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HETEROCYCLIC AMIDE HYDRAPHILE SYNTHETIC CATION TRANSPORTERS

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Abstract - A family of hydraphile ionophores has been prepared in which various ~CH_2N~ to ~CON~ replacements have been made to assess the effect on Na^+ transport through phospholipid bilayers. When the central relay (see graphical abstract) was a third macrocycle, symmetrical carbonyl for methylene replacements enhanced activity, but the presence of four or six amide residues diminished transport. When a pair of amides was incorporated into compounds having a 4,4'-bipiperidyl central relay, both significant increases and decreases were observed depending upon the amide positions. The presence of amides alters both the donor group type and strength and the conformation of the structural unit in which it occurs. These changes are shown to depend on the liposomes in which the Na^+ release studies were conducted. These changes are shown to affect the toxicity of the hydraphiles to *E. coli.*

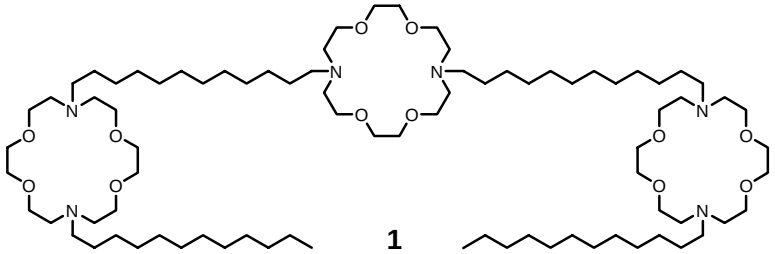
This paper is dedicated to the memory of Prof. Dr. Ivar Karl Ugi

George Gokel worked with Ivar Ugi as a graduate student at the University of Southern California from 1968-1971. He continued for 9 months more as a post-doctoral fellow at USC before moving to UCLA to work with Donald Cram. At that time, Prof. Ugi was working on chiral ferrocene derivatives as asymmetric inducing agents for the four-component condensation that now is universally called “the Ugi Reaction.” Ugi was a fountain of ideas and he was becoming increasingly interested in the mathematical description of reactions and the use of computer software to predict new synthetic pathways. Owing to this evolution of interests, the four-component condensation work gradually found the back burner, but it is this reaction that has become immortal.

INTRODUCTION

Crown ethers are generally considered to be the first hosts in the family of supramolecules,[1,2] but they are fundamentally large heterocycles. They are often referred to as heteromacrocycles but the distinction between 12-crown-4 and dioxane is, except for ring size, somewhat artificial. Of course, the multiple heteroatom sites permit crowns to complex metal and organic cations[3] much more effectively than do either THF or dioxane. The molecular voids that characterize the large ring heteromacrocycles may also include compounds such as nitromethane, acetonitrile, and urea in their crystalline lattices.[4]

Crown ethers not only complex ions, they can serve as the basis for ion transporters as well.[5,6] The compounds we refer to as "hydraphiles" typically possess three macrocyclic rings linked by oligomethylene chains. The distal macrocycles have attached side arms or side chains that may be aliphatic or aromatic. The structures of the hydraphile compounds may be generalized as shown in Figure 1. We also use a chemical shorthand[7] to represent the structures as text. Thus, the compound pictured below (**1**) can also be represented as $CH_3(CH_2)_{11}$<N18N>$(CH_2)_{12}$<N18N>$(CH_2)_{12}$<N18N>$(CH_2)_{11}CH_3$ in which <N18N> is shorthand for 4,13-diaza-18-crown-6.



1

Compound **1**

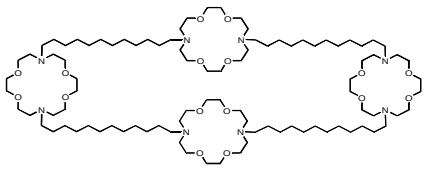
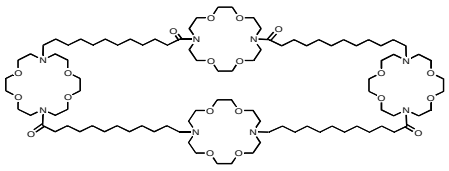
Extensive studies and substantial evidence show that this compound inserts into the phospholipid bilayer of liposomes[8] or cells[9] and permits the passage of Na^+ cations. We recently reported transport and biological activity data for several compounds that are included in the present survey.[10] We anticipated that the presence of an amide function would diminish ion transport, but one of the bis(amides) was significantly more active than the other amides and than the saturated parent. Transport was found not to correlate well with biological activity against *Escherichia coli* and *Bacillus subtilis* as had been the case for non-amidic hydraphiles.[11] We therefore felt that it was important to expand the series and probe this issue further. A key point is that amides are often synthetically more accessible than amines. If their transport efficacy was as good as, or better than, that of the corresponding amines, different synthetic strategies could be envisioned. We have therefore expanded the range of amide compounds whose transport behavior has been studied and report the results of that effort here.

RESULTS AND DISCUSSION

Sodium cation transport for eighteen hydraphile compounds has been studied. The hydraphiles include twelve structures in which one or more methylene groups in the parent structure is replaced by an amide residue (*i.e.*, $CH_2 \rightarrow CO$). These compounds are shown in Table 1 as **2-8**, **10**, **12**, **14, 16**,[12] and **18**.[13]

Compounds **1**,[14] **9**, **11**, **13**, **15**,[12] and **17** are the analogs to which they are compared. The ultimate sodium cation release at 1500 s or release depending on the experimental method is also included for convenience. In some cases, the data were obtained by NMR methods and are interpolated for comparison. Additional information may be found in the sections below and in the experimental section.

