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Macrocyclic Ligands Composed of Tetrahydrofuran for Selective Transport of Monovalent Cations through Liquid Membrane

Yoshiaki Kobuke,* Katsumi Hanji, Koichi Horiguchi, Masahiro Asada, Yoshinori Nakayama, and Junji Furukawa

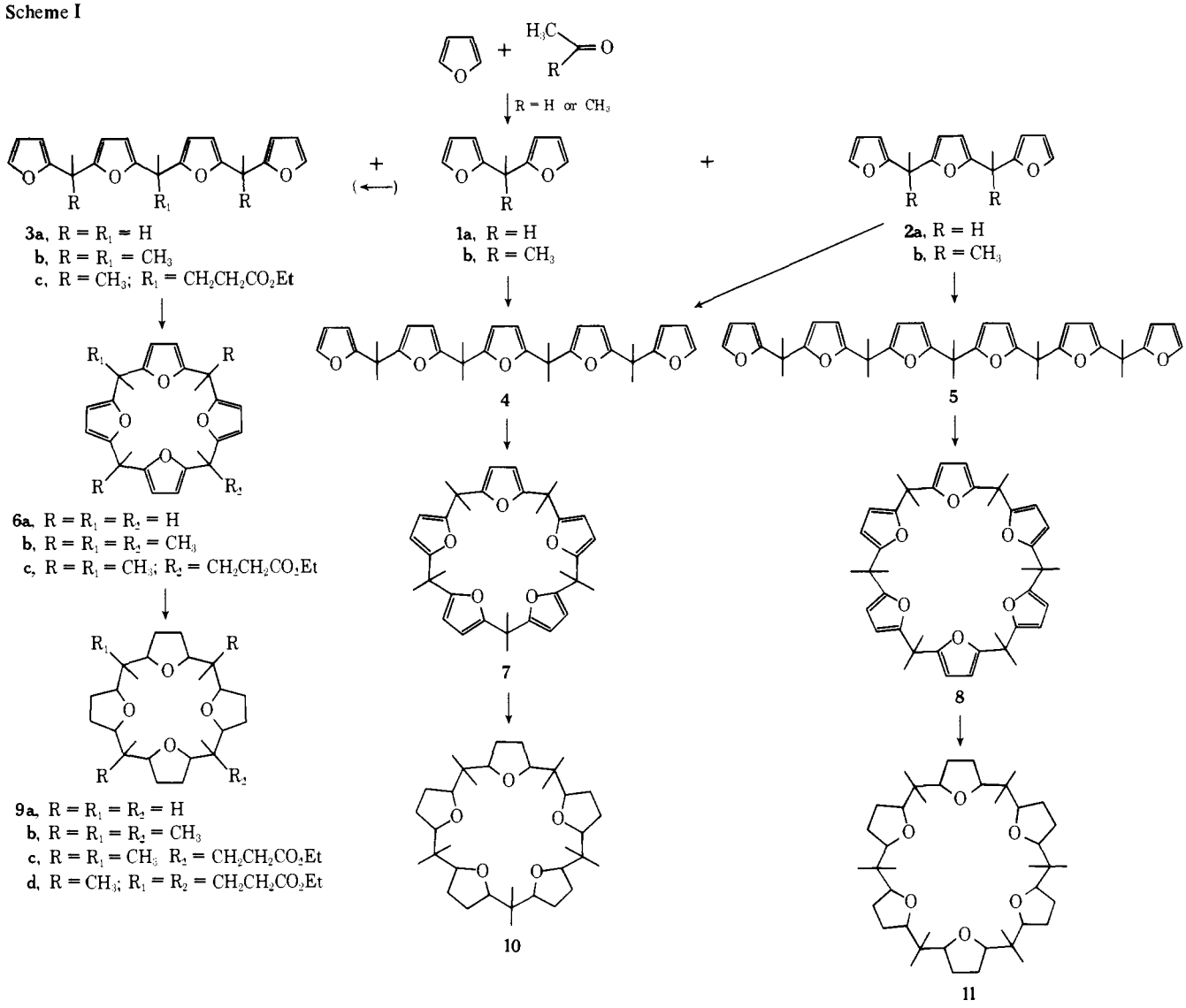
Contribution from the Department of Synthetic Chemistry, Kyoto University, Yoshida, Kyoto 606, Japan. *Received January 30, 1976*

Abstract: A series of macrocyclic compounds having tetrahydrofuran as a principal chain component was synthesized by an acid-catalyzed condensation of furan and carbonyl components followed by hydrogenation. These compounds were shown to extract alkali metal, ammonium, and silver ions from the aqueous to the organic phase. The selectivity in partitioning varied with the relative fit of the ionic radius of the metal ion to the hole size of the ring compound. For a typical macroring–metal ion combination, the formation of a 1:1 complex was suggested by uv spectroscopy, and the binding constant was estimated to be more than 10^6 in chloroform. A kinetic study of the transport of alkali metal cations through a liquid membrane revealed that the best carrier for transport is a ligand that gives a moderately stable rather than the very stable complex in the extraction. This was ascribed to the rate-determining release of metal cation from the complex to the aqueous medium.

Macrocyclic polyethers have drawn attention in both chemistry and biology to selective complexation of various metal cations.[1,2] These compounds are characterized by a hydrophilic cavity in their centers in which metal cations are selectively bound depending on their ionic diameters. Such a cavity is covered with hydrophobic alkyl chains which are also indispensable for the complex with metal cations to go through lipophilic biological membrane. Most synthetic ligands are composed of the linear $-CH_2OCH_2-$ unit as a principal chain component. We also know that some of the antibiotic ionophores, e.g., actins, nigericin, and monensin, contain tetrahydrofuran units. Tetrahydrofuran is thought to have a potential utility as a macrocyclic chain component because of its greater donor ability as well as its hydrophilic and lipophilic balance.

