be prepared from calcium hydride in dry methanol, from strontium chloride/tetramethylammonium hydroxide in methanol, or from solid barium hydroxide. The crude salts can be freed of impurities by subjecting only the organic soluble material to chromatography on reversed-phase supports (Merck RP8, $CH_3OH/CHCl_3$). The demonstrated ability of these carriers to extract alkaline-earth cations in exchange for protons leads to the conclusion that cation–proton-coupled countertransport will occur artificial membranes. Our further experiments in this line will be reported separately.

Experimental Section

General Details. Melting points were taken with a Koefler hot-stage microscope and are uncorrected. The IR spectra were recorded with a Perkin-Elmer 283 spectrometer in $CHCl_3$ as solvent unless otherwise noted. Proton NMR spectra were recorded with a Perkin-Elmer R32 (90 MHz, cw) or Bruker WM250 (250 MHz, ft) spectrometer in $CDCl_3$ as solvent with tetra-

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methylsilane (Me_4Si) as internal standard. Carbon NMR spectra were recorded at 93.6 MHz (WM250) in $CDCl_3$, using the central line as internal standard (77.0 ppm relative to Me_4Si). The mass spectra were recorded with a Finnegan 3300 GC–MS instrument with methane or isobutane chemical ionization. Specific rotations were calculated from the observed rotation obtained, using a Perkin-Elmer 141 polarimeter and a 1-dm (2 mL) cell. Elemental analyses were performed by Canadian Microanalytical Services, Vancouver, B.C.

1-Iodo-7-phenyl-3,6-dioxaheptane (10). This precursor was prepared in three steps from diethylene glycol by monoalkylation, chlorination, and halide exchange. Following the general procedure outlined by Gibson,[34] a 5-L flask was charged with 3.8 kg of diethylene glycol (37 mol) and 206 g of KOH (4.35 mol) and heated to 90 °C under an argon atmosphere. Benzyl bromide (540 g, 4.35 mol) was added and the mixture was stirred at 110 °C for 14 h. The mixture was cooled, diluted with water (500 mL), and extracted with CH_2Cl_2 (10 × 500 mL). The combined extracts were dried, evaporated, and twice distilled (bp 130–136 °C (0.5 torr)) to give 7-phenyl-3,6-dioxaheptanol (646 g, 76%): ^1H NMR δ 2.6 (1 H, br, D_2O exchange), 3.5–3.7 (8 H, m), 4.53 (2 H s), 7.29 (5 H, br s); ^{13}C NMR δ 61.2, 70.0, 72.2 (2), 72.8, 127.2 (3), 137.8; IR 3700-3150, 1100 cm^{-1}; MS, m/e 197 (M + 1, 4), 91 (100). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.33; H, 8.22. Found: C, 67.65; H, 8.86.

This alcohol (345 g, 1.76 mol) in 1750 mL of benzene and 160 mL of pyridine was stirred mechanically and heated to reflux. A total of 135 mL of $SOCl_2$ (1.87 mol) was added in portions over 3 h at such a rate that the evolution of SO_2 was controlled. The mixture was allowed to reflux a further 16 h, cooled, and diluted with 250 mL of 50% HCl. The organic layer was washed with 5% NaOH, dried, evaporated, and distilled (bp 110–120 °C (0.5 torr)) to give 1-chloro-7-phenyl-3,6-dioxaheptane (265 g, 70%): ^1H NMR δ 3.4–3.7 (8 H, m), 4.45 (2 H, s), 7.25 (5 H, br s); ^{13}C NMR δ 42.7, 69.4, 70.7, 71.3, 73.2, 127.3 (3), 138.2; MS, m/e 217, 215 (M + 1, <1), 91 (100). Anal. Calcd for $C_{11}H_{15}O_2Cl$: C, 61.54; H, 7.04; Cl, 16.52. Found: C, 61.40; H, 6.97; Cl, 16.54.

This chloride (217 g, 2.0 mol) was added to a solution of NaI (750 g, 5 mol) in 1 L of acetone and 100 mL of ethanol, stirred at reflux for 14 h, and evaporated to a slurry. The slurry was taken up in the minimum amount of water and extracted with CH_2Cl_2, and the combined extracts were evaporated. The resultant oil was filtered through a short (25 × 100 mm) column of neutral alumina, eluted with CH_2Cl_2, and evaporated to give **10** (307 g, 99%): ^1H NMR δ 2.18 (2 H, br t, J = 7 Hz), 3.5–3.8 (6 H, m), 4.50 (2 H, s), 7.28 (5 H, br s); ^{13}C NMR δ 2.9, 69.5, 70.3, 72.0, 73.3, 127.6 (3), 138.3; MS, m/e 307 (M + 1, <1), 91 (100).