Table 1. Structures of hydraphiles and composite sodium cation release data

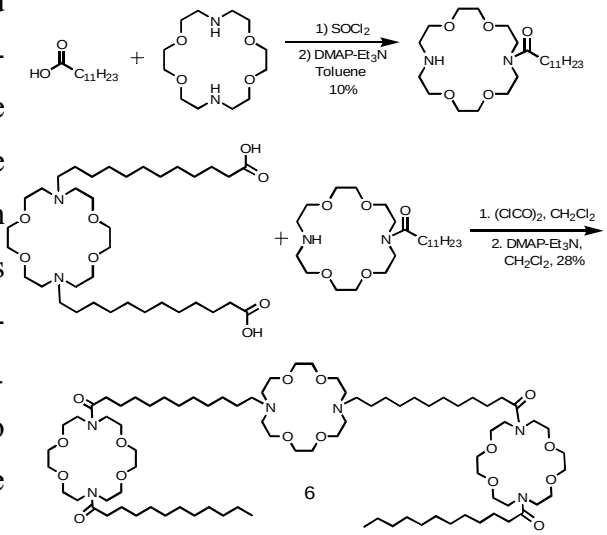
No	Structure[a]	Rel.[b]
1	$CH_3(CH_2)_{11}$<N18N>$(CH_2)_{12}$<N18N>$(CH_2)_{12}$<N18N>$(CH_2)_{11}CH_3$	0.20
2	$CH_3(CH_2)_{11}$<N18N>$(CH_2)_{11}$**CO**<N18N>**CO**$(CH_2)_{11}$<N18N>$(CH_2)_{11}CH_3$	0.48
3	$CH_3(CH_2)_{11}$<N18N>**CO**$(CH_2)_{11}$<N18N>$(CH_2)_{11}$**CO**<N18N>$(CH_2)_{11}CH_3$	0.55
4	$CH_3(CH_2)_{10}$**CO**<N18N>$(CH_2)_{12}$<N18N>$(CH_2)_{12}$<N18N>**CO**$(CH_2)_{10}CH_3$	0.70
5	$CH_3(CH_2)_{11}$<N18N>**CO**$(CH_2)_{10}$**CO**<N18N>**CO**$(CH_2)_{10}$**CO**<N18N>$(CH_2)_{11}CH_3$	0.10
6	$CH_3(CH_2)_{10}$**CO**<N18N>**CO**$(CH_2)_{11}$<N18N>$(CH_2)_{11}$**CO**<N18N>**CO**$(CH_2)_{10}CH_3$	0.09
7	$CH_3(CH_2)_{10}$**CO**<N18N>$(CH_2)_{11}$**CO**<N18N>**CO**$(CH_2)_{11}$<N18N>**CO**$(CH_2)_{10}CH_3$	0.10
8	$CH_3(CH_2)_{10}$**CO**<N18N>**CO**$(CH_2)_{10}$**CO**<N18N>**CO**$(CH_2)_{10}$**CO**<N18N>**CO**$(CH_2)_{10}CH_3$	0.06
9	$CH_3(CH_2)_{11}$<N18N>$(CH_2)_{12}$<bipip>$(CH_2)_{12}$<N18N>$(CH_2)_{11}CH_3$	0.16
10	$CH_3(CH_2)_{11}$<N18N>$(CH_2)_{11}$**CO**<bipip>**CO**$(CH_2)_{11}$<N18N>$(CH_2)_{11}CH_3$	0.12
11	$PhCH_2$<N18N>$(CH_2)_{12}$<N18N>$(CH_2)_{12}$<N18N>CH_2Ph	0.27[c]
12	$PhCH_2$<N18N>$(CH_2)_{11}$**CO**<N18N>**CO**$(CH_2)_{11}$<N18N>CH_2Ph	0.10[d]
13	$PhCH_2$<N18N>$(CH_2)_{12}$<bipip>$(CH_2)_{12}$<N18N>CH_2Ph	0.12
14	$PhCH_2$<N18N>$(CH_2)_{11}$**CO**<bipip>**CO**$(CH_2)_{11}$<N18N>CH_2Ph	0.44
15	$(C_{12}H_{25})_2NCH_2CH_2$<N18N>$(CH_2)_{12}$<N18N>$(CH_2)_{12}$<N18N>$CH_2CH_2N(C_{12}H_{25})_2$	0.13[d]
16	$(C_{12}H_{25})_2N$**CO**CH_2<N18N>$(CH_2)_{11}$**CO**<N18N>**CO**$(CH_2)_{11}$<N18N>CH_2**CO**$N(C_{12}H_{25})_2$	0.09[d]
17		0.65[e]
18		0.48[e]

a. <N18N> represents 4,13-diaza-18-crown-6 and <bipip> represents 4,4'-bipiperidyl. b. Fractional release

of Na^+ from DOPA:DOPC liposomes. c. Data reported in or interpolated from *Chem. Comm.* **2000**, 2371-2372. d. Data reported in or interpolated from *J. Heterocyclic Chem.* **2001**, *38*, 1393-1400. e. Data reported in or interpolated from *Chem. Comm.* **2000**, 2373-2374.

Synthetic access to amidic hydraphiles

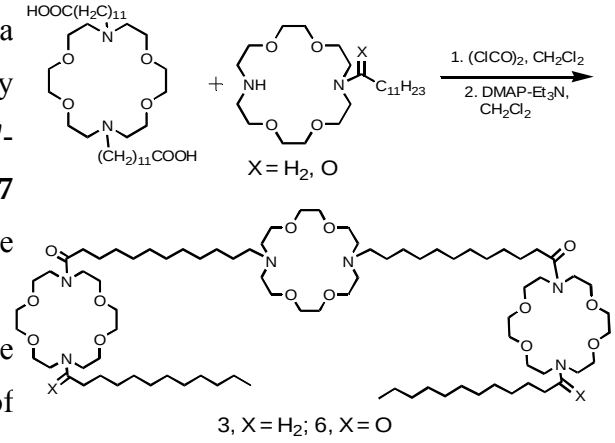
The compounds presented here were typically prepared sequentially by amide bond formation reactions using classical methods. The preparation of **6** is shown in Scheme 1. Dodecanoic acid was converted into its acid chloride by treatment with thionyl chloride and then coupled to 4,13-diaza-18-crown-6.[15] Both mono- and diamides are formed. The two compounds can be separated chromatographically owing to the difference in hydrophobicity. Only the monoamide, obtained in 10% yield, was carried forward. The diacid was prepared from methyl 12-bromododecanoate and 4,13-diaza-18-crown-6 (59%) followed by hydrolysis (aq. NaOH, 93%).[10] The crown-diacid was converted into the dichloride [$(COCl)_2$], and coupled to the monoamide to give **6** in 28% yield.



Scheme 1. Preparation of compound **6**

A similar approach was used to obtain **3**. The strategy in this case (and generally) involves the conversion of a carboxylic acid into its acyl chloride, followed by coupling. This approach was also followed for the 4,4'-bipiperidyl compounds **9**, **10**, and **14**. The synthesis of **17** and **18** required high dilution conditions because of the extremely large rings being formed.[13]

Details of the preparation may be found in the experimental section. Scheme 2, the preparation of compounds **3** and **6**, is shown at the right.



Scheme 2

Sodium ion release from liposomes mediated by 1-8. We have previously documented the ability of hydraphiles generally to mediate the transport of Na^+ through phospholipid bilayers. We have used NMR methods[16] and direct detection of Na^+ release by use of sodium-sensitive ion selective electrodes.[8] We have also used the planar bilayer clamp method to confirm channel-like behavior for these

compounds.[17,18] The latter method provides considerable detail about ion transport through the bilayer but it is a complex technique that requires quite specialized instrumentation.[19] The use of ion-selective electrodes has proved to be particularly convenient for obtaining quantitative information but the results obtained reflect the macroscopic situation rather than single channel behavior. We have also noted recently that ion transport may significantly reflect the nature of the bilayer.[20]

Figure 1 shows Na^+ release data for compounds **1**-**8** in liposomes prepared from either 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC) or a mixture of DOPC and 1,2-dioleoyl-*sn*-glycero-3-phosphate (DOPA)[21] in the proportion (DOPC:DOPA 7:3 by weight). The two compounds differ only in the "headgroup" residues that are attached to glycerol. In DOPC, a primary hydroxy group is esterified to $OPO_2OCH_2CH_2N(CH_3)_3^+$. In DOPA, the choline residue of DOPC is lacking, leaving the negatively charged phosphate as the headgroup.