In this paper, we describe the preparation of some new macroheterocycles containing tetrahydrofuran as a main constituent with a variation of ring size.[3] These compounds are demonstrated to extract alkali metal cations including ammonium and silver ions into organic media with preference

Scheme I



toward metal ions that fit into the cavity. Kinetic study on the transport of alkali metal ions through model liquid membrane revealed an interesting tendency that the best carrier for a given metal ion is a ligand that gives a loose complex rather than a strong one in the extraction.

Results and Discussion

Synthesis of Macrocycles. The acid-catalyzed condensation of furan and acetone or other ketonic compounds was studied intensively by Brown et al.[3a,b] who isolated linear oligomers of two to four furan units as well as cyclic tetra- and hexamers in the reaction with acetone. We extended this reaction to the preparation of potentially important macrocycles possessing four, five, and six furan units with variation of the carbonyl component.

Furan and acetone or acetaldehyde were condensed in ethanol in the presence of concentrated hydrochloric acid to give linear oligomers possessing two, three, and four furan units (**1**, **2**, and **3**, respectively). Linear pentamer and hexamer (**4** and **5**) were prepared from their smaller fragments **2** and **3** through their condensation with acetone. These linear oligomers were cyclized with acetaldehyde, acetone, or ethyl levulinate in the presence of hydrochloric acid to provide the macrocyclic compounds **6–8**. In the preparation of some cyclic tetramers, the addition of lithium salts raised the cyclization yield considerably possibly by the so-called template effect.[3c] The furan unit of these macrocycles was hydrogenated over ruthenium/carbon or ruthenium–rhodium/carbon in ethanol to yield isomeric mixtures of the designed macrocyclic compounds **9–11** composed of tetrahydrofuran unit. No attempt was undertaken here to separate these isomers. Combination of ruthenium–rhodium catalyst greatly diminished the hydrogenolysis of macrocycles containing ester functionality. Scheme I illustrates the whole aspect of the present syntheses.

Complexation Studies in Organic Solvent. The ability of these macrocycles to bind metal cations was examined by equilibrating a chloroform solution of each macrocycle with aqueous picrate solutions. Metal picrates, nearly insoluble in chloroform except for lithium picrate, are extracted with complex formation, and the decrease in absorbance of the picrate in aqueous phase was taken to be a measure of efficiencies of macrocycles as a complexing agent for the cation.[4] The results are listed in Table I.

A clear tendency to be noted is the close relation between the hole size of macrocycles and the ionic diameter of metal cations to be partitioned most favorably. The smallest cyclic tetramer **9** discriminates between lithium or sodium and the other cations with preference for lithium. It should be worth emphasizing that there is a complete discrimination between sodium and potassium ions in the cases of **9a** and **9b**. The pentamer **10** maximally complexes potassium with less complexation of the adjacent sodium and rubidium ions and rejects both the smallest lithium and the biggest cesium ions. Cyclic hexamer **11** is no longer effective for the binding of most alkali

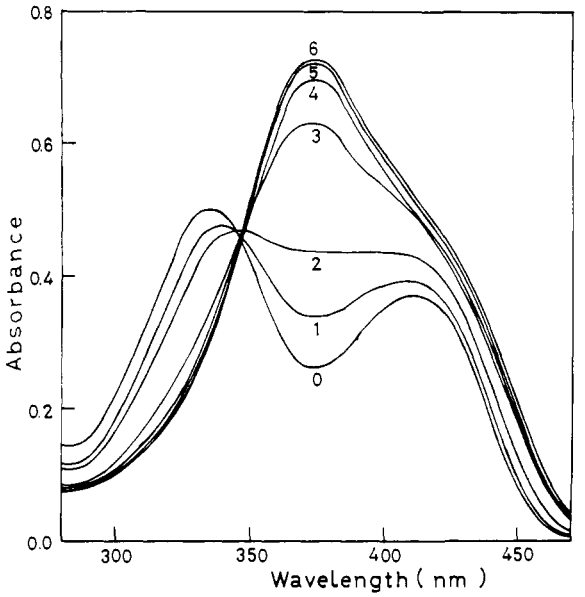


Figure 1. Change of the absorption of lithium picrate on the addition of the ring **9b**. The ratio ring **9b**–lithium picrate is varied as follows: 0, 0.00; 1, 0.16; 2, 0.32; 3, 0.64; 4, 0.80; 5, 0.96; 6, 1.12.

Table I. Extraction of Metal Picrates from Aqueous to Organic Phase (%)[a,b]

Compd	Li^+ (0.60)[c]	Na^+ (0.95)	K^+ (1.33)	Rb^+ (1.48)	Cs^+ (1.69)	NH_4^+ (1.48)	Ag^+ (1.26)
9a	96	66	~0	~0	~0		
9b	84	36	~0	~0	~0		5
9c	39	4	3	~0	~0		
9d	6	3	0				
10[d]	~0	9	23	6	~0	12	52
11	~0	~0	~0	~0	13	4	17

[a] [Ring] = 7.0×10^{-4} M in chloroform, [metal picrate] = 7.0×10^{-5} M, [metal nitrate] = 0.1 M. [b] Blank experiments exhibited no observable extraction for all metal picrates. [c] Values in parentheses are the ionic diameter of the metal ions. [d] [Ring] = 1.0×10^{-3} M. Other conditions are identical with those for the remaining runs.

metal cations and only weakly binds cesium ion. These relationships for alkali metal cations also hold for ammonium and silver ions which are bound most favorably by cyclic pentamer as expected from their ionic diameters.