(2*R*,3*R*)-*N*,*N*,*N*′,*N*′-Tetramethyl-2,3-bis[2-[2-(benzyloxy)ethoxy]ethyl]tartaramide (11). To 39.7 g of **9**[8] (0.195 mol) and 750 mL of DMF under an argon atmosphere was added 120 g (0.40 mol) of thallous ethoxide (TlOEt)[35] and the resultant slurry was stirred at ambient temperature for 40 min. To this slurry was added **10** (125 g, 0.40 mol) and 100 mL of DMF and the mixture was heated to 60 °C for 20 h, cooled, and quenched with 20 mL of water. The mixture was filtered through Celite, the filter cake was washed with ether, and the combined filtrates were evaporated and refiltered through a short column (25 × 100 mm) of neutral alumina with CH_2Cl_2 eluent. The filtrate was evaporated in vacuo (45 °C (0.1 torr), 18 h) and taken up in 1000 mL of water. The aqueous layer was extracted with pentane (4 × 500 mL, the pentane extract contained **10**) and then with $CHCl_3$ (6 × 500 mL). The $CHCl_3$ extract was dried, evaporated, and evaporated in vacuo to **11** as a clear, viscous oil (54.6 g, 50%): ^1H NMR δ 2.85 (6 H, s), 3.10 (6 H, s), 3.5–3.75 (16 H, br m), 4.51 (4 H, s), 4.76 (2 H, s), 7.30 (10 H, br s); ^{13}C NMR δ 35.7, 37.2, 69–70 (4), 73.1, 77.5, 127.7 (3), 138.4, 169.5; IR 1645, 1100 cm^{-1}; MS, m/e 589 (M + 29, 1), 561 (M + 1, 5), 516 (2), 91 (100); $[\alpha]^{20}_D$ +52.5° (c 0.4, $CHCl_3$). Anal. Calcd for $C_{30}H_{44}N_2O_8$: C, 64.27; H 7.91; N, 5.00. Found: C, 64.53; H, 8.10; N, 5.23.

(2*R*,3*R*)-*N*,*N*,*N*′,*N*′-Tetramethyl-2,3-bis[2-(2-iodoethoxy)ethyl]tartaramide (12).[22] The conversion of **11** to **12** was achieved in three steps by hydrogenolysis, bromination, and halide exchange. A 500-mL pressure flask was charged with 225 mL of absolute ethanol, 25 mL of concentrated HCl, 5 g of 10% Pd on C, and 54.5 g of **11** (97 mmol) and was shaken under an H_2 atmosphere (3.5 atm) until H_2 uptake ceased. The mixture was filtered onto 200 g of solid $NaHCO_3$, the slurry was stirred until gas evolution ceased and filtered, the filter cake was washed with $CHCl_3$, and the combined filtrates were evaporated. The oily product was filtered through a short (25 × 150 mm) column of neutral alumina with 1% CH_3OH in CH_2Cl_2 as eluent and the filtrate was evaporated to yield an oil (31.6 g, 86%): ^1H NMR δ 2.90 (6 H, s), 3.15 (6 H, s), 3.45–3.85 (16 H, m), 4.78 (2 H, s); ^{13}C NMR δ 35.8, 37.2, 61.5, 68.9, 70.4, 72.8, 77.1, 169.3; IR 3450, 1645, 1100 cm^{-1}; MS, m/e 409 (M + 29, 14), 381 (M + 1, 100).

This diol (31.5 g, 82.8 mmol) was dissolved in 500 mL of benzene and 9.3 mL of PBr_3 (98 mmol) was added dropwise with cooling. The mixture was stirred at 45 °C for 6 h, cooled, and diluted with 150 mL of water. The aqueous layer was separated and extracted with $CHCl_3$ in a continuous extractor for 16 h. The combined organic layers were evaporated to produce an oil (34.6 g, 82%): ^1H NMR δ 2.89 (6 H, s), 3.15 (6 H, s), 3.41 (4 H, t, J = 7 Hz), 3.55–3.85 (12 H, m), 4.78 (2 H, s); ^{13}C NMR δ 30.4, 35.9, 37.6, 69.2, 70.5, 71.2, 76.5, 169.6; IR 1645, 1100 cm^{-1}; MS, m/e 507, 505 (M + 1, 50) 464, 462 (100). Anal. Calcd for $C_{16}H_{30}N_2O_6Br_2$: C, 37.95; H, 5.97; N, 5.53. Found: C, 38.13; H, 6.18; N, 5.27.

The dibromide (34.4 g, 68 mmol) was converted to **12** with NaI in acetone as described for **10** (39.0 g, 96%): ^1H NMR δ 2.90 (6 H, s), 3.16 (6 H, s), 3.22 (4 H, t, J = 7 Hz), 3.55–3.85 (12 H, m), 4.79 (2 H, s); ^{13}C NMR δ 2.8, 35.8, 37.4, 68.9, 70.3, 71.9, 77.3, 169.3; IR 1465, 1100 cm^{-1}.

(*Z*)-11-Docosene (14). Compound **14** was prepared by successive alkylations of acetylene followed by partial hydrogenation. 1-Dodecyne was prepared from monolithioacetylide[36] (0.75 mol) in THF (700 mL) and 1-bromodecane in 300 mL of HMPT (−78 → 90 °C, 2 h): ^1H NMR δ 0.88 (3 H, br t), 1.30 (16 H, m), 1.84 (1 H, t, J = 2 Hz), 2.12 (2 H, txd, J = 2, 7 Hz). Crude 1-dodecyne in 700 mL of THF was treated with n-butyllithium (0.75 mol, 0 °C) followed by 1-bromodecane (0.75 mol) in 200 mL of HMPT (0 → 80 °C, 4 h) to give 11-docosyne (**13**) after distillation (bp 138–140 °C (1 torr)) (110 g, 47%): ^1H NMR δ 0.88 (6 H, br t), 1.25 (32 H, m), 2.1 (4 H, br t); ^{13}C NMR δ 14.0, 18.8, 22.7, 29.6 (m), 32.0, 70.9, 80.1; IR 2260 cm^{-1}; MS, m/e 306 (M + 1, <1), 81 (100). Anal. Calcd for $C_{22}H_{42}$: C, 86.19; H, 13.81. Found: C, 86.38; H, 13.81. The atmospheric pressure hydrogenation of **13** (15.3 g, 50 mmol) in absolute ethanol (500 mL) over Lindlar catalyst (0.5 g) was allowed to proceed until 1 equiv of H_2 was consumed to give **14** (15.4 g, 99%) as a >90:<10 mixture of *Z*:*E* isomers (^{13}C NMR integration of inverse gated spectrum): ^1H NMR δ 0.88 (6 H, br t), 1.32 (32 H, m), 2.0 (4, H, m), 5.34 (2 H, br t, J = 5 Hz); ^{13}C NMR δ 14.1, 22.8, 27.3, 29.5 (m), 32.0, 129.9 (*E* isomer 32.7, 130.4); IR 1655, 715 cm^{-1} (*E* isomer 965); MS, m/e (EI) 308 (M, 4). Anal. Calcd for $C_{22}H_{44}$: C, 85.63; H, 14.37. Found: C, 85.76; H, 14.76.

