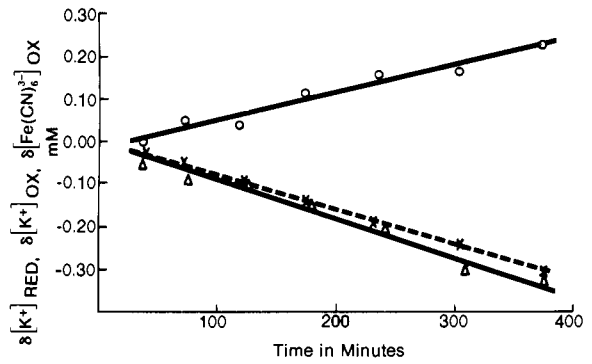

Figure 2. Time dependence of the concentrations of K^+ and $Fe(CN)_6^{3-}$ in RED and OX phases for run 3 (Table I): $\delta[K^+]_{RED}$ (△), $\delta[K^+]_{OX}$ (○), $\delta[Fe(CN)_6^{3-}]_{OX}$ (×), are differences in concentration at time t minus concentration at time $t = 0$.

tained under different conditions. The following comments may be made. (1) When neither **1** nor **2** is present in the membrane, the system remains unchanged. (2) With the complete system represented in Figure 1 (Table I, runs 1-3), the K^+ concentration decreases in RED and increases by about the same amount in OX where also the ferricyanide concentration decreases similarly (Figure 2). Thus, the membrane has become permeable to electrons and to K^+ cations which flow simultaneously from RED to OX: compounds **1** and **2** function as *electron* and *cation carriers*, respectively. (3) No transport is observed when *either* **1** (Table I, runs 4, 5) or **2** (Table I, runs 6, 7) are absent in the membrane. (4) The observed e^-/K^+ *symport* may be explained by a four-step reaction sequence: (i) at the RED/M interface, (**1**-Ni^0) is reduced by $S_2O_4^{2-}$ and charge neutrality is maintained by simultaneous transfer of a K^+ cation to the ligand **2** to form the double-complex ion pair {(**1**-Ni^-),$[K^+]$}; (ii) the {(**1**-Ni^-),$[K^+]$} species diffuses across the membrane; (iii) it is oxidized by ferricyanide at the M/OX interface regenerating (**1**-Ni^0) and releasing K^+ at the same time; (iv) the oxidized electron carrier and the empty macrocyclic ligand diffuse back to the RED/M interface where the cycle starts again. (5) *Active K^+ transport* against its concentration gradient (uphill) occurs, driven by the redox gradient and the electron flow (see for instance Figure 2). (6) The transport rate is *cation dependent;* it is much slower when only Na^+ cations are present (Table I, runs 8, 9). Indeed **2** and similar ligands are known to complex and to transport K^+ more efficiently than Na^+.[10,12] (7) The total process thus involves a *redox pump*, via the electron carrier, a cation *selection* process, via the macrocyclic ligand, and a *regulation* process since transport rates depend on the carrier efficiency for a given ligand-cation pair.

The model system described in this report (Figure 1) may be considered as a prototype for the design of other multicarrier coupled transport systems. A number of variations and extensions may be envisaged either as biological models[2b] or as potential applications. For instance, employing other carriers for anions as well as for cations will provide different substrate selectivity; coupling with a light-driven process[1] also represents a promising extension.

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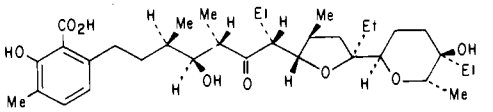
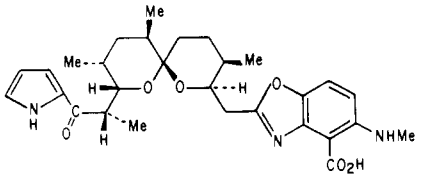
Synthesis of New, Noncyclic Ionophores Exhibiting Efficient Ca^{2+} Transport

Sir:

The phenomenon of ion transport across cell and organelle membranes which mediate numerous cellular events is receiving ever-increasing attention.[1] Although a number of naturally occurring molecules are known which substantially enhance the passive transport of ions across cell membranes (ionophores),[2,3] they are all relatively complex structures requiring multistep procedures for organic synthesis. Two of the more oft-employed ionophores as biochemical tools are the polyether antibiotics, X-537A[4] and A-23187, which represent



X-537A (LASALOCID)



A23187

the class of monobasic, carrier-type ionophores.[1a] We believed that the intriguing possibility of designing and constructing a synthetic ligand system capable of mimicking the transport properties of these complex ionophores merited further attention[5] and report herein our approach to this goal.

To fulfill the interrelated criteria for ion selectivity and

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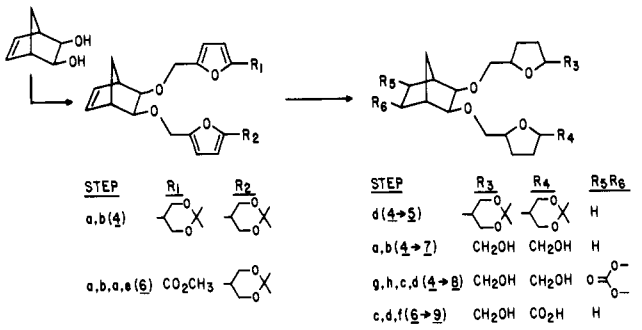
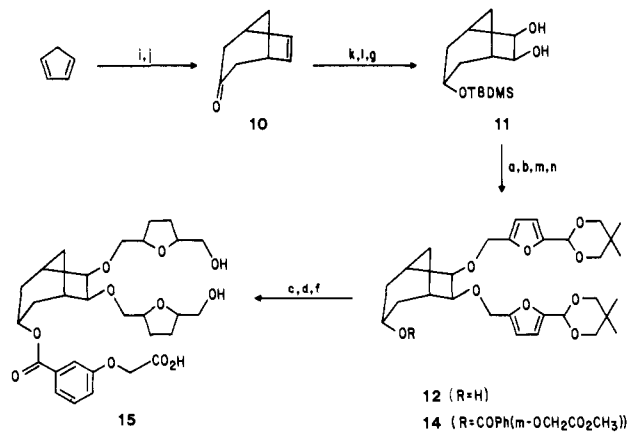
Scheme I[a]



[a] (a) NaH (2 equiv where required), DMF; (b) **2**; (c) CH_3COCO_2H (10 equiv), toluene; (d) Ni(Ra), H_2, ethanol; (e) **3**; (f) KOH, CH_3OH; (g) OsO_4, NMO, acetone, water; (h) Im_2CO, toluene, Δ; (i) Br_2-$CHCOCHBr_2$, $Fe(CO)_5$; (j) Zn–Cu, CH_3OH; (k) LiBH (*s*-Bu)$_3$; (l) $(CH_3)_3C(CH_3)_2SiCl$, Im, DMF; (m) Bu_4NF, THF; (n) **13** acid chloride, pyridine.

Scheme II[a]



[a] See footnote, *a*, Scheme I.

transport kinetics[6-10] we have designed two related systems employing the 2,5-dioxytetrahydrofuran as the ligand subunit. To maintain a degree of symmetry, and thus simplify the required chemical synthesis, as well as restrict rotomer possibilities and provide for a directing, neutralizing group (CO_2H) for divalent ion transport, we have bridged these ligand subunits with the bicyclo[2.2.1]heptane and bicyclo[3.2.1]octane systems (Schemes I and II).