The substituent of the cycle coming from the carbonyl component has a significant effect on the extent of metal ion extraction. Of a series of cyclic tetramers, the least substituted ring **9a** has the best complexing ability. Introduction of methyl or carbethoxyethyl substituents decreases the extent of extraction, and ligand **9d** is almost ineffective. This effect is not fully understood but might be attributable to steric inhibition by the substituent of the host cycle assuming a geometry favorable to coordination.

These results might be best explained by assuming 1:1 complex formation between macrocyclic ligands and monovalent metal cations. This was confirmed for the combination of **9b** and lithium picrate as a typical example. The ultraviolet spectrum of lithium picrate exhibited two absorptions at 334 and 410 nm in chloroform solution. On addition of **9b**, the spectrum changed gradually to a single absorption at 375.5 nm with a shoulder near 420 nm (Figure 1).[5] Variations in the absorptions at 320, 375.5, and 395.5 nm with the mole ratio of ring to lithium picrate are shown in Figure 2, which clearly indicate the 1:1 complex formation. An equilibrium constant

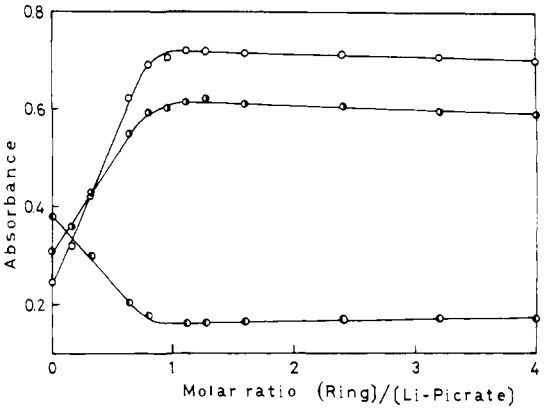


Figure 2. A plot of the absorbance vs. the ratio ring **9b**–lithium picrate at different wavelengths: ○, 375.5 nm; ◑, 395.5 nm; ●, 320 nm.

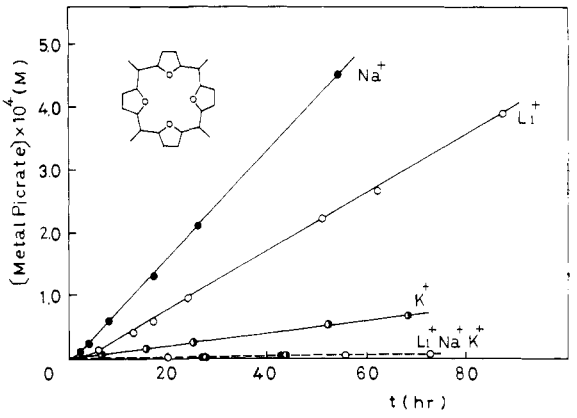
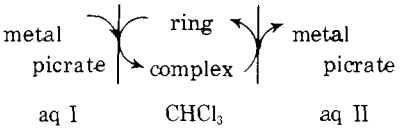


Figure 3. Amount of metal picrates in aqueous phase II as a function of time of transport by **9a**. The broken lines show the blank amount transported without ring compounds.

was estimated to be more than 10^6 by Rose-Drago's method.[6]

Transport of Alkali Metal Cations. The passive transport of alkali metal cations through a liquid membrane[7] was examined using these macrocyclic compounds as a carrier. The metal picrate in the aqueous phase I moves into chloroform solution containing a macrocycle with complex formation and is liberated to the aqueous phase II. The macrocycles employed



were **9a, 9b,** and **11** as well as dibenzo-18-crown-6. A typical run with **9a** was illustrated in Figure 3, where the concentrations of metal picrate in aq II increased proportionally with time. Blank experiments without cyclic carriers showed small transport rates. The net rate of transport by a carrier mechanism was expressed as differences of apparent rates from blank experiments. The transport rates and selectivities are summarized in Table II.

The cyclic tetramer **9a** is the most efficient carrier for the transport of sodium ion and its transport selectivity over potassium ion is calculated to be 9.2. Introduction of more methyl substituent (**9b**) produces a significant decrease of rate and Na^+/K^+ selectivity ratio. Cyclic hexamer cannot be a good carrier for the selective transport of alkali metal cations. These transport rates are of the same order of magnitude as reported for antibiotic beauvericin[8] or cryptate[9] mediated transport of metal picrates, although a direct comparison is difficult by different experimental arrangements. Dibenzo-18-crown-6,

Table II. Transport Rates and Selectivity Ratios of Alkali Metal Picrates through a Liquid Membrane[a]

Carrier	Cation	Carrier concn (10^{-3} mol/l.)	Picrate concn (10^{-3} mol/l.)	Transport rate (10^{-7} mol/h)	Transport selectivity Li^+/Na^+	Transport selectivity Na^+/K^+
9a	Li^+	0.7	2.0	0.56		
		0.7	70	3.75		
	Na^+	0.7	2.0	1.01	0.55	9.2
		0.7	70	10.1		
	K^+	0.7	2.0	0.11		
9b	Li^+	0.7	2.0	0.025		
		0.7	70	*b*		
	Na^+	0.7	2.0	0.052	0.48	5.8
		0.7	70	0.46		
	K^+	0.7	2.0	0.009		
11	Li^+	0.7	70	0.64		
	Na^+	0.7	70	0.63	1.02	
	K^+	0.7	2.4	0.43		
	Rb^+	0.7	1.3	0.36		
	Cs^+	0.7	0.83	0.09		
Dibenzo-18-crown-6	Li^+	0.7	2.0	0.29		
		0.7	70	0.9		
	Na^+	0.7	2.0	4.62	0.06	0.06
		0.7	70	40.3		
	K^+	0.7	2.0	73.5		
Beauvericin[c]	Na^+	0.068	10	0.022		
	K^+	0.068	10	0.026		0.85
Cryptate[d] [2.2.2]	Na^+	1.5	10	6.0		
	K^+	1.5	10	0.3		20

[a] Aq I contains 0.1 M metal nitrate, unless otherwise indicated. [b] Gradual increase of the transport rate was observed. The initial rate was lower than that of sodium. [c] Calculated from ref 8. Aq I contains 1.0 M MCl. [d] Taken from ref 9. Aq II started at the concentration of metal picrate: 1.0×10^{-5} M.