***erythro*-11,12-Docosanediol (15).** A mixture of **14** (22.7 g, 74 mol), KIO_3 (3.93 g, 18.4 mmol), I_2 (7.33 g, 37 mmol), and glacial acetic acid (175 mL) was stirred at 70 °C for 14 h, 7.25 g of potassium acetate (75 mmol) was added, and the mixture was heated to reflux for 3.5 h. The mixture was cooled, quenched with 250 mL of water, and extracted with ether, and the extracts were dried and evaporated. The residue was hydrolyzed with 200 mL of 10% KOH in CH_3OH added to 500 mL of benzene at reflux for 3 h. The mixture was cooled, 100 mL of water was added, and the organic solvents were removed by an rotary evaporator. The residue was suspended in water and triturated with portions of 5% HCl, dried, and recrystallized from pentane/acetone to give **15** (18.1 g, 72%): mp 135–137 °C; ^1H NMR δ 0.89 (6 H, t, J = 7 Hz), 1.27 (36 H, m), 1.84 (2 H, d, J = 5, D_2O exchange), 3.60 (2 H, br t); ^{13}C NMR δ 14.1, 22.7, 26.0, 29.6 (m), 31.3, 31.9, 74.7; IR 3620 cm^{-1} (3270 Nujol mull); MS, m/e 343 (M + 1, 6), 325 (100). Anal. Calcd for $C_{22}H_{46}O_2$: C, 77.12; H, 13.54. Found: C, 76.86; H, 13.45.

***threo*-11,12-Docosanediol (16).** A mixture of **14** (63.4 g, 0.205 mol), 37 mL of 30% H_2O_2 (0.30 mol), and 250 mL of formic acid was stirred at 40 °C for 14 h. The mixture was concentrated on a rotary evaporator and the residue was dissolved in 400 mL of

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10% KOH in CH_3OH and added to 1 L of benzene. The mixture was stirred at reflux for 12 h, neutralized with concentrated HCl, evaporated, and triturated with 5% HCl and the residue was dried and recrystallized from hexane/benzene to give **16** (50 g, 70%): mp 85–87 °C; ^{1}H NMR δ 0.89 (6 H, t, J = 7 Hz), 1.27 (36 H, m), 1.98 (2 H, d, J = 5 Hz, D_2O exchange), 3.42 (2 H, br t); ^{13}C NMR δ 14.1, 22.7, 25.6, 29.69 (m), 31.9, 33.7, 74.6; IR 3620, 3580 cm^{-1} (3330, 3250 Nujol mull); MS, m/e 343 (M + 1, 4), 325 (100). Anal. Calcd for $C_{22}H_{46}O_2$: C, 77.12; H, 13.54. Found: C, 77.17; H, 13.54.

(2*R*,3*R*)-*N*,*N*,*N*′,*N*′-Tetramethyl-11,12-didecyl-1,4,7,10,13,16-hexaoxacyclooctadecane-2,3-dicarboxamide (17, 18). A solution of **16** (20.0 g, 58 mmol) in 750 mL of DMF was heated under argon to 50 °C and 8.3 mL of TlOEt (116 mmol) was added dropwise via a syringe over 20 min. The cloudy solution was stirred for a further 30 min and 36 g of **12** (60 mmol) in 100 mL of DMF was added dropwise. The mixture was stirred at 65 °C for 12 h and cooled, 2 mL of water was added, and the solids were removed by filtration. The filter cake was washed with ether, and the filtrate was evaporated and filtered through a short column (25 × 100 mm) of alumina, eluted with 1000 mL of CH_2Cl_2, and evaporated to a thick oil, which was evaporated in vacuo to remove residual DMF (0.1 torr, 40 °C, 16 h). The oil was vigorously stirred with hexane (3 × 250 mL) and the hexane-soluble material was taken to chromatography on neutral alumina (50 × 800 mm), using a toluene/$CHCl_3$ gradient. (The hexane-insoluble fractions were mostly **19** and polymeric products.) The product containing fractions eluted at 80% $CHCl_3$/20% toluene (^{1}H and ^{13}C NMR) were again subjected to chromatography on silica (BioSil-A, 200–400 mesh, 50 mmHg overpressure of argon, 35 × 450 mm) with a $CH_3OH/CHCl_3$ gradient. Product-containing fractions eluted at 1% CH_3OH and were further purified by HPLC on silica (BioSil-A, 20 μm, 7 × 500 mm) with 7.5% isopropyl alcohol/CH_2Cl_2 as eluent (RI detector). The product obtained was a 1:1 mixture of **17** and **18** (400 mg, 1%): ^{1}H NMR δ (both isomers) 0.85 (12 H, br t), 1.25 (72 H, m), 2.88, 2.89 (12 H, s), 3.12, 3.15 (12 H, s), 3.24 (4 H, br m), 3.60–3.90 (34 H, m), 4.70 (2 H, s, one isomer), 4.85 (2 H, s, other isomer); ^{13}C NMR δ 14.0, 22.6, 25.5, 29.6 (m), 31.1, 35.6, 37.3, 68–71.2 (m), 77.38 and 75.79, 83.1 and 82.8, 169.4 and 169.5; IR 1645, 1100 cm^{-1}; MS, m/e ~688 (M + 1, <1). Anal. Calcd for $C_{32}H_{74}N_2O_2$: C, 66.44; H, 10.86; N, 4.08. Found: C, 66.51; H, 10.67; N, 4.06.