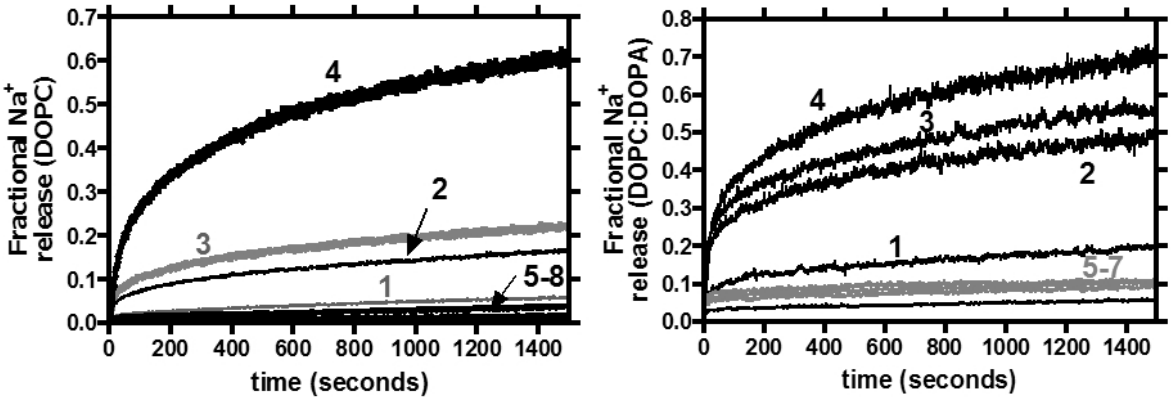


Figure 1: Fractional sodium cation release mediated by **1**-**8** in (left panel) DOPC liposomes and (right panel) DOPC:DOPA (7:3 w/w). Concentrations (both lipid mixtures): 400 μM lipids in 2 mL aq. suspension; ionophore added, 12 μM.

Whether DOPC or a DOPC:DOPA mixture of lipids is used, $C_{11}CO<N18N>C_{12}<N18N>C_{12}<N18N>COC_{11}$ (**4**) best mediates Na^+ release. In pure DOPC, **2** and **3** are superior to **1** and **5**-**8** but **4** is about threefold better than either **2** or **3**. This changes significantly when the lipid mixture is altered from DOPC to 7:3 DOPC:DOPA (lower panel of Figure 1). In either case, the ultimate release of Na^+ is similar (0.6-0.7). In the lipid mixture, however, the transport of Na^+ mediated by **2** and **3** more than doubles. There are also transport rate increases apparent in the lipid mixture for **1** and **5**-**8** but the increases over pure DOPC lipids is small.

In previous studies, we have noted significant differences in lipid mixtures.[20] These have involved hydraphiles that have aromatic sidechains. We found that ion transport was more effective when only the ammonium headgroups of DOPC were present and only when the sidechains were terminated by such electron rich aromatics as methoxybenzyl. There was nearly a 90% decline in Na^+ transport activity when DOPC was replaced by DOPC:DOPA 7:3. When the sidearms were electron poor fluorobenzyl or

nitrobenzyl, transport activity was lower than for electron rich aromatic sidearms and there was little difference apparent when the lipids were changed.

For compounds **1**-**8**, Na^+ transport is superior in the DOPC:DOPA lipid mixture compared to pure DOPC. There are no aromatic residues present in any of these eight compounds so cation-π effects seem unlikely. In this case, amide residues are present that can serve as both hydrogen bond donors and acceptors. The interactions of appropriately placed amide residues with lipid headgroups may enhance the organization of hydraphiles within the membrane. This may help the hydraphile to more quickly achieve and to maintain a Na^+ conductance path. In principle, the amides should form excellent N—H•••$^-$O—P assemblies.[22] Figure 2 compares the Na^+ transport of each compound in pure DOPC and the DOPC:DOPA mixture.

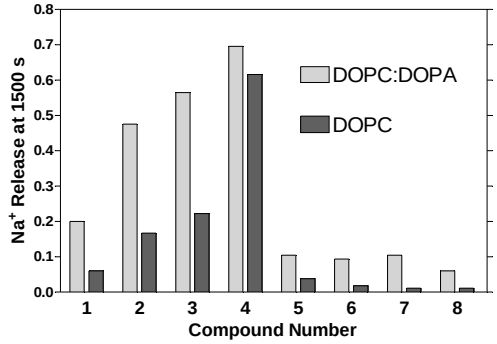
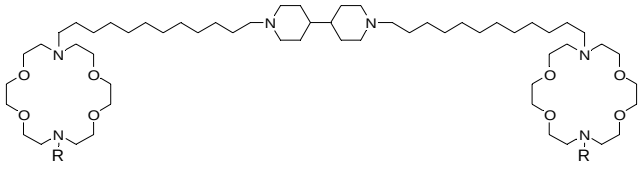


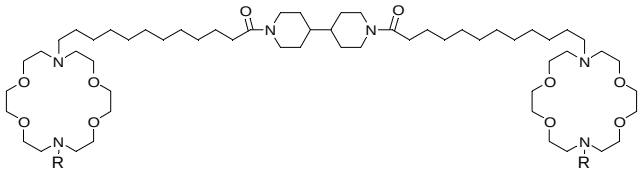
Figure 2: Comparison of Na^+ transport mediated by **1**-**8** in pure DOPC lipids compared to a DOPC:DOPA 7:3 lipid mixture.

Sodium cation transport mediated by bipiperidyl hydraphiles

In compounds **9**, **10**, **13**, and **14**, the central macrocycle has been replaced by a 4,4'-bipiperidine residue. Space-filling molecular models suggest that the N↔N distance in 4,4'-bipiperidine is similar to that in 4,13-diaza-18-crown-6, if the linkage between the piperidine subunits is *trans* diequatorial. The structures are shown.