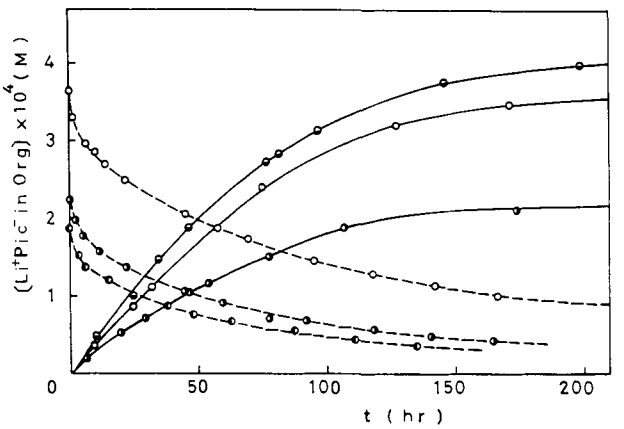


Figure 4. Amount of lithium picrate partitioned as a function of time for the cases: (—) uptake; (- - -) release. The concentration of the ring **9b** is varied as follows: ●, 6.0×10^{-4} M; ○, 5.0×10^{-4} M; ◑, 3.0×10^{-4} M; ◐, 2.5×10^{-4} M.

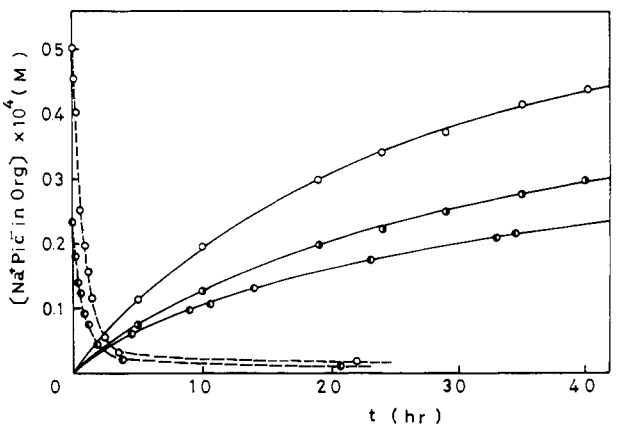


Figure 5. Amount of sodium picrate partitioned as a function of time for the cases: (—) uptake; (- - -) release. The concentration of the ring **9b** is varied as follows: ○, 5.0×10^{-4} M; ◑, 3.0×10^{-4} M; ◐, 2.5×10^{-4} M.

however, transports metal ions much more efficiently under the same experimental conditions. Although the tetrahydrofuran unit is expected to have greater donor ability to metal ions, the transport rate is not very high. This may be due either to steric inhibition by the methyl substituent for oxygen atoms to coordinate to metal ions or to the slower displacement rate of hydrated water from $M^+(H_2O)_n$ by too hydrophobic character of macrorings here prepared.

The effective transport of sodium ion as compared with lithium ion is interesting in that tetramers rather prefer lithium to sodium in the partitioning (Table I). An effect of optimum complex stability for efficient transport of metal ions was demonstrated in the cryptate mediated transport experiments.[9] The tetramers **9a** and **9b** are thought to complex sodium ion rather loosely but transport it most efficiently.

In order to clarify the cause of the apparently contradictory behaviors observed for partition and transport, we studied the time-concentration profiles for the uptake and release of metal picrates by ring **9b** from water to methylene chloride and vice versa. The courses of uptake and release were traced by measuring the absorbances of the complex in the organic phase at specified time intervals. The results are shown in Figures 4 and 5 for the cases of lithium and sodium picrates, respectively.

The release of sodium picrate into the aqueous phase took place much more rapidly than the uptake into the organic phase. In the case of lithium picrate, the rate of release is comparable to that of uptake, allowing much higher accumulation of lithium ion in the organic phase as a complex compared with that of sodium ion. In other words, the lithium ion taken into the organic phase is relatively slowly released to the aqueous phase. These results may suggest that the overall rate of transport is dependent on that of release rather than that of uptake. This conclusion may be useful for the design of effective carrier for transport.

Experimental Section

Infrared spectra were taken on a Hitachi EPl-G spectrophotometer, and ultraviolet spectra were recorded on a Shimadzu UV-200 spectrophotometer. NMR spectra were measured on $CDCl_3$ solution with Varian EM-360 and HA-100D spectrometers. Chemical shifts are given in parts per million relative to tetramethylsilane as an internal standard. Mass spectra were obtained with Hitachi RMS-4 and RMU-6C mass spectrometers at an ionization potential of 70 eV. TLC and column chromatography were performed utilizing Merck silica gel G and 60 (70–230 mesh), respectively.