(2*R*,3*R*)-11,12-Didecyl-1,4,7,10,13,16-hexaoxacyclooctadecane-2,3-dicarboxylic Acid (1). The mixed diamides **17** and **18** (140 mg, 0.20 mmol) were dissolved in 20 mL of dioxane and 10 mL of 1 M HCl and allowed to reflux for 14 h. The mixture was diluted with water and evaporated to remove the bulk of the dioxane, was extracted with CH_2Cl_2, and evaporated to give the crude diacid. The calcium salt was prepared from the diacid by addition of 50 mg of CaH_2 to the diacid in dry CH_3OH, filtered (glass frit followed by Millipore 0.2 μm Teflon), and purified by gel permeation chromatography on Sephadex LH20, using $CH_3OH/CHCl_3$ (3:4) as eluent. Product-containing fractions (TLC on Merck RP-2, 10% CH_3OH in $CHCl_3$, R_f 0.15) were evaporated, taken up in CH_2Cl_2, and stirred with several portions of 0.5 M HCl. The diacid solution was "dried" by filtration through a Teflon 0.2 μm filter and evaporated to give **1** as a clear glass (120 mg, 92%): ^{1}H NMR δ (both isomers) 0.85 (12 H, br t), 1.23 (72 H, m), 3.6–2.8 (34 H, m), 3.27 (4 H, br m), 4.73 (2 H, s, one isomer), 4.56 (2 H, s, other isomer); ^{13}C NMR δ 14.0, 22.6, 25.9, 29.6 (m), 30.5, 69.5–71 (m), 80.0 and 79.6, 81.9 and 81.7, 170.9 and 170.7; IR 3650–2300 (br), 1740, 1100 cm^{-1}; MS, m/e ~634 (M + 1, 2), 626 (17), 588 (15).

Diethyl (2*R*,3*R*)-2,3-Bis[2-[2-(benzyloxy)ethoxy]ethyl]-tartarate (20). To 62 g of diethyl tartarate (0.3 mol) in 450 mL of DMF under argon was added a total of 42 mL of TlOEt (0.60 mol) in portions over 20 min. The mixture was heated to 75 °C and 220 g of **10** (0.72 mol) was added. The temperature was maintained for 14 h, the mixture was cooled and filtered through Celite, the filter cake was washed with CH_2Cl_2, and the filtrates were evaporated and evaporated in vacuo to remove DMF (40 °C (0.1 torr), 18 h). The product was chromatography on neutral alumina (60 × 800 mm), using a $CHCl_3$/toluene gradient from 1:1 to 4:1. The product-bearing fractions eluted at 4:1 solvent mixture and had a combined weight of 55 g ("late frac"). Earlier fractions eluted at about 2:1 $CHCl_3$/toluene and had a combined weight of 80 g ("early frac"). The ^{13}C NMR spectra of these two fractions indicated that the "early frac" was C-alkylated material, i.e., **21** and/or **22** (chemical shifts for the fragment δ O_2CCC-H_2CH_2O; 167.0, 98.1, 40.8, 60.2), while the "late frac" was an approximately 40:60 **21** + **22**/**20**. The "late frac" was chromatographed on silica (60 × 750 mm) with a pentane/ether gradient as eluent (80:20 to 1:1). The desired compound was eluted at 1:1 pentane/ether (26 g, 15%): ^{1}H NMR δ 1.25 (3 H, t, J = 7.1 Hz), 3.6 (8 H, br s), 4.24 (2 H, q, J = 7.1 Hz), 4.38 (1 H, s), 4.51 (2 H, s), 7.3 (5 H, br s); ^{13}C NMR δ 13.8, 61.0, 69.71 (4), 72.8, 80.1, 127.6 (3), 138.0.

A 5-g sample of **20** (10 mmol) was hydrogenated (10% Pd on C, ethanol, 1 atm) to the diol (3.75 g, 98%), which was chlorinated with $SOCl_2$/pyridine as described for **10**. Chromatography (alumina, toluene/$CHCl_3$ (1:1)) gave the dichloride, which was converted to the diiodide as described for **10** (73% from **20**). The diiodide was added to the dithallium salt of **9** (1.5 g of **9**, 0.55 mL of TlOEt, 150 mL of DMF) and treated as described above. Only minor amounts of material eluted with toluene-containing solvents. The major products eluted at 10% CH_3OH in $CHCl_3$; ^{1}H and ^{13}C NMR showed it to be predominantly C-alkylated material free of $N(CH_3)_2$ residues.

1,4-Di-*O*-benzyl-L-threitol (23). Compound **23** was prepared by literature methods from diethyl tartrate by protection of the alcohols as the acetone ketal,[28] reduction of the esters with $LiAlH_4$,[29] and protection of the primary alcohols as benzyl ethers:[30] mp 66–68 °C (lit. mp 58–59 °C[37]); $[\alpha]^{25}_D$ −5.8° (c 5.0, $CHCl_3$) (lit. $[\alpha]^{25}_D$ −5.0°,[27] −5.5°[38]).