9, R = *n*-dodecyl; **13**, R = benzyl



10, R = *n*-dodecyl; **14**, R = benzyl

Sodium cation transport was measured in a DOPC:DOPA (7:3, 400 μM total lipids) lipid mixture. Each compound (12 μM) was added to the aqueous lipid suspension and Na^+ release was monitored as

described above and in the experimental section. Among these four piperidine derivatives, only **14** shows significant Na^+ transport activity. We note that in the *tris*(macrocycle) family, ion transport is typically greater for benzyl-sidearmed derivatives than otherwise identical compounds having *n*-dodecyl sidearms. The difference in sidearms accounts in part for the difference in transport activity. Compound **14** corresponds in amide positions to **2** and **12**,[12] the latter of which is a poor sodium transporter (*see* Table 1). The activity of **14** is particularly notable as its aromatic residues are not electron rich and it cannot take advantage of cation-π interactions with lipid headgroups.

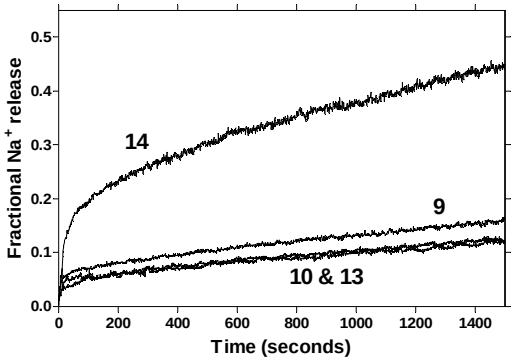


Figure 3: Fractional sodium release from liposomes mediated by bipiperidine-containing compounds **9**, **10**, **13**, and **14**. Lipid mixture: DOPC:DOPA (7:3 w/w), 400 μM; compound: 12 μM.

Replacement of the diazacrown central relay by piperidine permits a number of interesting comparisons to be made. First, compounds **1** and **9** differ only by the replacement of the central macrocycle (**1**) by 4,4'-bipiperidine (**9**). In both cases the sidearms are *n*-dodecyl and the fractional Na^+ release differs little (0.20 and 0.16, respectively). When the central relay is diazacrown but the sidearms change from *n*-dodecyl (**1**) to benzyl (**11**), fractional Na^+ release increases from 0.20 to 0.27, or about 35%. When the sidearms are both benzyl and the central relay is changed from diazacrown (**11**) to bipiperidyl (**13**), the activity of the latter is only about half that of the former.

A similar series of comparisons can be made within the group **9**-**14**. When the ~$(CH_2)_{12}$<bipip>$(CH_2)_{12}$~ of **9** (dodecyl sidearms) is replaced by ~$(CH_2)_{11}CO$<bipip>$CO(CH_2)_{11}$~ (**10**), the fractional Na^+ release drops only from 0.16 to 0.12. In contrast, an identical replacement in the benzyl-sidearmed series (**13**, **14**) leads to an increase in fractional Na^+ release from 0.12 to 0.44, a change of more than three-fold. It should also be noted that the change from **1** to **2** in the dodecyl-sidearmed series, in which ~$(CH_2)_{12}$<N18N>$(CH_2)_{12}$~ (**1**) ~$(CH_2)_{11}CO$<N18N>$CO(CH_2)_{11}$~ (**2**) leads to a an increase in Na^+ fractional release from 0.20 to 0.48, or about at 2.4-fold increase.

Although we can predict neither the direction nor the magnitude of the change in transport efficacy that may take place when amides are incorporated, they may have dramatic effects. We presumed at the outset that amides would rigidify a fragment including it and the change from amine to amide would reduce Lewis basic donor ability. Clearly, the amide oxygen may replace the amine nitrogen as a donor element and efficacy will be determined by how the conducting conformation is altered by the amide's presence.

Biological activity

The hydraphile family of compounds has shown significant biological activity. In a previous study, it was found that antibiotic activity against *E. coli* and *B. subtilis* correlated well with Na^+ transport efficacy.[11] Only limited studies of the amide family have been conducted,[10] but antibacterial activity for **1**-**4** against *B. subtilis* was excellent (0.5-2 μM MIC) while only **1** showed low micromolar activity against *E. coli*. With the exception of **1**, toxicity studies conducted at pH 7 showed essentially no activity against *E. coli*. For compounds **2**-**8**, the minimum inhibitory concentration (MIC) was ≥ 32 μM. This level of activity is at least 4-5-fold lower than that of penicillin (~8 μM). Remarkably, when the same experimental toxicity study was conducted at pH 6.5, different results were obtained for the diamide compounds. In agreement with results of Na^+ transport activity in vesicles (Figure 2), **5**-**8** are not biologically active at pH 6.5. These toxicity results are summarized in Table 2.

Table 2. Effect of pH on hydraphile toxicity[a] to *E. coli*

Cpd.	*Abbreviated structure*	*pH 7*	*pH 6.5*
1	C_{12}<N18N>C_{12}<N18N>C_{12}<N18N>C_{12}	4	1
2	C_{12}<N18N>C_{11}**CO**<N18N>**CO**C_{11}<N18N>C_{12}	>32	4
3	C_{12}<N18N>**CO**C_{11}<N18N>C_{11}**CO**<N18N>C_{12}	32	2
4	C_{11}**CO**<N18N>C_{12}<N18N>C_{12}<N18N>**CO**C_{11}	>32	16
5	C_{12}<N18N>**CO**C_{10}**CO**<N18N>**CO**C_{10}**CO**<N18N>C_{12}	>32	>32
6	C_{11}**CO**<N18N>**CO**C_{11}<N18N>C_{11}**CO**<N18N>**CO**C_{11}	>32	>32
7	C_{11}**CO**<N18N>C_{11}**CO**<N18N>**CO**C_{11}<N18N>**CO**C_{11}	>32	>32
8	C_{11}**CO**<N18N>**CO**C_{11}**CO**<N18N>**CO**C_{11}**CO**<N18N>**CO**C_{12}	>32	>32

a. Data reported are minimum inhibitory concentration (MIC) expressed in micromolar units.

CONCLUSIONS

The replacement of a methylene adjacent to nitrogen by a carbonyl in a wide range of Na^+ transporters gave the corresponding amide compounds. When the central unit was 4,13-diaza-18-crown-6, the symmetrical incorporation of two amide residues generally led to an increase in Na^+ transport efficacy. When two or more pairs of amides replaced methylenes adjacent to nitrogen, activity was adversely affected. When the central relay unit was 4,4'-bipiperidyl, the effect of amide incorporation was unpredictable, sometimes leading to increased transport of Na^+ and diminished activity in other cases. In all cases, we surmise that the combination the change from ~CH_2N~ to ~CON~ alters both the Lewis basic donor group strength and the conformation of the ion-conductance pathway. Several of the amides

show improved transport activity compared to their non-amidic counterparts that incorporation of amides should be considered in the future design of synthetic transmembrane ionophores. The increase in toxicity towards *E. coli* is also notable, but our ability to predict the magnitude of any change is currently limited.