Linear Oligomers. 2,2-Difurylpropane (1b), 2,5-bis(dimethylfurfuryl)furan (2b), and 2,2′-isopropylidenebis[5-(dimethylfurfuryl)furan] (3b) were prepared from acetone and furan according to the procedure described by Brown et al.[3a]

(a) 2,5-Bis[5-(dimethylfurfuryl)dimethylfurfuryl]furan (4). A mixture of 8.8 g (0.05 mol) of **1b**, 14.2 g (0.05 mol) of **2b**, 5.8 g (0.1 mol) of acetone, and 20 ml of 35% hydrochloric acid in 200 ml of ethanol was let stand for 4 days with occasional shaking. After evaporation of solvent, the residue was dissolved in ether, washed with aqueous sodium bicarbonate, dried (Na_2SO_4), and evaporated to leave an yellow oil, which was distilled by using a Kügelrohr microdistilling apparatus at 170–180 °C (0.02 mm). The product was finally purified by column chromatography (25% benzene–hexane) to give 7.9 g (32%) of pure **4**: ir (neat) 2990, 2950, 2885, 1510, 1390, 1370, 1205, 1160, 1100, 1015, 955, 930, 785, and 730 cm^{-1}; NMR ($CDCl_3$) δ 1.56 (s, 12 H, $-CH_3$), 1.58 (s, 12 H, $-CH_3$), 5.72 (s, 2 H, central furan), 5.75 (AB quartet, 4 H, J = 3.2 Hz, furan next to terminal), 5.82 (d of d, 2 H, J = 3.2, 1.0 Hz, inside β-H of terminal furan), 6.16 (d of d, 2 H, J = 3.2, 1.8 Hz, outside β-H of terminal furan), 7.21 (d of d, 2 H, J = 1.8, 1.0 Hz, α-H); mass spectrum m/e (%) 500 (100), 486 (150), 485 (390), 377 (100), 269 (40). Anal. Calcd for $C_{32}H_{36}O_2$: C, 76.77; H, 7.25; O, 15.98. Found: C, 76.50; H, 7.74; O, 16.01.

(b) 2,2′-Isopropylidenebis[[5-(dimethylfurfuryl)dimethylfurfuryl]furan] (5). To a warm solution of 5.0 g (17.6 mmol) of 2,5-bis(dimethylfurfuryl)furan (**2b**) in a mixture of 40 ml of ethanol and 7 ml of 35% hydrochloric acid was added 1.02 g (17.6 mmol) acetone. The solid was precipitated during stirring for 2 days at room temperature, dissolved in ether, washed with sodium bicarbonate, dried, and concentrated. Column chromatography (30% benzene–hexane) afforded 2.03 g (38%) of **5** as a white solid: mp 83–85 °C; ir (KBr) 3155, 3130, 3010, 2980, 2942, 2875, 1600, 1580, 1550, 1500, 1445, 1380, 1360, 1280, 1245, 1205, 1170, 1160, 1150, 1135, 1100, 1080, 1025, 1015, 970, 965, 995, 935, 900, 890, 840, 810, 800, 795, and 730 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 18 H, $-CH_3$), 1.59 (s, 12 H, $-CH_3$), 5.78 (s, 4 H, central furan), 5.83 (AB quartet, 4 H, J = 3.2 Hz, furan next to terminal), 5.93 (d of d, 2 H, J = 3.2, 1.0 Hz, inside β-H of terminal furan), 6.23 (d of d, 2 H, J = 3.2, 1.8 Hz, outside β-H of terminal furan), 7.27 (d of d, J = 1.8, 1.0 Hz, α-H); mass spectrum m/e (%) 608 (100), 594 (180), 593 (440), 289 (290), 217 (240). Anal. Calcd for $C_{39}H_{44}O_6$: C, 76.95; H, 7.29; O, 15.77. Found: C, 76.90; H, 7.46; O, 15.41.

(c) 1,1-Difurylethane (1a), 2,5-Bis(methylfurfuryl)furan (2a), and 1,1′-Ethylidenebis[5-(methylfurfuryl)furan] (3a). To a ice-cooled mixture of 68 g (1.0 mol) of furan, 30 ml of ethanol, and 20 ml of 35% hydrochloric acid, 22 g (0.5 mol) of acetaldehyde was added with stirring. The addition required 30 min and the reaction was continued for 20 h at room temperature. The resulting dark green solution was diluted with ether, washed with sodium bicarbonate, and dried. After evaporation of solvents and unreacted furan, a mixture of **1a, 2a,** and **3a** was fractionally distilled.

1a: bp 91 °C (21 mm); yield 27.1 g (33.4%); ir (neat) 3125, 2985, 2940, 2885, 1585, 1500, 1445, 1365, 1310, 1240, 1230, 1175, 1150, 1010, 930, 910, 885, 805, and 735 cm^{-1}; NMR ($CDCl_3$) δ 1.56 (d, 3 H, J = 7.0 Hz, $-CH_3$), 4.19 (q, 1 H, J = 3.2, 1.8 Hz, outside β-H of furan), 7.27 (d of d, 2 H, J = 1.8, 0.8 Hz, α-H); mass spectrum m/e (%) 162 (100), 148 (27), 91 (95), 77 (27), 65 (49). Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21; O, 19.73. Found: C, 73.95; H, 5.98; O, 19.70.

2a: bp 114–116 °C (0.1 mm); yield 23.7 g (28%); ir (neat) 3120, 2980, 2940, 1590, 1550, 1500, 1450, 1370, 1230, 1170, 1150, 1010, 950, 915, 885, 805, 790, and 735 cm^{-1}; NMR ($CDCl_3$) δ 1.54 (d, 6 H, J = 7.0 Hz, $-CH_3$), 4.15 (q, 2 H, J = 7.0 Hz, $-CH$), 5.90 (d, 2 H, J = 0.4 Hz, central furan), 5.98 (d of t, 2 H, J = 3.2, 0.8 Hz, inside β-H of terminal furan), 6.24 (d of d of d, 2 H, J = 3.2, 1.8, 0.3 Hz, outside β-H of terminal furan), 7.27 (d of d, 2 H, J = 1.8, 0.8 Hz, α-H); mass spectrum m/e (%) 256 (100), 242 (30), 241 (190), 161 (68), 141 (30), 113 (23), 105 (58), 95 (66), 81 (51), 77 (34). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29; O, 18.73. Found: C, 74.99; H, 6.38; O, 18.43.