2-(2-Iodoethoxy)ethyl 2-Tetrahydropyranyl Ether (24). The iodide **24** was prepared from the known chloride[31] as described for **10**: ^{1}H NMR δ 1.5 (6 H, m), 3.19 (2 H, t, J = 7 Hz), 3.70 (2 H, t, J = 7 Hz), 3.6 (6 H, br s), 4.61 (1 H, br).

1,4-Di-*O*-benzyl-2,3-bis-*O*-[2-[2-(2-tetrahydropyranyloxy)ethoxy]ethyl]-L-threitol (25). To 50 g of **23** (0.165 mol) in 1000 mL of DMF under an argon atmosphere was added a total of 23.5 mL of TlOEt (0.33 mol) in portions over 10 min. The mixture was warmed to 65 °C, 130 g of **24** (0.43 mol) was added, and the mixture was stirred at 65 °C for 16 h. The mixture was cooled, 5 mL of water was added and filtered through Celite, the filter cake was washed with CH_2Cl_2, and the filtrates were evaporated and evaporated in vacuo (45 °C (0.1 torr), 24 h) to remove residual DMF. The residue was chromatographed on alumina (100 × 350 mm), using 2-L portions of toluene, toluene/$CHCl_3$ (1:1), and $CHCl_3$. The final $CHCl_3$ fraction gave 51 g of crude **25**. ^{13}C NMR showed this material to be mixed mono- and di-OThp ethers. A small portion of this sample was further purified by chromatography on alumina with $CHCl_3$ as eluent: ^{1}H NMR δ 1.5 (6 H, br s), 3.6–3.8 (13 H, m), 4.50 (2 H, s), 4.60 (1 H, br), 7.3 (5 H, br s). Anal. Calcd for $C_{36}H_{54}O_{10}$: C, 66.85; H, 8.43. Found: 66.49; H, 8.78.

1,4-Di-*O*-benzyl-2,3-bis-*O*-[2-(2-iodoethoxy)ethyl]-L-threitol (26). The crude sample of **25** (48 g) was hydrolyzed with 200 mL of 5% HCl in 200 mL of CH_3OH for 2 h at reflux temperature. The mixture was evaporated, H_2O and pentane were added, the pentane layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 × 100 mL). The CH_2Cl_2 extract was dried and evaporated to yield the crude diol (41 g, 52%). The diol was dissolved in benzene (500 mL) and pyridine (14 mL) and heated to reflux. A total of 12 mL of $SOCl_2$ was added in portions over 2 h, and the mixture was stirred at reflux a further 14 h, cooled, diluted with water, and extracted with benzene (2 × 100 mL). The combined organic layers were washed with 5% NaOH (2 × 100 mL), dried, and evaporated. The crude dichloride was chromatographed on silica (35 × 500 mm), using a gradient of toluene/$CHCl_3$. The desired dichloride eluted with 4:1 $CHCl_3$/toluene (27 g, 62%): ^{1}H NMR δ 3.5–3.7 (10 H, br s), 3.83 (1 H, m), 4.45 (2 H, s), 7.24 (5 H, br s); ^{13}C NMR δ 42.4, 69.2–70.8 (4), 72.9, 78.9, 127.5 (3), 137.9 Anal. Calcd for $C_{26}H_{36}O_6Cl_2$: C, 60.59; H, 7.04; Cl, 13.75. Found: C, 60.51; H, 7.22; Cl, 13.60.

The dichloride was converted to **26** (quantitative) as outlined for the preparation of **10**.

(2*R*,3*R*,11*R*,12*R*)-*N*,*N*,*N*′,*N*′-Tetramethyl-11,12-bis-[(benzyloxy)methyl]-1,4,7,10,13,16-hexaoxacyclooctade-

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cane-2,3-dicarboxamide (27). A solution of 8.73 g of **9** (42 mmol) in 500 mL of DMF under argon was treated with 6.1 mL of TlOEt (85 mmol). The mixture was stirred at ambient temperature for $^1/_2$ h and then warmed to 60 °C, whereupon 30 g of **26** (42 mmol) was added. The mixture was stirred at 60 °C for 16 h, cooled, and filtered through Celite, the filter cake was washed with CH_2Cl_2, and the combined filtrates were evaporated to yield a thick oil. This oil, adsorbed on Celite, was placed on the top of a silica column (100 × 450 mm) and eluted with 1.5 L each of toluene, toluene/$CHCl_3$ (1:1), $CHCl_3$, 2% $CH_3OH/CHCl_3$, and 5% $CH_3OH/CHCl_3$. The 5% $CH_3OH/CHCl_3$ fraction was rechromatographed on silica (35 × 500 mm), using a $CHCl_3/CH_3OH$ gradient to 5% CH_3OH to give **27** as a clear oil (4.8 g, 18%): ^1H NMR δ 2.85 (6 H, s), 3.10 (6 H, s), 3.55–3.7 (22 H, m), 4.50 (4 H, s), 4.75 (2 H, s), 7.3 (10 H, br s); ^{13}C NMR δ 35.3, 36.8, 68.9–70.8 (5), 72.9, 78.9, 79.2, 127.6 (3), 138.0, 168.9; MS, *m/e* ~648 (M + 1, 3), 602 (15), 91 (100). Anal. Calcd for $C_{34}H_{53}N_2O_{10}$: C, 63.14; H, 7.79; N, 4.33. Found: C, 62.97; H, 7.80; N, 3.95.

