SILACROWN IONOPHORES

KEITH H. PANNELL, EDNA RICO, CINDY LA NEAVE, KAMYAR RAHIMIAN, ALBERTO AMAYA

Department of Chemistry, University of Texas at El Paso, El Paso, TX 79968-0513 (U.S.A.)

and BARRY ARKLES

Petrarch Systems Inc., Bristol, PA 19007 (U.S.A.)

Summary

A study is reported on the metal ion transport efficiency of various silacrown ether ionophores and their ethyleneoxy glycol hydrolysis products. The silacrowns are modified crown ethers in which an ethylene bridge has been replaced by a difunctional silyl group, e.g. dimethylsilyl. We have studied the relative transport efficiencies of the silacrowns with 4, 5, 6 and 7 oxygen atoms in the macrocycle for the alkali metals ions Li^+, Na^+, K^+, Rb^+, and Cs^+. We have also performed experiments which illustrate that the silacrowns behave as short-term ion transporters. They will slowly hydrolyse in hydrophobic environments in contact with water to yield ethyleneoxy glycols which partition out of the hydrophobic phase into the hydrophilic phase. This terminates significant transport since the glycols are relatively inefficient ionophores. The potential of such short-term ionophores is discussed.

Introduction

During the past decade there has developed a considerable interest in the use of synthetic ionophores, such as crown ethers and cryptates, as mimics of naturally occurring materials with respect to metal ion transport across both liquid and real membranes [1-7]. The naturally occurring ionophores such as monensin and valinomycin exhibit a very striking metal ion selectivity based upon their structures [8,9]. All are macrocycles, or capable of adopting a macrocyclic conformation upon metal ion complexation. The synthetic variety, e.g. crown ethers, often exhibit selectivity patterns founded upon such variables as ring size, base atom composition and number [10], and substituents [6]; however, to date no synthetic materials come close to rivalling the efficiency and selectivity, often specificity, of naturally occurring species.

A common feature of the ionophores, both synthetic and natural, is their tendency to possess nasty physiological properties ranging from being poten-
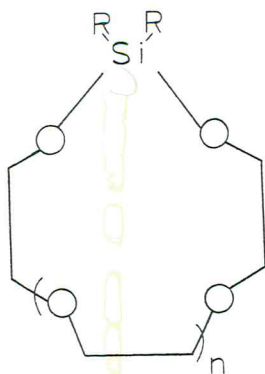
Fig. 1. Substitution of an ethylene bridge of a regular crown ether by a silyl group. Radical R represents a methyl, phenyl or vinyl group. $n=1$: sila-11-crown-4; $n=2$: sila-14-crown-5; $n=3$: sila-17-crown-6; $n=4$: sila-20-crown-7.

tial carcinogens to causing testicular atrophy in laboratory animals [11–13]. This is to be expected since the molecules possess the ability to complex and transport metal ions causing a change in the ion gradients needed for normal physiological activity. Since it has been reported that several naturally occurring ionophores and related derivatives have potential therapeutic usage [14,15], the problem of their potential toxicity has been a major drawback to their full utilization. This applies to both health and chemically related areas, such as phase-transfer catalysis, that have been developed in various research laboratories.

In this article we report the transporting properties of silacrowns, a new variety of crown ether in which a single ethylene bridge has been replaced by an R_2Si group, e.g. R=methyl, phenyl, or vinyl (Fig. 1) [16,17]. This substitution may be expected to have several effects upon the ionophoric properties of the new materials. For example, while molecular models indicate that ring size will be relatively unchanged, a reduction of approximately 4%, the presence of the Si–O oxygen atoms would be expected to cause a reduction in base strength of the ionophore since it is well established that both nitrogen and oxygen atoms directly bonded to silicon will possess markedly less base character than their carbon analogs [18]. Furthermore, the presence of the Si–O linkage will make the ionophores more susceptible to hydrolysis. Although the Si–O bond is more thermodynamically stable than the C–O bond, it is much more kinetically labile with respect to hydrolysis. This aspect of the silacrowns was expected to have significance with respect to their potential use as ionophore materials, since metal transport implies the ability to function in environments in close proximity to water.

We have addressed this hydrolytic instability and show how it may be a potentially most useful aspect of the silacrowns. We suggest that the introduc-

tion of a Si–O linkage into ionophores may be a desirable strategy for the synthesis of useful chemotherapeutic and industrial agents, since it probably accounts for their relative non-toxicity [16,17]. Indeed, the importance of the silacrowns may be judged by their recently patented use as industrial additives [19].