3a: bp 165–168 °C (0.03 mm); yield 9.1 g (10%); ir (neat) 3120, 2980, 2940, 2880, 1700, 1585, 1545, 1500, 1445, 1370, 1300, 1295, 1235, 1170, 1150, 1055, 1010, 965, 950, 915, 885, 790, and 735 cm^{-1}; NMR ($CDCl_3$) δ 1.52 (d, 3 H, J = 7.2 Hz, central $-CH_3$), 1.54 (d, 6H, J = 7.2 Hz, terminal-CH_3), 4.11 (q, 1 H, J = 7.2 Hz, central-CH), 4.16 (q, 2 H, J = 7.2 Hz, terminal -CH), 5.88 (AB quartet, 4 H, J = 3.2 Hz, inside furan), 5.99 (d of t, 2 H, J = 3.2, 0.8 Hz, inside β-H of terminal furan), 6.25 (d of d, 2 H, J = 3.2, 1.8 Hz, outside β-H of terminal furan), 7.28 (d of d, 2 H, J = 1.8, 0.8 Hz, α-H); mass spectrum m/e (%) 351 (100), 350 (440), 336 (140), 335 (130), 189 (170). Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33; O, 18.26. Found: C, 75.51; H, 6.47; O, 18.36.

(d) 4-Carbethoxy-2,2′-*sec*-butylidenebis[5-(dimethylfurfuryl)furan] (3c). A solution of 5.3 g (0.03 mol) of **1b**, 4.3 g (0.03 mol) of ethyl levulinate, and 10 ml of concentrated hydrochloric acid in 40 ml of ethanol was saturated with gaseous hydrochloric acid. Yellowish oil separated out during 7 h of stirring, when the solution was neutralized with sodium bicarbonate, extracted with ether, dried, and evaporated. Column chromatography (30% hexane–benzene) afforded 4.3 g (60%) of **3c**: ir (neat) 3120, 2980, 2940, 2875, 1740, 1550, 1500, 1460, 1380, 1100, 1015, 960, 930, 790, and 735 cm^{-1}; NMR ($CDCl_3$) δ 1.18 (t, 3 H, J = 6.5 Hz, $-CH_3$), 1.52 (s, 3 H, $-CH_3$), 1.59 (s, 12 H, $-CH_3$), 2.21 (s, 4 H, $-CH_2CH_2$), 4.02 (q, 2 H, J = 6.5 Hz, $-OCH_2$), 5.85 (q, 4 H, J = 3.2 Hz, central furan), 5.93 (d of d, 2 H, J = 3.2, 1.0 Hz, inside β-H of terminal furan), 6.16 (d of d, 2 H, J = 3.2, 1.8 Hz, outside β-H of terminal furan), 7.21 (d of d, 2 H, J = 1.8, 1.0 Hz, α-H). Anal. Calcd for $C_{29}H_{34}O_6$: C, 72.78; H, 7.16; O, 20.06. Found: C, 72.64; H, 7.13; O, 20.00.

Macrocycles of Furan. The cyclic tetramer of furan and acetone, **6b,** was obtained according to the method described by Brown et al.[3a]

(a) 5,10,15,20-Tetramethyl-1,4,6,9,11,14,16,19-tetraoxocycloeicosa-1,3,6,8,11,13,16,18-octaene (6a). A mixture of 1 g (6.2 mmol) of 1,1-difurylethane (**1a**), 1 ml of 90% acetaldehyde, 1 ml of 60% perchloric acid, 0.5 g of lithium sulfate, and 20 ml of ethanol was stirred at room temperature for 2 days. The resulting brown solution was diluted with benzene, washed with sodium bicarbonate, and dried. After evaporation of solvents, the product was subjected to column chromatography to give almost pure **6a,** which was finally purified by sublimation at 120–130 °C in vacuo to give 150 mg (13%) of pure **6a:** mp 140–142 °C; ir (KBr) 2980, 2940, 2885, 1565, 1455, 1260, 1235, 1015, 955, 780, and 745 cm^{-1}; NMR ($CDCl_3$) δ 1.49 (d, 24 H, J = 7.0 Hz, $-CH_3$), 3.98 4.00, 4.02 (three sets of t, 4 H, J = 7.0 Hz, -CH, rel intensity 1:0.8:0.6), 5.94 (s, 8 H, furan); mass spectrum m/e (%) 377 (25), 376 (100), 362 (53), 361 (220), 346 (16), 331 (24), 316 (18), 173 (36), 158 (43). Anal. Calcd for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43; O, 17.00. Found: C, 76.34; H, 6.46; O, 17.28.

(b) 5-(β-Carbethoxyethyl)-5,10,10,15,15,20,20-heptamethyl-1,4,6,9,11,14,16,19-tetraoxocycloeicosa-1,3,6,8,11,13,16,18-octaene (6c). Hydrogen chloride gas was bubbled into a solution of 3.92 g (0.01 mol) of **3b** and 7.2 g (0.05 mol) of ethyl levulinate in 150 ml of benzene and the solution was stirred at room temperature for 3 days. The reaction mixture was washed with sodium bicarbonate, dried, and evaporated. The unreacted ethyl levulinate was distilled under reduced pressure and the crude solid was recrystallized twice from ethanol to give 1.8 g (36%) of white crystals of **6c:** mp 150–152 °C; ir (KBr) 2980, 1740, 1560, 1260, 1210, 1155, 1110, 1025, 955, and 775 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (t, 3 H, J = 7.0 Hz, $-CH_3$), 1.41 and 1.46 (s, 21 H, $-CH_3$), 2.16 (s, 4 H, $-CH_2CH_2$), 4.09 (q, 2 H, J = 7.0 Hz, $-OCH_2$), 5.92 (s, 8 H, furan). Anal. Calcd for $C_{32}H_{38}O_6$: C, 74.11; H, 7.39; O, 18.51. Found: C, 73.91; H, 7.60; O, 18.23.