(2*R*,3*R*,11*R*,12*R*)-*N*,*N*,*N*′,*N*′-Tetraoctyl-11,12-bis[benzyloxy)methyl]-1,4,7,10,13,16-hexaoxacyclooctadecane-2,3-dicarboxamide (28). To the diamide crown ether **27** (4 g, 6.2 mmol) was added a mixture of 50 mL of dioxane, 10 mL of concentrated HCl, and 20 mL of water and the mixture was stirred at reflux for 4 h. The mixture was cooled, diluted with 200 mL of water, and extracted with pentane (2 × 25 mL) and the aqueous layer was exhaustively extracted with CH_2Cl_2 (10 × 75 mL). The combined CH_2Cl_2 extracts were evaporated to form a thick oil, which was taken up in glacial acetic acid and precipitated by slow addition of ether/pentane (1:1). The gummy precipitate coalesced to a clear glass, which was crushed and evaporated in vacuo until constant weight was acheived (2.5 g, 68%): ^1H NMR δ 3.5–3.7 (22 H, m), 4.31 (2 H, s), 4.50 (4 H, s), 7.30 (10 H, br s); ^{15}C NMR δ 6.90–71.1 (5), 72.7, 79.1, 79.7, 127.4 (3), 137.7, 170.2.

The diacid (1.7 g, 2.9 mmol) was dissolved in 25 mL of $CHCl_3$ and 10 mL of $SOCl_2$ was added. The mixture was heated to reflux for 3 h, cooled, and evaporated in vacuo (0.1 torr, 2 h). The oily diacid chloride was dissolved in 20 mL of CH_2Cl_2 and was added to 2.0 g of dioctylamine and 4.5 mL of triethylamine in 20 mL of CH_2Cl_2. The mixture was stirred at ambient temperature for 16 h, extracted with 5% HCl (3 × 50 mL), dried, and evaporated. The product was chromatographed on deactivated alumina (Brockmann VI, 25 × 250 mm) with a $CHCl_3/CH_3OH$ gradient to 20% CH_3OH as eluent to give **28** as a waxy solid (1.2 g, 40%): ^1H NMR δ 0.85 (12 H, br t), 1.28 (48 H, s), 3.24 (8 H, m), 3.6–3.8 (22 H, br m), 4.20 (2 H, br), 4.47 (4 H, s), 7.24 (10 H, s); ^{13}C NMR δ 13.9, 22.6, 26.9, 29.6 (m), 31.8, 39.6, 68.0–71.1 (5), 72.7, 79.2, 80.2, 127.4 (3), 138.0, 169.5. Anal. Calcd for $C_{62}H_{106}N_2O_{10}$: C, 71.63; H, 10.27; N, 2.70. Found: C, 71.78; H, 10.43; N, 2.50.

(2*R*,3*R*,11*R*,12*R*)-11,12-Bis[(dioctylamino)carbonyl]-1,4,7,10,13,16-hexaoxacyclooctadecane-2,3-dicarboxylic Acid (4). A mixture of 71 mg of **28** (69 μmol) and 5 mg of 10% Pd on C in 10 mL of ethanol was stirred under 1 atm of H_2 for 6 h, filtered, evaporated, redissolved in CH_2Cl_2, washed with 5% HCl, and evaporated to yield 57 mg of a diol (97%): ^1H NMR δ 0.9 (12 H, br t), 1.30 (48 H, br s), 3.40 (8 H, br m), 3.6–3.7 (22 H, br s), 4.28 (2 H, s); ^{13}C NMR δ 13.98 22.6, 26.9, 29.6 (m), 31.4, 29.6 (br), 61.17, 70.0–71.1 (4), 73.6, 80.9, 169.5; MS, *m/e* ~860 (M + 1, <1), 242 (100).

The diol (57 mg) was dissolved in 5 mL of acetone and a total of 0.085 mL of 8 N (oxygen) Jones reagent was added over 5 min. The mixture was stirred for 15 min, 5 mL of water was added, and the acetone was removed at reduced pressure. The aqueous phase was extracted with CH_2Cl_2, and the organic layer was washed with 5% HCl and evaporated to give **4** (65 mg) clean enough (>97%) for transport studies. The crude diacid **4** could be purified on a Merck Lobar RP-8 column with CH_3OH as eluent to give 16 mg (27% recovery) of **9**: ^1H NMR δ 0.89 (12 H, br t), 1.3 (48 H, br s), 3.30 (8 H, br m), 3.6 (16 H, m), 4.30 (2 H, s), 4.45 (2 H, s); ^{13}C NMR δ 13.9, 22.6, 26.9, 29.2 (m), 31.8, 39.6 (br), 68.1–70.9 (4), 81.2, 82.2, 168.2, 175 (br); MS, *m/e* ~888 (M + 1), 242 (100). Anal. Calcd for $C_{48}H_{90}N_2O_{12}$: C, 64.98; H, 10.22; N, 3.16. Found: C, 65.08; H, 10.30; N, 3.13.

(2*R*,3*R*,11*R*,12*R*)-3,12-Bis[(octylamino)carbonyl]-1,4,7,10,13,16-hexaoxacyclooctadecane-2,11-dicarboxylic Acid (6) and (2*R*,3*R*,11*R*,12*R*)-3,11-Bis[(octylamino)carbonyl]-1,4,7,10,13,16-hexaoxacyclooctadecane-2,12,-dicarboxylic Acid (7). The bis anhydride **8** was prepared from the tetraacid and converted to the diamide following procedures reported by Behr et al.[22,23] Thus 0.99 g of **8** (1.9 mmol) in 20 mL of CH_2Cl_2 was added dropwise over 20 min to a solution of 0.70 mL of triethylamine (4.8 mmol) and 0.72 mL of octylamine (4.3 mmol) in 20 mL of CH_2Cl_2. The mixture was stirred for 16 h at ambient temperature and then passed through a bed of strong acid ion exchange resin (Rexyn 101H, 25 × 300 mm) and eluted with 35% isopropyl alcohol/65% $CHCl_3$. The column eluent was evaporated and redissolved in wet CH_3OH and 150 mg of CaH_2 was added and the mixture was stirred 1–2 h. The solution was filtered (Millipore Teflon 0.2 μm) and evaporated to give a mixture of calcium salts, which were separated by chromatography on a Merck Lobar column RP8 (20 × 450 mm) with 0.02% triethylamine and 5% $CHCl_3$ in CH_3OH as eluent. Purified fractions were dissolved in CH_2Cl_2 and stirred with several portions of 0.5 M HCl and recrystallized from CH_2Cl_2/hexane to give the separated isomers **6** and **7**. Assignment of stereochemistry is outlined in the text.