Experimental

All silacrowns were used as received in El Paso from Petrarch Systems Inc. In the middle stages of the research it was found that the transport efficiency of silacrown-6, Si-C-6, differed significantly from that obtained at the onset of the research. It was determined that the synthetic route used to obtain Si-C-6 [16] led to the "double" ring Si-C-12 as a side-product impurity. Pure samples are now obtained by purification using chromatography through 3% OV-101 on Chromasorb (waw, 80–100 mesh) solid phases in glass columns. Along with the normal spectroscopic techniques, it has been found that viscosity measurements represent accurate criteria for purity of the particular crowns: dimethylsilacrown-4 = 5.25 cP; Si-C-5 = 14.8 cP; Si-C-6 = 23.1 cP; Si-C-7 = 35.6 cP.

Transport of the metal ions across a liquid membrane was studied using the same technique as previously published [6]. In this experiment, a "source" arm of a U-tube apparatus containing an aqueous buffered solution of the metal picrate (10^{-2} mol/l) was separated from a similarly buffered aqueous solution containing no salt in the "out" arm by a chloroform solution containing the specific ionophore to be studied. The concentration of the silacrown in this solution was either 10^{-2} or 10^{-3} mol/l, dependent upon the transport efficiency, vide infra. All three regions of the apparatus were stirred at 60 rpm, and the appearance of the metal ion in the "out" phase was monitored by measuring the absorbance of the picrate anion at 357 nm. A plot of A vs time from such a monitoring produced a straight line, the slope of which is the measure of the rate of metal ion transport. The entire system was maintained at 21°C. The principle that the metal ion transports as a tight ion pair with the picrate anion has been previously established, such that the measurement of this anion is a true measure of the metal ion concentration [2]. All aqueous solutions were buffered with TRISMA systems at pH = 7.

Studies on the hydrolysis of the silacrowns were performed in the following manner. An equal amount of silacrown-5 and an isotonic saline solution (pH = 7, 0.1% NaCl, 0.03% gelatin) were permitted to react over a 24-hr period. Periodically an aliquot was examined by liquid chromatography using a 500 A Styragel column. A measure of the hydrolysis was the relative amount of starting silacrown and tetraethyleneoxy glycol. The results are presented in Table 1 and exhibit clear hydrolysis activity.

Experiments to study the partitioning of the silacrowns and their ethyle-

TABLE 1

Hydrolysis of sila-14-crown-5 in isotonic saline solution, pH = 7.4[a]

Time (min)	% Si-C-5	% TEG[b]
0	100	—
5	90	—
25	44	34
66	37	38

[a]Analysis by liquid chromatography using 500A Styragel column at 30°C.
[b]TEG = tetraethyleneoxy glycol. While this is the final hydrolysis product, an intermediate is readily observed, probably $Me_2Si(OH)(OCH_2CH_2)_4OH$. If the silacrown to isotonic solution ratio is increased, e.g. to 5:1, formation of the intermediate is the predominant initial reaction, with much less glycol.

neoxy glycol hydrolysis products were performed in the following manner. A normal U-tube experiment was set up with buffered solutions in both the "source" and "out" arms, and ionophore in the chloroform phase. *No salts were added to the "source" phase.* A transport run was performed, i.e. the solutions were stirred for periods of up to 60 minutes. At the end of the stirring period, the two aqueous phases were removed and discarded. They were replaced with a salt solution in the "source" phase and a buffer solution in the "out" phase, and a normal transport run performed with monitoring every 20 minutes. The concept behind this experiment is that during the "transport" run with no salt present, if the ionophore in the chloroform layer is able to partition into the aqueous phases, it will. Thus, upon removal of these phases and their replacement with normal solutions, a certain amount of the ionophore will also be removed. The degree to which there is a subsequent decrease in the ionophore concentration in the chloroform phase for the second, real, transport run will correlate with the ability of the ionophore to partition out of the hydrophobic phase. Any removal of the ionophore will cause a reduction in the rate of metal ion transport, since it has been well established that such rates are directly proportional to ionophore concentration. Thus, if no change in transport rate is observed subsequent to the pre-equilibration experiments it may be concluded that no partitioning of that particular ionophore occurs under the conditions of the experiment.

The pre-equilibrium experiments were performed with the silacrowns, ethyleneoxy glycols, and the regular crown ether ionophore, 15-C-5.