Cis-hydroxylation of bicyclo[2.2.1]heptadiene with catalytic osmium tetroxide-*N*-methylmorpholine *N*-oxide[11] afforded the exo diol, **1**.[12] Bisalkylation of **1** with furan, **2**[22a] (mp 72–74 °C), prepared in 78% yield from 5-hydroxymethylfurfural[13] via acetalization with 2,2-dimethyl-1,3-propanediol (followed by thionyl chloride (2,6-lutidine, EtOAc) to give **4**[22b,23]), can

2 **3**

be realized in 92% yield at room temperature with the careful exclusion of moisture employing only 10% mol excess of **2**. Alternatively, the alkylation can be readily stopped at the monoalkylated stage, and a second furan reagent, **3**,[14] introduced to afford the unsymmetrical **6**[22b,23] in a one-flask operation (55%; oil; IR (neat) 1725 cm^{-1} (CO)). Deprotection of **4** with pyruvic acid (distilled) followed by reduction afforded **7** (oil; IR (neat) 3500 cm^{-1}) presumed to be a mixture of cis-syn and cis-anti isomers.[15] To modify the lipophilicity of **7** a carbonate function was introduced by cis-hydroxylation (only one isomer detected, undoubtedly exo)[16] followed by addition

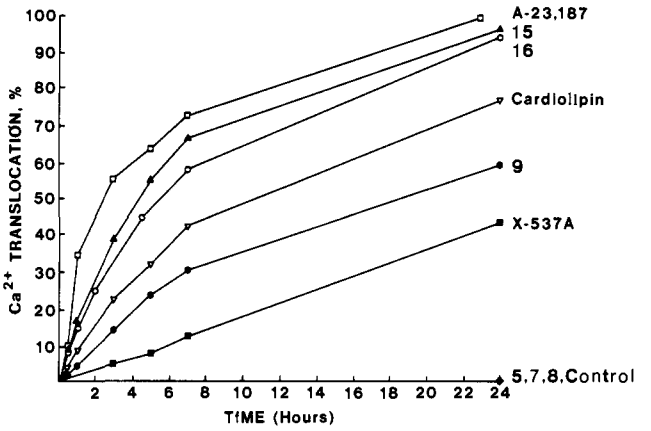
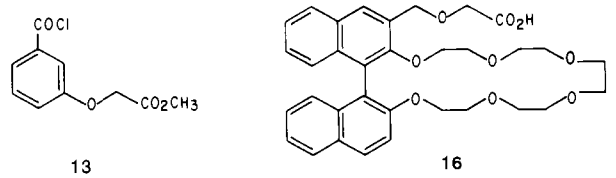


Figure 1. Ionophore mediated Ca^{2+} translocation through a chloroform (10% ethanol) layer of U-tube[25] (Pressman cell). A 1-mL donor aqueous phase (25 mM Tris buffer, pH 8.5, 0.1 mM picrate, 0.1 mM $CaCl_2$, and $^{45}Ca^{2+}$) is separated from the aqueous acceptor phase (50 mM citrate, pH 5.5) by a stirred 10% ethanol–chloroform (3 mL) phase (0.6 μmol of ionophore), except for **16** which is present as 4 μmol. At each time point duplicate 10-μl aliquots are withdrawn from the acceptor phase and counted. Reproducibility (duplicate runs) was ±10%.

of diimidazole carbonyl,[17] deprotection, and reduction to give **8**[22b] (70% from **4**; oil; IR (neat) 3500, 1810 cm^{-1}; ^{13}C NMR ($CDCl_3$) 155.4 (CO)).[15b] As an example of an open "crown" **4** was reduced directly to **5**[22a] (60%; oil; ^1H NMR ($CDCl_3$) 4.38 (2 H, d, J = 5 Hz)). The unsymmetrical **6** was deprotected, reduced, and hydrolyzed to provide the *cis*-tetrahydrofuran isomers[15a] of **9**[22a] which incorporates a CO_2H for comparison (30%; oil; IR (neat) 3400 (br), 1745 cm^{-1}).

Scheme II depicts the chemistry employed to furnish the bicyclo[3.2.1]octane bridged system designed to provide for spatial orientation of an ionizable group in the vicinity of the 2,5-dioxytetrahydrofuran ligand framework (based on CPK models).