***syn*-6**: mp (CCl_4/hexane) 74–78 °C; ^1H NMR δ 0.85 (6 H, t), 1.24 (24 H, br s), 3.30 (4 H, br q), 3.65–3.8 (16 H, m), 4.42 (2 H, d, *J* = 2.6 Hz), 4.44 (2 H, d, *J* = 2.6 Hz), 7.30 (1 H, br t), 8.28 (1 H, br); ^{13}C NMR δ 14.0, 22.6, 26.9, 29.6 (m), 31.8, 39.6, 69.6–71.2 (4), 80.4, 80.9, 169.5, 171.2; IR 3500–2400, 3250, 1730, 1630, 1540, 1090 cm^{-1}; MS, *m/e* 663 (M + 1, <1), 645 (1), 627 (3), 534 (2), 130 (100); $[\alpha]^{20}_D$ +61.0° (*c* 0.43). Anal. Calcd for $C_{32}H_{60}N_2O_{13}$ (**6** + H_2O): C, 56.45; H, 8.90; N, 4.12. Found: C, 56.58; H, 9.17; N, 4.13.

***anti*-7**: 180–83 °C; ^1H NMR δ 0.85 (6 H, t), 1.24 (24 H, br s), 3.30 (4 H, br q), 3.60–3.75 (16 H, m), 4.26 (2 H, d, *J* = 1.5 Hz), 4.43 (2 H, d, *J* = 1.5 Hz), 7.24 (1 H, br t); ^{13}C NMR δ 14.0, 22.6, 26.9, 29.6 (m), 31.8, 39.5, 69.3–71.4 (4), 80.4, 81.3, 168.7, 171.2; IR 3500–2400, 3380, 1755, 1735, 1655, 1540, 1100 cm^{-1}; MS *m/e* 663 (M + 1, <1), 645 (1), 627 (<1), 534 (2), 130 (100); $[\alpha]^{20}_D$ +51.6° (*c* 0.33). Anal. Calcd for $C_{32}H_{58}N_2O_{12}$: C, 57.99; H, 8.82; N, 4.23. Found: C, 57.88; H, 8.69; N, 4.13.

The syn and anti tetraoctyl diamides **29** and **30** were prepared in a directly analogous manner from **8** and dioctylamine. Purification on a Merck Lobar RP-8 column was achieved with use of the strontium salts prepared from 1.42 g of mixed **29** and **30** in 5 mL of CH_3OH containing 0.45 g of $SrCl_2{\cdot}6H_2O$ and 0.55 g of $(CH_3)_4NOH{\cdot}5H_2O$. The mixture was evaporated, taken up in 5 mL of CH_2Cl_2, filtered (glass frit and Millipore Teflon 0.2 μm), and evaporated to give the salts. Only partial separation was achieved; pure **30** was eventually obtained by recycling of mixed fractions, but **29** was isolated only as an 80:20 mixture of **29**/**30**.

***anti*-30**: ^1H NMR δ 0.82 (12 H, br t), 1.27 (48 H, br s), 3.2–3.8 (24 H, m), 4.22 (2 H, d, *J* = 1.2 Hz), 4.54 (2 H, d, *J* = 1.2 Hz); ^{13}C NMR δ 13.9, 22.5, 26.8, 29.6 (m), 31.7, 46.4, 47.3, 69.0–70.9 (4), 78.6, 80.9, 168.0, 171.0; IR 3600–2400, 1745, 1640, cm^{-1}. Anal. Calcd for $C_{48}H_{90}N_2O_{12}$: C, 64.97; H, 10.22; N, 3.15. Found: C, 65.11; H, 10.31; N, 3.01.

***syn*-29**: ^1H NMR as **30** except 4.62 (4 H, br s); ^{13}C NMR as **30** except 78.3 and 80.6.

Preparations of Salts. Alkali-metal and alkaline-earth salts of the carriers are readily prepared by a variety of methods: (i) from hydrides as outlined in the preparation of **6** and **7**, (ii) from hydroxides as outlined in the preparation of **29** and **30**, (iii) from fluorides [typically a solution of carrier in dry CH_3OH was stirred for 5 days with stoichiometric solid SrF_2 in a loosely stoppered flask. The mixture was evaporated, taken up in CH_2Cl_2, filtered (Millipore Teflon 0.2 μm), and evaporated to give the strontium salt. This method is advantageous for preparing clean samples since high-purity metal fluorides are readily available.], (iv) by two-phase cation–proton exchange. Typically, 100 mg of **30** in 25 mL of CH_2Cl_2 was gently stirred with 50 mL of Tris buffer, pH 8.0, containing 10^{-2} M $Ba(NO_3)_2$. After 12 h, the layers were separated, and the organic layer was evaporated to give the barium salt. In general, the salts prepared by method iv contained larger amounts of water than those obtained by other methods (^1H NMR), but all salts were hydrated to a variable extent (analysis, ^1H NMR).