(c) 5,15-Bis(β-carbethoxyethyl)-5,10,10,15,20,20-hexamethyl-1,4,6,9,11,14,16,19-tetraoxocycloeicosa-1,3,6,8,11,13,16,18-octaene (6d). A similar treatment of **3c** and ethyl levulinate as described above afforded crystalline compound **6d** in a yield of 56% after purification through column chromatography (benzene); mp 126–128 °C; ir (KBr) 2980, 2940, 2880, 1740, 1605, 1560, 1460, 1420, 1380, 1305, 1180, 1095, 1025, 950, and 775 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, 6 H, J = 7.0 Hz, $-CH_3$), 1.42 (s, 6 H, $-CH_3$), 1.46 (s, 12 H, $-CH_3$), 2.18 (br s, 8 H, $-CH_2$), 4.08 (q, 4 H, J = 7 Hz, $-OCH_2$), 5.91 (AB quartet, 8 H, J = 4 Hz, furan). Anal. Calcd for $C_{36}H_{44}O_8$: C, 71.50; H, 7.33; O, 21.17. Found: C, 71.76; H, 7.45; O, 21.04.

(d) 5,5,10,10,15,15,20,20,25,25-Decamethyl-1,4,6,9,11,14,16,-19,21,24-pentaoxocyclopentacosa-1,3,6,8,11,13,16,18,21,23-decaene (7). Hydrogen chloride gas was bubbled into a solution of 1.3 g (2.6 mmol) of **4** and 4 ml of acetone in 30 ml of benzene. The red solution was stirred at room temperature for 2 days, washed with sodium bicarbonate, and dried. Column chromatography (30% benzene–hexane) gave 0.64 g (45%) of **7** as an oil: ir (neat) 2980, 2940, 2875, 1545, 1460, 1380, 1360, 1205, 1155, 1135, 1105, 1025, 955, and 780 cm^{-1}; NMR ($CDCl_3$) δ 1.52 (s, 30 H, $-CH_3$), 5.76 (s, 10 H, furan); mass spectrum *m/e* (%) 540 (100), 526 (93), 525 (240), 255 (59), 223 (59), 205 (41). Anal. Calcd for $C_{35}H_{40}O_5$: C, 77.75; H, 7.46; O, 14.79. Found: C, 77.65; H, 7.42; O, 14.59.

(e) 5,5,10,10,15,15,20,20,25,25,30,30-Dodecamethyl-1,4,6,-9,11,14,16,19,21,24,26,29-hexaoxocyclotriaconta-1,3,6,8,11,13,16,-18,21,23,26,28-dodecaene (8). Hydrogen chloride gas was bubbled into a solution of 1.9 g (3.13 mmol) of **5** and 4 ml of acetone in 60 ml of benzene. The mixture was stirred overnight at room temperature and worked up as usual. Chromatography (30% benzene–hexane) provided 1.05 g (52%) of white crystals of **8:** mp 182 °C; ir (KBr) 3110, 2980, 2940, 2875, 1550, 1445, 1360, 1205, 1155, 1110, 1025, 960, 790, and 720 cm^{-1}; NMR ($CDCl_3$) δ 1.54 (s, $-CH_3$), 5.74 (s, furan); mass spectrum *m/e* (%) 648 (100), 634 (125), 633 (280), 309 (75). Anal. Calcd for $C_{42}H_{48}O_6$: C, 77.75; H, 7.46; O, 14.79. Found: C, 77.96; H, 7.41; O, 14.93.

Macrocycles of Tetrahydrofuran. (a) 5,10,15,20-Tetramethyl-1,4,6,9,11,14,16,19-tetraoxocycloeicosane (9a). A solution of 250 mg (0.57 mmol) of **6a** and 200 mg of ruthenium carbon (5%) in 30 ml of ethanol was pressured in a microbomb with hydrogen to 120 atm and heated at 190 °C for 6 h. After removal of catalyst by filtration and evaporation of solvent, the crude product was chromatographed (50% benzene–ethyl acetate) to give 165 mg (73%) of oily product **9a** which is possibly mixtures of configurational isomers: ir (neat) 2980, 2940, 2890, 1460, 1380, and 1080 cm^{-1}; NMR ($CDCl_3$) δ 0.86 (br s, 12 H, $-CH_3$), 1.2–2.2 (br, 20 H, $-CH_2$ and $-CH$), 3.3–4.2 (br, 8 H, $-OCH$); mass spectrum *m/e* (%) 392 (100), 376 (51), 374 (32), 323 (26), 295 (76), 279 (44), 267)37), 265 (49). Anal. Calcd for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27; O, 16.30. Found: C, 73.49; H, 10.40; O, 15.89.

(b) 5,5,10,10,15,15,20,20-Octamethyl-1,4,6,9,11,14,16,19-tetraoxocycloeicosane (9b)[3c] was prepared by the hydrogenation in a similar manner described above.