Bicyclo[3.2.1]octenone (**10**), prepared via the method of Noyori et al.,[18] was reduced to the known endo alcohol exclusively with lithium tri(*sec*-butyl)borohydride.[19] Protection[20] and hydroxylation afforded only the exo diol **11**[21,22b] (18% yield from cyclopentadiene; oil; IR (neat) 3500 cm^{-1}; ^1H NMR ($CDCl_3$), 4.52 ("d", J = 2 Hz, C*H*OH)). Bisalkylation with furyl chloride **2** (88%) followed by deprotection gave **12**.[22b] The meta-substituted benzoyl chloride **13**[24] was selected for the directional ligand containing an ionizable group and



13 **16**

introduced via acylation in pyridine to yield **14**[22b,23] (IR (neat) 1770, 1730 cm^{-1}). Acetal removal, reduction, and hydrolysis afforded the desired target molecule, **15** (65%; IR (neat) 3500, 3000–2500, 1740, 1720 cm^{-1}; ^{13}C NMR ($CDCl_3$), 168.9 (PhCO), 165.2 ($-CO_2-$)).[15b,22b]

Now in hand were a series of ligands which contained a directional, ethereal ligand framework (noncyclic "crown") in **5** (dipole–dipole) which was modified to (1) decrease lipophilicity as in **7** and **8**, (2) introduce pole–dipole capabilities within the ligand system as in **9**, and (3) incorporate a three-dimensional, directed ligand system with pole–dipole interactions possible with structure **15**. Since the directed, noncyclic "crown" of **5** has a best plane (three oxygen atoms) capability of a 2.0–2.6-Å diameter (by CPK models), one might, therefore, predict for divalent ion complexation and transport, such as Ca^{2+}, that **15** > **9** > **8** ~ **7** ≳ **5**.

Table I. Complexation of Na^+/K^+ by Neutral Ligands[a]

	K picrate, %	Na picrate, %
5	10	33
7	5	25
8	5	28
18-crown-6	100	100
blank	0.7	0.4

[a] Determined by measuring A_{360} (nm) of a stirred chloroform solution, 10 mM in ligand, 10 mM picrate after 30 min.

In fact, as indicated in Figure 1, the Ca^{2+} transport properties were in exactly that order, as measured in the standard U-tube test system. Secondly, the transport capability of **15**, particularly, compares very favorably with the best known Ca^{2+} ionophores, A-23187 and X-537A. It is of interest also to compare the transport efficiencies of **15** and **9** with a crown ether possessing a directional carboxyl ligand such as **16**.[26] Although the bridging components differ (binapthyl vs. bicyclooctane) it is apparent that a cyclic ligand system is less efficient, since, as depicted in Figure 1, nearly 7 equiv of **16** are required to approach the transport capabilities of **15**.[28]

Although nonionizable ligands such as **5**, **7**, and **8** do not exhibit Ca^{2+} translocation in this system, they do bind monovalent ions as seen in the solubilization of sodium and potassium picrate (Table I). We are continuing our investigation into synthetic ionophores and will report the interesting biological properties of these ligands in due course.

Acknowledgments. We thank Mr. R. J. Seeley for technical assistance with some of the transport work, Mr. R. Wnuk for mass spectral determinations, Mr. P. A. Marlatt for scale-up preparations of hydroxymethylfurfural, and Professor D. J. Cram for helpful discussions.