EXPERIMENTAL

General

^{1}H-NMR spectra were recorded at 300 MHz and ^{13}C-NMR spectra were recorded at 75 MHz in $CDCl_3$ and are reported in ppm (δ) downfield from internal TMS unless otherwise noted. Infrared spectra were recorded on a Perkin-Elmer 1710 Fourier Transform Infrared Spectrophotometer and were calibrated against the 1601 cm^{-1} band of polystyrene. Melting points were determined on a Thomas Hoover apparatus in open capillaries and are uncorrected. Thin layer chromatographic (TLC) analyses were performed on aluminum oxide 60 (F-254 neutral, Type E) with a 0.2 mm layer thickness or on silica gel 60 F-254 with a 0.2 mm layer thickness. Preparative chromatography columns were packed with silica gel (Kieselgel 60, 70-230mesh or Merck grade 9385, 230-240 mesh, 60A). All reactions were conducted under dry N_2 unless otherwise stated. All reagents were the best (non-LC) grade commercially available and were distilled, recrystallized, or used without further purification, as appropriate. Molecular distillation temperatures refer to the oven temperature of a Kugelrohr apparatus. Fast atom bombardment (FAB) mass spectra were obtained with a JEOL Mstation (JMS-700) mass spectrometer.

Vesicle experiments

Hydroxyethylpiperazine-*N*'-2-ethanesulfonic acid (HEPES) and the inorganic salts NaCl and cholineCl were all purchased from Sigma-Aldrich. The water used was Milli-Q Plus quality, which is essential to avoid salt contamination in the buffer systems. *n*-Octylglucoside was purchased from CalBioChem. The vesicles used were prepared by the reverse evaporation method of Szoka and Papahadjopoulos.[23] 1,2-Dioleoyl-*sn*-glycero-3-phosphocholine (DOPC) and 1,2-dioleoyl-*sn*-glycero-3-phosphate (DOPA) were purchased from Avanti Polar Lipids as a chloroform solution, which was dried to a lipid film and stored at 0 ^oC (under N_2). The dry lipid film (DOPC and 0% or 30% w/w DOPA) was dissolved in Et_2O (0.35 mL) and buffer (0.35 mL, 750 mM NaCl/15 mM HEPES, pH 7.0). The mixture was sonicated for ~20 s to give an opaque solution. The organic solvent was removed (*in vacuo*) and the solution was passed through a mini extruder containing a 0.2 mm polycarbonate membrane filter. The residual, external buffer solution was exchanged for a sodium-free buffer (750 mM cholineCl/15 mM HEPES, pH 7.0) by passing it over a Sephadex G25 column. Vesicle concentration was measured as previously reported[24] and vesicle size was determined by using a Coulter N4MD submicron particle analyzer. The vesicles used in the transport studies had diameters of 200 ± 10 nm.

Sodium cation transport measurements

Changes in the concentration of sodium were measured using a Micro-Combination pH/sodium electrode

(Thermo-Orion) in aqueous sodium-free buffer (750 mM cholineCl/15 mM HEPES, pH 7.0). Data were collected by Axoscope 7.0 using a Digidata 1322A series interface. After equilibration in external buffer, the electrode was placed in a 5-mL disposable beaker containing external buffer and vesicle solution to achieve a lipid concentration of 0.4 mM and a total volume of 2 mL. In order to set the baseline, the voltage output was recorded for five minutes prior to addition of the channel. The channel, dissolved in 2-propanol, was added and conductivity was measured over an appropriate time period, typically 25 minutes. Addition of 200 μL 10% aqueous *n*-octylglucoside induced complete lysis of the vesicles to achieve total sodium release. All Na^+ release data were normalized to this value (1.00). All experiments were performed at room temperature. The data were collected in units of mV and converted to units of concentration, using the appropriate electrode calibration curve. The data were normalized (OriginPro 7) to the total sodium concentration, as determined by lysing the vesicles with *n*-octylglucoside.

Compounds 1-4 were prepared as previously reported.[10]

Compound 5. $CH_3(CH_2)_{11}$<N18N>$CO(CH_2)_{10}CO$<N18N>$CO(CH_2)_{10}CO$<N18N>$(CH_2)_{11}CH_3$.

$HOOC(CH_2)_{10}COOCH_2Ph$. To a solution of dodecanoic acid (10 g, 43.4 mmol) in MeOH (300 mL) was added dropwise with stirring 10% KOH (2.86 g, 43.4 mmol) in MeOH. The reaction was stirred at rt for an additional 20 min. The solvent was evaporated and dried under high vacuum. The residue was suspended in toluene (75 mL) and Bu_4NBr (1.4 g, 4.34 mmol) and $PhCH_2Br$ (9.2 g, 47.9 mmol) were added. The solution was heated under reflux for 6 h. After cooling, the solution was acidified by pouring it into 0.5M HCl (100 mL). The mixture was extracted with Et_2O (100 mL x 3), the organics were washed with water (50 mL x 2) and brine (50 mL x 2), dried ($MgSO_4$), concentrated *in vacuo* and chromatographed (SiO_2, hexane, 20% acetone/hexane) to afford the benzyl ester (5.40g, 39%) as a white solid, mp 65-66 ^oC. ^{1}H-NMR: 1.270 (12H, bs), 1.614-1.649 (4H, m), 2.317-2.377 (4H, m), 3.115 (2H, m), 7.334-7.367(5H, m). ^{13}C-NMR: 24.878, 25.152, 29.219, 29.295, 29.371, 29.523, 34.183, 34.547, 66.286, 128.367, 128.747, 136.382, 173.934, 179.793.

$PhCH_2OCO(CH_2)_{10}CO$<N18N>$CO(CH_2)_{10}COOCH_2Ph$. Oxalyl chloride (5.23 g, 41.2 mmol) was added (0 ^oC) to a solution of $HOOC(CH_2)_{10}COOCH_2Ph$ (1.32 g, 4.12 mmol) in dry CH_2Cl_2 (20 mL). The mixture warmed to rt during 20 min and was stirred for an additional 2 h. The solvent was evaporated and the residue was dried under high vacuum for 1 h. The residue was dissolved in dry CH_2Cl_2 (10 mL) and added dropwise (0^{o}C) to a solution of diaza-18-crown-6[15] (0.51 g, 1.94 mmol), DMAP (20 mg, catalyst), Et_3N (3 mL) in dry CH_2Cl_2 (20 mL). The mixture was stirred at rt for 2 d then washed with 5% aq. HCl (20 mL), 5% aq. Na_2CO_3 solution (20 mL) and brine solution (20 mL), dried ($MgSO_4$) and evaporated to afford a yellow oil (1.67g, 99%). ^{1}H-NMR: 1.261 (24H, bs), 1.604-1.627 (8H, m), 2.315-2.365 (8H, m,), 3.573-3.635 (24H, m), 5.105 (4H, s), 7.345-7.357 (10H, m). ^{13}C-NMR: 25.011, 25.439, 29.168, 29.282, 29.453, 29.487, 29.514, 33.182, 33.239, 34.385, 47.002, 48.850, 66.088, 69.719, 70.174, 70.511, 70.659, 70.845, 70.986, 128.205, 128.596, 136.251, 173.433, 173.679.