Stability Constant Determinations. Acidity and stability constants in 90:10 CH_3OH/water (v:v) were determined by using the procedures and computations previously described.[8] The data were collected by using the automatic titration system described

more recently,[38] adapted to equilibrium potentiometric titrations.

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Registry No. 1 (isomer 1), 88454-79-9; 1 (isomer 2), 88495-25-4; 1·Ca, 88455-06-5; **4**, 88454-80-2; **6**, 88454-81-3; **7**, 88454-82-4; **8**, 76777-45-2; **9**, 26549-65-5; **10**, 88454-83-5; **11**, 88454-84-6; 11-diol, 88475-83-6; 11 (dibromo derivative), 88454-85-7; **12**, 57207-20-2; **13**, 88454-86-8; **14**, 61759-30-6; **15**, 88454-87-9; **16**, 88454-88-0; **17**, 88454-89-1; **18**, 88495-26-5; **19**, 76980-05-7; **20**, 88454-90-4; **20** (diiodide derivative), 88454-91-5; **21**, 88454-92-6; **22**, 88475-84-7; **23**, 17401-06-8; **24**, 88454-93-7; **24** (chloride derivative), 54533-84-5; **25**, 88454-94-8; **25** mono-Othp ether, 88454-95-9; 25-diol, 88454-96-0; **25** (dichloride derivative), 88454-97-1; **26**, 88454-98-2; **27**, 88454-99-3; **27** (diacid derivative), 88455-00-9; **27** (diacid chloride derivative), 88455-01-0; **28**, 88455-02-1; **28**-diol, 88455-03-2; **29**, 88455-04-3; **30**, 88455-05-4; **31**, 83458-45-1; **32**, 83458-46-2; 7-phenyl-3,6-dioxaheptanol, 2050-25-1; 1-chloro-7-phenyl-3,6-dioxaheptane, 64352-98-3; lithioacetylide, 1111-64-4; octylamine, 111-86-4; diethylene glycol, 111-46-6; benzyl bromide, 100-39-0; 1-dodecyne, 765-03-7; 1-bromodecane, 112-29-8; diethyl tartrate, 87-91-2; dioctylamine, 1120-48-5.

Nonlinear Least-Squares Method of Separating the Second- and Third-Order Rate Constants for the Ionic Bromination of Alkenes in CCl_4 at 25 °C†

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A nonlinear least-squares method of obtaining reliable values of both the second- and third-order rate constants for electrophilic addition of bromine to alkenes when $[alkene]_0 \gg [Br_2]_0$ is described. The kinetics of the reaction must be followed to at least 80% completion for this method to be successful. The method is applied to the bromination of (*Z*)-2-butene and 2-methyl-2-butene in CCl_4 at 25 °C. For (*Z*)-2-butene $k_2 = (8.9 \pm 0.3) \times 10^{-4}$ M^{-1} s^{-1} and $k_3 = 4.0 \pm 0.6$ M^{-2} s^{-1} while for 2-methyl-2-butene $k_2 = (6 \pm 2) \times 10^{-3}$ M^{-1} s^{-1} and $k_3 = 240 \pm 40$ M^{-2} s^{-1}.

The general rate law for the ionic bromination of alkenes is generally accepted to be as shown in eq 1.[1] This rate

$$-d[Br_2]/dt = (k_2[Br_2] + k_3[Br_2]^2 + k'_{Br_3^-}[Br_3^-])[alkene] \quad (1)$$

law contains terms that account for first- and second-order dependences on bromine and an additional term for bromide ion participation.

On the basis of existing literature,[2,3] bromination in a nonpolar solvent such as CCl_4 should display third-order kinetics exclusively, i.e., the k_3 process. The $k_{Br_3^-}$ process is not expected to be in operation, especially in the absence of added bromide ion. The k_2 process is favored only under conditions of low bromine concentration in polar solvents. It has been proposed that a solvent molecule participates in the rate-determining transition state of the k_2 process. Nonpolar solvents cannot participate in that fashion, hence a second molecule of bromine is thought to act as a replacement, giving rise to an observed second-order dependance on bromine.

Recently, it has been shown that both the k_2 and the k_3 processes occur in CCl_4.[4] However it is difficult to obtain values of both k_2 and k_3. We present a method of obtaining reliable values of both k_2 and k_3 from bromine absorbance–time data in CCl_4 at 25 °C.

Results and Discussion

The rates of bromination were followed by monitoring the decrease in absorbance of bromine at 415 ± 1 nm under conditions of at least a 20-fold excess of alkene by means of either a Pye Unicam SP 1800 or Cary 16 UV/vis spectrophotometer. The rates of bromination were unaffected by addition of up to 10^{-3} M cyclohexene epoxide.[5] Purging the CCl_4 solutions with oxygen and nitrogen had no effect on the kinetic results compared to those obtained without purging. The results are all consistent with an ionic reaction.[1,5]

The results of analysis of typical absorbance vs. time data for the addition of bromine to (*Z*)-2-butene in CCl_4 at 25 °C by means of a pseudo-first-order (P1O) and a pseudo-second-order (P2O) rate law are shown in Figures 1 and 2, respectively. While the P2O analysis gives the better correlation coefficient, both Figures 1 and 2 shown definite curvature. The P1O plot shows greater curvature than the P2O plot, indicating that the second-order dependence on bromine is the more important process. However, the first-order dependence on bromine cannot be ignored. Thus the experimental rate law does not have either a simple first- or second-order dependence on bromine.

Under conditions of excess alkene, a combined first- and second-order dependence on bromine of the rate of reaction can be expressed as eq 2 where $k_2' = k_2[alkene]$ and

$$-d[Br_2]/dt = k_2'[Br_2] + k_3'[Br_2]^2 \quad (2)$$

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