(c) 5-(β-Carbethoxyethyl)-5,10,10,15,15,20,20-heptamethyl-1,4,6,9,11,14,16,19-tetraoxocycloeicosane (9c). A solution of 100 mg (0.20 mmol) of **6c,** 50 mg of ruthenium carbon (5%), and 7.5 mg of rhodium chloride in 30 ml of ethanol was pressured in a microbomb with hydrogen to 140 atm and heated at 250 °C for 5 h. After removal of catalyst and evaporation of solvent, the crude product was chromatographed (30% hexane–benzene) to give 16 mg (15%) of isomeric mixtures of **9c** as an oil: ir (neat) 2970, 2880, 1740, 1460, 1380, 1295, 1260, 1175, and 1080 cm^{-1}; NMR ($CDCl_3$) δ 0.74, 0.80, 0.92, 1.02, and 1.05 (s, $-CH_3$, rel intensity 22:19:20:3:6), 1.04 and 1.05 (t, J = 7.0 Hz, $-CH_3$ of ester, rel intensity 9:6), 1.3–1.8 and 2.2–2.5 (br, $-CH_2$, rel intensity 46:14), 3.15–4.1 (br m, $-CH$, rel intensity 26), 4.10 and 4.11 (q, $-OCH_2$, rel intensity 3.5:2.5). Anal. Calcd for $C_{32}H_{54}O_6$: C, 71.87; H, 10.18; O, 17.95. Found: C, 71.72; H, 10.31; O, 17.85.

(d) 5,15-Bis(β-carbethoxyethyl)-5,10,10,15,20,20-hexamethyl-1,4,6,9,11,14,16,19-tetraoxocycloeicosane (9d). A sample of 100 mg (0.17 mmol) of **6c** was hydrogenated at 200–230 °C as described above to give 70 mg (68%) of isomeric mixtures of **9d** as an oil: ir (neat) 2970, 2880, 1730, 1550, 1455, 1360, 1290, 1080, 1020, and 785 cm^{-1}; NMR ($CDCl_3$) δ 0.76, 0.80, 0.92, and 1.02 (s, $-CH_3$, rel intensity 14:17:12:6), 1.24 (t, J = 7.0 Hz, $-CH_3$ of ester, rel intensity 18), 1.3–2.0 and 2.1–2.7 (br m, $-CH_2$, rel intensity 16:47), 3.2–4.0 (br, $-CH$, rel intensity 18), 4.10 (q, J = 7.0 Hz, $-CH_2$ of ester, rel intensity 10). Anal. Calcd for $C_{36}H_{60}O_8$: C, 69.64; H, 9.74; O, 20.62. Found: C, 69.73; H, 9.95; O, 20.35.

(e) 5,5,10,10,15,15,20,20,25,25-Decamethyl-1,4,6,9,11,14,16,-19,21,24-pentaoxocyclopentacosane (10). A sample of 1.3 g (2.4 mmol) of **7** was hydrogenated under 140 atm at 190 °C for 8 h as described in the preparation of **9a.** After purification through column chromatography (benzene), 0.98 g (68%) of isomeric mixtures of **10** was obtained as an oil: ir (neat) 2970, 2880, 1470, 1390, 1360, 1290, and 1075 cm^{-1}; NMR ($CDCl_3$) δ 0.77, 0.79, 0.82, 0.84, 0.89, and 0.95 (s, $-CH_3$, rel intensity 84), 1.4–1.8 (br q, $-CH_2$, rel intensity 58), 3.5–3.8 (br q, $-CH$, rel intensity 28); mass spectrum *m/e* (%) 561 (41), 560 (100), 542 (16), 449 (19), 337 (32), 295 (28), 293 (47), 267 (49), 251 (66), 225 (300). Anal. Calcd for $C_{35}H_{60}O_5$: C, 74.95; H, 10.78; O, 14.26. Found: C, 75.13; H, 10.90; O, 14.23.

(f) 5,5,10,10,15,15,20,20,25,25,30,30-Dodecamethyl-1,4,6,9,-11,14,16,19,21,24,26,29-hexaoxocyclotriacontane (11). A sample of **8** (200 mg, 0.31 mmol) was hydrogenated under 140 atm at 160 °C for 6 h as described in the preparation of **9a** to give 130 mg (63%) of oily product **11,** which is possibly mixtures of configurational isomers but did not contain unhydrogenated furan protons in NMR. Separation of the main fraction through column chromatography (benzene) afforded 60 mg of solid material: mp 75–80 °C; ir (KBr) 2980, 2880, 1470, 1390, 1360, and 1070 cm^{-1}; NMR ($CDCl_3$) δ 0.74–0.93 (6 s, $-CH_3$), 1.63 (2 br peaks, $-CH_2$), 3.59 (br q, $-CH$); mass spectrum *m/e* (%) 673 (64), 672 (100), 653 (22), 561 (13), 449 (26), 407 (21), 405 (20). Anal. Calcd for $C_{42}H_{72}O_6$: C, 74.95; H, 10.78; O, 14.26. Found: C, 74.71; H, 10.77; O, 14.41.

Kinetics of Transport. In a cylindrical glass cell (4.9 cm i.d.) was held a glass tube (2.7 cm i.d.) which separates the two aqueous phases. The inner aq I contains specified concentrations of metal picrate and 0.1 M metal nitrate in 3 ml of water. The outer aq II contains 12 ml of water purified through ion-exchange resin. The organic layer (25 ml of chloroform containing 7.0×10^{-4} M ring compound) lies below these aqueous phases and bridges them across the separation by the central glass tube. The chloroform layer was stirred at a constant speed. The absorptions of the picrate present in the aq II were measured at specified time intervals. The change of organic layer from chloroform to methylene chloride showed no significant difference in the transport rate.

Kinetics of Partition. In a glass cell were placed 10 ml each of methylene chloride and aqueous solution. For the uptake of metal picrates, the aqueous solution contained 7.0×10^{-2} M metal picrate and 0.1 M metal nitrate. The ring concentration in the organic layer was varied from 2.5×10^{-4} to 6.0×10^{-4} M. For the release, the organic layer contained the ring–metal picrate complex which was obtained by equilibrating the organic solution containing the ring compound and the aqueous metal picrate and nitrate solution. For both cases, the lower organic layer was stirred at a constant speed, and the absorptions of metal picrates in the organic layer were monitored at 375 and 358 nm for lithium and sodium picrates, respectively.

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