$HOOC(CH_2)_{10}CO$<N18N>$CO(CH_2)_{10}COOH$. Palladium on carbon (10%, 0.17 g) was added to a hot

solution of $PhCH_2OCO(CH_2)_{10}CO<N18N>CO(CH_2)_{10}COOCH_2Ph$ (1.57 g, 1.81 mmol) in EtOH (25 mL). The mixture was shaken using a Parr apparatus at 60 psi H_2 for 5 h. The reaction was filtered and concentrated *in vacuo* to afford the diacid (1.22g, 98%) as a white solid, mp 118-120 °C. ^{1}H-NMR: 1.207 (24H, bs), 1.531 (8H, m), 2.216-2.241 (8H, m), 3.511-3.574 (24H, m). ^{13}C-NMR: 25.001, 25.521, 29.178, 29.292, 29.474, 29.531, 33.279, 34.185, 47.228, 49.049, 69.724, 69.978, 70.160, 70.346, 70.574, 70.703, 70.893, 71.037, 174.273, 176.819.

Compound 5. $CH_3(CH_2)_{11}<N18N>CO(CH_2)_{10}CO<N18N>CO(CH_2)_{10}CO<N18N>(CH_2)_{11}CH_3$. A solution of $CH_3(CH_2)_{11}<N18N>H$ (0.10 g, 0.232 mmol), EDCI (0.40 g, 2.32 mmol), $HOOC(CH_2)_{10}CO<N18N>CO(CH_2)_{10}COOH$ (0.07 g, 0.102 mmol), DMAP (cat.) and Et_3N (2 mL) in dry CH_2Cl_2 (20 mL) was stirred at rt overnight. The reaction mixture was washed with 5% aq. citric acid (25 mL), satd. $NaHCO_3$ (25 mL), and brine solution (25 mL). The organic phase was dried ($MgSO_4$). the solvent was removed *in vacuo*, and the crude product was chromatographed (SiO_2, 2% Et_3N:acetone) to afford **5** as yellow oil (0.07 g, 45%). ^{1}H-NMR: 0.783 (6H, t), 1.132-1.522 (72H, m), 2.215 (8H, t), 2.470 (4H, t), 2.738 (8H, t), 3.486-3.575 (64H, m). ^{13}C-NMR: 14.238, 22.829, 25.561, 27.610, 29.493, 29.660, 29.781, 32.073, 32.363, 34.153, 47.176, 49.043, 54.143, 56.086, 69.975, 70.263, 70.430, 70.597, 70.718, 70.840, 70.931, 71.158, 173.539. FAB MS: m/z calculated for (M+Na): 1534.1945. Found: 1534.1960.

Compound 6. $CH_3(CH_2)_{10}CO<N18N>CO(CH_2)_{11}<N18N>(CH_2)_{11}CO<N18N>CO(CH_2)_{10}CH_3$.

$CH_3(CH_2)_{10}CO<N18N>H$. Dodecanoic acid (0.61 g, 3.05 mmol) was dissolved by the slow addition of $SOCl_2$ (6.45 g, 55.0 mmol) (0°C, N_2). The reaction was heated to reflux (N_2) for 1 h. The $SOCl_2$ was removed *in vacuo*. Toluene (5 mL x 2) was added and evaporated to ensure removal of residual $SOCl_2$. The resulting acid chloride was dissolved in toluene (5 mL) and added dropwise (0 °C, N_2) to a toluene solution of diaza-18-crown-6 (0.8 g, 3.05 mmol), Et_3N (3.1 g, 30.6 mmol), DMAP (cat.) (0 °C, N_2). The reaction warmed to rt during 20 min and was stirred for an additional 4 h. The mixture was concentrated *in vacuo* and chromatographed (SiO_2, 2% Et_3N:acetone) to give a yellow oil (0.14 g, 10%). ^{1}H-NMR: 1.247-1.292 (16H, m), 1.616 (2H, m), 2.309 (2H, t), 2.802-2.843 (4H, m), 3.585-3.656 (20H, m). ^{13}C-NMR: 14.2, 22.8, 25.5, 29.66, 29.77, 32.05, 33.3, 49.4, 70.6, 173.5.

$CH_3(CH_2)_{10}CO<N18N>CO(CH_2)_{11}<N18N>(CH_2)_{11}CO<N18N>CO(CH_2)_{10}CH_3$, 6. Oxalyl chloride (0.183 g, 1.43 mmol) was added (0 °C) to a suspension of $HOOC(CH_2)_{11}<N18N>(CH_2)_{11}COOH$ (0.10 g, 0.152 mmol) in dry CH_2Cl_2 (20 mL). The mixture warmed to rt during 20 min and was stirred for an additional 2 h. The solvent was evaporated and the residue was dried under high vacuum for 1 h. The residue was dissolved in anhydrous CH_2Cl_2 (10 mL) and added dropwise (0 °C) to a solution of $CH_3(CH_2)_{10}CO<N18N>H$ (0.14 g, 0.315 mmol), Et_3N (2 mL) and DMAP (cat) in dry CH_2Cl_2 (20 mL). The mixture was stirred at rt for 2 d, then washed with 5% aq. HCl (20 mL), 5% aq. Na_2CO_3 (20 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (SiO_2, 2% Et_3N:acetone) to afford **6** as thick yellow oil (60 mg, 28%). ^{1}H-NMR: 0.766 (6H, t), 1.145-1.319 (68H, m, 1.511 (8H, t), 2.199 (8H, t), 2.383 (4H, t), 2.673 (8H, t), 3.471-3.531 (64H,

m). ^{13}C-NMR: 14.238, 22.799, 25.470, 25.501, 27.185, 27.626, 29.447, 29.629, 29.736, 32.028, 33.257, 33.303, 47.009, 47.146, 48.876, 48.997, 54.037, 56.086, 69.747, 69.990, 70.172, 70.688, 70.825, 70.885, 71.037, 173.464, 173.509. MS-FAB: m/z calcd for (M+Na): 1534.1945; Found: 1534.1973.