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(15) (a) See H. Gerlach and H. Wetter, *Helv. Chim. Acta*, **57**, 2087 (1974); M. J. Arco, M. H. Trammell, and J. D. White, *J. Org. Chem.*, **41**, 2075 (1976); D. Gragnaire and P. Monzeglio, *Bull. Soc. Chim. Fr.*, 474 (1965). (b) The ^{13}C NMR decoupled spectrum indicated two sets of singlets for the carbons of the furan ring and the CHO carbon of the bicyclo[2.2.1]heptane and furan appended CH_2O. This is in agreement with the symmetry that would still exist in the cis-syn and cis-anti isomers of **7**. NMR units are given in parts per million.
(16) See papers by H. Z. Sable and H. Katchian (*Carbohydr. Res.*, **5**, 109 (1967)), Y. F. Shealy and J. D. Clayton (*J. Am. Chem. Soc.*, **91**, 3075 (1969)), M. C. Thorpe and W. C. Coburn, Jr. (*J. Org. Chem.*, **34**, 2576 (1969)), for examples of norbornenediols and tetraols. Furthermore, examination of the 7s,7a protons in **4** relative to the diol (reaction g) and the cyclic carbonate (reaction h) show the expected coalescing of the AB of **4** (7s, 1.68, m; 7a, 2.08, d, J = 9 Hz) to a broad multiplet in the more symmetrical diol (1.74, 7a and 7s) and back to the AB of the carbonate with both 7a and 7s showing similar W coupling with the endo protons (1.70 and 2.15, br d, J = 12 Hz).
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(22) Satisfactory (a) ^1H NMR and elemental analysis/mass spectral data or (b) ^1H and ^{13}C NMR and elemental analysis–mass spectral data were obtained for this compound.
(23) ^1H NMR ($CDCl_3$): **4**, 6.38, 6.25 (4 H, dd, J = 3.5 Hz), 5.95 (2 H, m), 5.42 (2 H, s), 4.52 (4 H, s); **6**, 7.12, 6.42, 6.26 (4 H, dd, J = 3.5 Hz), 5.98 (2 H, s), 5.42 (1 H, s), 3.82 (3 H, s); **14**, 7.6–7.1 (4 H, m), 6.33 and 6.22 (4 H, dd), 3.76 (3 H, s).
(24) Prepared by alkylation of *m*-hydroxybenzaldehyde with α-bromomethyl acetate (NaH, THF) followed by oxidation ($KMnO_4$, C_6H_6, 18-crown-6)[25] to the acid (45%; mp 117–119°; IR (mull) 3200–2600, 1770, 1690 cm^{-1})[22a] and chlorination in thionyl chloride.
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(28) Transport is a function of ionophore concentration. For example, changing the concentration of A-23187 from 100 μg/mL to 200 μg/mL to 500 μg/mL produces percent transport (1 h) of 29, 54, and 72%, respectively. Similarly, ligand **15** exhibits percent transport of 11 (20 μg/mL), 21 (50 μg/mL), 52 (100 μg/mL), and 78% (500 μg/mL) after 16 h in one experiment.

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On the Mechanism of Friedel–Crafts Acylation and Sulfonylation Reactions

Sir:

There is general agreement that the transition state for the attack of a weak electrophile on an aromatic substrate resembles a benzenium ion or σ complex. The nature of the reaction pathway for the attack of a strong electrophile, on the other hand, is less certain. Highest energy transition states resembling either a σ complex or a π complex have been proposed.[1]

As part of our systematic study of the mechanisms of electrophilic aromatic substitutions, we undertook a statistical analysis of acylation studies[2] reported by Olah to be supportive of the π-complex mechanism, i.e., those proposed to involve strong but selective electrophiles. We included the studies of the similar sulfonylation reaction in our analysis.[3] From the reported k_T/k_B values and toluene product isomer percentages, we calculated partial rate factors and attempted to correlate the results according to the Brown–Stock selectivity relationship. A graph of calculated values is given in Figure 1.

The linear regression analysis of this plot yielded a slope and intercept, together with their 95% confidence limits, of 1.30 ± 0.20 (standard deviation, ±0.10) and 0.05 ± 0.34. The linear correlation was 0.9437. These values are in remarkable agreement with those obtained for 47 reactions by Brown and Stock;[1a] i.e., the slope was 1.31 ± 0.10 (standard deviation) and the intercept 0.007.

Even Olah's individual points show little deviation from Brown and Stock's line. Of the 24 reactions plotted, only 3 are outside the 95% confidence limits (±0.20), while 14 lie within

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