Compound 7. $CH_3(CH_2)_{10}CO<N18N>(CH_2)_{11}CO<N18N>CO(CH_2)_{11}<N18N>CO(CH_2)_{10}CH_3$. A solution of $CH_3(CH_2)_{10}CO<N18N>H$ (0.16 g, 0.360 mmol), $Br(CH_2)_{11}CO<N18N>CO(CH_2)_{11}Br$[10] (0.134 g, 0.171 mmol), Na_2CO_3 (0.90 g, 8.49 mmol), KI (20 mg) in *n*-PrCN (20 mL) was heated to reflux for 4 days. The reaction was cooled, filtered and concentrated. The crude product was purified by chromatography (SiO_2, 2% Et_3N:acetone) to afford **7** as a yellow oil (0.20 g, 76%). ^{1}H-NMR: 0.861 (6H, t), 1.239-1.626 (72H, m), 2.294 (8H, t), 2.617 (4H, t), 2.903 (8H, t), 3.566-3.627 (64H, m). ^{13}C-NMR: 14.268, 22.860, 25.577, 27.565, 29.508, 29.690, 29.751, 29.796, 32.088, 33.378, 47.146, 49.013, 54.098, 55.980, 69.914, 70.324, 70.825, 71.128, 173.555. FAB MS: m/z calcd for (M+Na): 1534.1945; Found: 1534.1956.

Compound 8. $CH_3(CH_2)_{10}CO<N18N>CO(CH_2)_{10}CO<N18N>CO(CH_2)_{10}CO<N18N>CO(CH_2)_{10}CH_3$. A solution of $CH_3(CH_2)_{10}CO<N18N>H$ (0.10 g, 0.225 mmol), EDCI (0.20 g, 1.04 mmol), $HOOC(CH_2)_{10}CO<N18N>CO(CH_2)_{10}COOH$ (0.08 g, 0.116 mmol), DMAP (cat.) and Et_3N (2 mL) in dry CH_2Cl_2 (20 mL) was stirred at rt overnight. The reaction mixture was washed with 5% aq. citric acid (25 mL), satd $NaHCO_3$ (25 mL), and brine (25 mL). The organic phase was dried over $MgSO_4$, concentrated, and the residue was chromatographed (SiO_2, 2% Et_3N:acetone) to afford **8** as a slightly yellow oil (0.04 g, 22 %). ^{1}H-NMR: 0.838 (6H, t), 1.216-1.580 (68H, m), 2.209 (12H, t), 3.543-3.603 (72H, m).^{13}C-NMR: 14.292, 22.853, 29.391, 29.506, 29.665, 29.791, 32.077, 33.305, 33.365, 47.066, 47.192, 48.919, 49.034, 69.791, 70.263, 70.606, 70.737, 70.941, 71.085, 173.547. FAB MS: m/z calcd for (M+Na): 1562.1530; Found: 1562.1530.

Compound 9. $CH_3(CH_2)_{11}<N18N>(CH_2)_{12}<bipip>(CH_2)_{12}<N18N>(CH_2)_{11}CH_3$, 9, Compound 10 (0.03 g, 0.0215 mmol) in THF (5 mL) was added (0 ^{o}C) slowly to a suspension of $LiAlH_4$ (0.04 g, 1.054 mmol) in THF (10 mL). The mixture was stirred at rt for 3 h. The reaction was carefully quenched by addition of water (0.04 mL), 15% aq. NaOH solution (0.04 mL), and water (0.12 mL). The white solid was filtered and washed twice with hot THF (2 x 5 mL). The combined organic material was concentrated *in vacuo,* the residue was dissolved in hot acetone, and **9** (0.016 g, 59%) crystallized during overnight cooling (freezer) as a white solid, mp 62-63 ^{o}C. ^{1}H-NMR: 0.803 (6H, t), 1.178-1.803 (94H, m), 2.235 (4H, t), 2.404 (8H, t), 2.696 (16H, t), 2.933-2.895 (4H, d), 3.507-3.540 (32H, m). ^{13}C-NMR: 14.284, 22.875, 27.261, 27.504, 27.732, 28.020, 29.553, 29.690, 29.827, 32.134, 41.211, 54.295, 54.583, 56.314, 59.532, 70.324, 70.992. MS-FAB: m/z calcd for (M+H) 1362.2689; Found: 1362.2725.

Compound 10. $CH_3(CH_2)_{11}<N18N>(CH_2)_{11}CO<bipip>CO(CH_2)_{11}<N18N>(CH_2)_{11}CH_3$.

$Br(CH_2)_{11}CO<bipip>CO(CH_2)_{11}Br$. Oxalyl chloride (2.72 g, 21.49 mmol) was added (0 ^{o}C) to a solution of 12-bromododecanoic acid (1.00 g, 3.58 mmol) in dry CH_2Cl_2 (20 mL). The mixture warmed to rt during 20 min and was stirred for an additional 2 h. The solvent was evaporated and the residue kept

under high vacuum for 2 h. The residue was dissolved in dry CH_2Cl_2 (10 mL) and added dropwise (0° C) to a solution of 4,4'-bipiperidyl (0.274 g, 1.63 mmol), Et_3N (0.337 g, 4.88 mmol), DMAP (cat.) in dry CH_2Cl_2 (30 mL). The mixture was stirred at 0 ºC for 20 min; the mixture was stirred with no further cooling for 18 h. The mixture was evaporated and the residue was washed with 5% aq. HCl (20 mL), 5% aq. Na_2CO_3 (20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford a white solid (0.914 g, 81%), mp 79-80 ºC, ^{1}H-NMR: 1.10-1.43 (34H, m), 1.56-1.87 (14H, m), 2.30 (4H, t), 2.42 (2H, t), 2.91 (2H, t), 3.40 (8H, t), 3.85 (2H, d), 4.66 (2H, d). ^{13}C-NMR: 25.2, 27.9, 28.5, 28.9, 29.2, 29.3, 29.6, 29.8, 32.6, 33.3, 33.9, 40.9, 41.8, 45.9, 171.5.

$CH_3(CH_2)_{11}$<N18N>$(CH_2)_{11}CO$<bipip>$CO(CH_2)_{11}$<N18N>$(CH_2)_{11}CH_3$, 10. A solution of $Br(CH_2)_{11}CO$<bipip>$CO(CH_2)_{11}Br$ (100 mg, 0.145 mmol), $C_{12}H_{25}$<N18N>H[10] (137 mg, 0.319 mmol), Na_2CO_3 (3.38 g, 31.9 mmol), KI (20 mg) in *n*-PrCN (30 mL) was heated to reflux for 3 d. The mixture was cooled, filtered, and concentrated. The residue was dissolved in chloroform (50 mL), washed with aqueous 5% aq. Na_2CO_3 (25 mL x 3). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Crude product was chromatographed (SiO_2, acetone, 2% Et_3N in acetone) to afford **10** as a waxy solid (0.125 g, 62%), mp 52-53 ºC, ^{1}H-NMR: 0.88 (6H, t), 1.25-1.73 (82H, m), 2.17-2.30 (12H, m), 2.45 (2H, t), 2.63 (8H, m), 2.91 (18H, m), 3.61-3.69 (32H, m), 3.87 (2H, d), 4.66 (2H, d). ^{13}C-NMR: 8.65, 14.10, 22.64, 25.44, 26.08,.27.44, 29.05, 29.3, 29.5, 29.6, 31.9, 33.5, 41.1, 41.9, 46.0, 53.8, 55.8, 69.6, 70.6, 171.4.MS-FAB: m/z calcd for (M+Na): 1412.2094, found: 1412.2074.

Compound 11 was prepared as previously reported.[16]

Compound 12 was prepared as previously reported**.**[12]

Compound 13. $PhCH_2$<N18N>$(CH_2)_{12}$<bipip>$(CH_2)_{12}$<N18N>CH_2Ph, 13.

$PhCH_2$<N18N>$(CH_2)_{12}Br$. A solution of *N*-benzyl-4,13-diaza-18-crown-6 (2.0 g, 5.68 mmol), 1,12-dibromododecane (5.59 g, 17.04 mmol), Na_2CO_3 (18.1 g, 170.4 mmol) and KI (20 mg) in *n*-PrCN (50 mL) was heated to reflux for 2 h. The mixture was cooled, filtered, and concentrated. The residue was chromatographed (SiO_2, 2:1 hexane:acetone, 1:1 hexane:acetone, pure acetone, 2% Et_3N in acetone, 5% Et_3N in acetone) to afford a light yellow oil (1.75 g, 51.4%). ^{1}H-NMR: 1.26 (18H, m), 1.85 (2H, m), 2.49 (2H, bt), 2.81 (8H, t), 3.60 (18H, m), 7.26 (5H, m). ^{13}C-NMR: 27.2, 27.7, 29.8, 53.9, 54.0, 56.1, 60.1, 70.0, 70.2, 70.8, 127.0, 128.3, 129.0, 139.7.

Compound 13. $PhCH_2$<N18N>$(CH_2)_{12}$<bipip>$(CH_2)_{12}$<N18N>CH_2Ph. A solution of $PhCH_2$<N18N>$(CH_2)_{12}Br$ (0.77g 1.29 mmol), 4,4'-bipiperidine dihydrochloride (0.14 g, 0.58 mmol), Na_2CO_3 (2.73 g, 25.8 mmol), KI (cat.) in *n*-PrCN (30 mL) was heated to reflux for 3 d. The mixture was cooled, filtered, and evaporated to give a yellow oil, which was chromatographed (SiO_2, 2% Et_3N:acetone) to afford **13** as a white solid (0.457 g, 65%), mp 58-59 ºC, ^{1}H-NMR: 0.98-1.17 (36H, m), 1.39 (8H, b), 1.61 (4H, d), 1.78-1.82 (4H, t), 2.19-2.24 (4H, t), 2.38-2.43 (4H, t), 2.69-2.75 (16H, m), 2.92-2.88 (4H, d), 3.53-3.59 (36H, m), 7.14-7.23 (10H, m). ^{13}C-NMR: 26.89, 27.03, 27.37, 27.63, 29.56, 29.48, 40.78, 53.63, 53.81, 54.25, 55.95, 59.24, 59.85, 69.93, 69.97, 70.64, 126.87, 128.19, 128.89,

139.69. IR (neat): 2920, 2850, 1639, 1470, 1128, 1073, 734 cm^{-1} MS-FAB: m/z calcd for (M+Na) 1227.9691, found: 1227.9680.

Compound 14. $PhCH_2$<N18N>$(CH_2)_{11}CO$<bipip>$CO(CH_2)_{11}$<N18N>CH_2Ph. A solution of $Br(CH_2)_{11}CO$<bipip>$CO(CH_2)_{11}Br$ (0.50 g, 0.723 mmol), *N*-benzyl-4,13-diaza-18-crown-6 (0.56 g, 1.60 mmol), Na_2CO_3 (3.39 g, 32.0 mmol), KI (cat.) in *n*-PrCN (40 mL) was heated under reflux for 3 d. The mixture was cooled, filtered, and concentrated. The residue was dissolved in $CHCl_3$ (50 mL), washed with 5% aq. Na_2CO_3 (3 x 25 mL), dried over $MgSO_4$, and chromatographed (SiO_2, 2% Et_3N:acetone) to afford **14** as a dark yellow oil (0.33 g, 38%). ^{1}H-NMR: 0.931-1.536 (44H, *m*), 2.10 (4H, t), 2.25-2.78 (24H, m), 3.37-3.46 (36H, m), 3.652-3.695 (2H, d), 4.440-4.482 (2H, d), 6.993-7.134 (10H,m). ^{13}C-NMR: 25.671, 27.648, 29.274, 29.646, 29.748, 33.686, 41.300, 42.195, 46.246, 54.048, 60.030, 69.593, 70.118, 70.829, 127.071, 128.361, 129.065, 139.657, 171.689. MS-FAB: m/z calcd for (M+H): 1233.9457, found: 1233.9467.

Compounds 15 and 16 were prepared as previously reported.[12]

Compounds 17 and 18 were prepared as previously reported.[13]

Biological Activity. The minimum inhibitory concentration (MIC) reported for each compound is the lowest serial 2-fold dilution that prevented microbial growth as outlined by the NLCCS.[25] Ethanol solutions of compounds **2-8** were made to yield a 32 μM concentration present in the final growth media. One half of each original solution was then diluted by a factor of two, from which another two-fold dilution was made, and so forth, resulting in dilutions for each compound of 32, 16, 8, 4, 2 and 1 μM. Thus, MIC values reported as ">32 μM" exhibited no activity at 32 μM. Compound **1**, which is less soluble in EtOH, was made to yield a 16 μM concentration in growth media and diluted to a low-end concentration of 0.5 μM.

Toxicity studies used *E. coli* DH5α cells with a plasmid having ampicillin resistance and used an inoculum size of 5 x 10^5 CFU ml^{-1}. Cells were grown at 37°C in 2 mL of LB Miller broth (10 g•L^{-1} peptone, 10 g•L^{-1} sodium chloride, 5 g•L^{-1} yeast extract) to which was added 20 μL ampicillin (100 mg•L^{-1}) and 20 μL of the appropriate serial dilution.

After 24 h of growth, the toxicity of each dilution was assayed by a visual observation of turbidity. The lowest concentration exhibiting no turbidity, and thus inhibiting microbial growth, is reported as the MIC. Each compound was assayed three times for each pH-variable growing condition using an independent dilution of compound for each trial.

The pH of LB Miller broth is between 7.0 and 7.1 and thus is used unadulterated as pH 7 growing conditions. A pH of 6.5 is attained by dissolving a requisite amount of malonic acid in LB Miller broth with 0.5 mM HEPES buffer.

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