Results

The rates of transport of the alkali metal ions using the silacrowns Si-C-4, Si-C-5, Si-C-6 and Si-C-7, the ethyleneoxy glycols, and two crown ethers, cyclohexano-15-C-5 and dibenzo-18-C-6, are recorded in Table 2. Each value

TABLE 2

Rates of transport of alkali metal ions using various crowns

Crown	Rate of transport $\times 10^8$ mol-l/min			
	Na$^+$	K$^+$	Rb$^+$	Cs$^+$
Si-C-4[a]	2.0	10	3.4	1.5
Si-C-5	5.0	18	12	7
Si-C-6[b]	35	2700	750	200
Si-C-7[b]	62	840	1200	1000
Dibenzo-18-C-6[b]	e	10000	7000	3200
CH15-C-5[b,c]	e	3000	e	e
PMSi-C-5[c]	5	12	e	e
HEG[d]	8	190	210	170
PEM	5	330	21	10
TEG	2	5	e	e

[a]Si-C-4, Si-C-5, Si-C-6, Si-C-7 are dimethylsilacrowns as per Fig. 1.
[b]All ionophores at 10^{-2} mol/l except those with [b] which are superior ion transporters and were used at 10^{-3} mol/l. All transport values have been normalized to the same 10^{-2} mol/l concentration.
[c]PSMi-C-5 is the phenylmethylsilacrown-5; CH15-C-5 is cyclohexano-15-C-5.
[d]HEG, PEG, and TEG = hexa-, penta-, and tetraethyleneoxy glycol, respectively.
[e]No transport run performed.

is the result of at least four independent experiments and is reproducible to 15%. The data illustrate that the silacrowns are competent ionophores with the capacity to transport metal ions, of efficiency comparable to, but less than, the widely used dibenzo-18-crown-6. The silacrowns also exhibit metal ion selectivity patterns reminiscent of the normal crown ethers. The ethyleneoxy glycols also exhibit transporting capacity, but are significantly less efficient.

Results from our pre-equilibration studies are presented graphically in Figs. 2 and 3 for the silacrowns and their hydrolysis products. The data show a dramatic distinction between the two potential ionophoric materials. The sil-acrowns do not partition into the aqueous phases, and hence transport rates do not diminish with pre-equilibration time periods. The regular crown ether 15-C-5 behaves in the same manner. On the other hand the glycols partition very rapidly, such that after 30 minutes pre-equilibration, subsequent use of the chloroform layer reduced the transport rates to almost negligible values.

Discussion

The various rates of metal ion transport using the silacrowns indicate that these ionophores are competent transporters of the alkali metal ions, with the exception of Li$^+$, across a chloroform liquid membrane. The efficiency is on a par with the regular crown ethers dibenzo-18-C-6 and cyclohexano-15-C-5. The
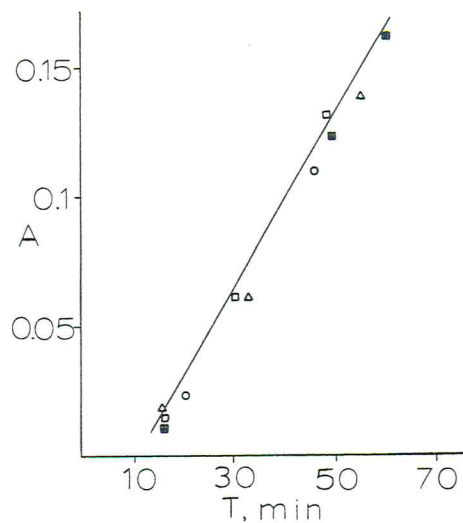
Fig. 2. Plot of absorbance in "out" arm versus time for the sila-14-crown-5. □, △, ○; ■: no, 15 min, 30 min, and 60 min pre-equilibration, respectively; K^+.
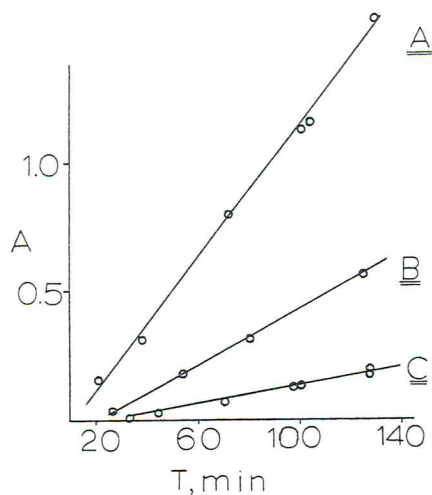

Fig. 3. Plot of absorbance in "out" arm versus time for the hexaethyleneoxy glycol. A, B, and C, $= 0$, 15, 30 min and 60 min pre-equilibration, respectively; K^+.

specific rates are less for the silacrowns, and this may be directly linked to the reduced basicity of the Si–O oxygen atoms, which, as noted above, are less basic than their carbon analogs. It has been previously reported that reductions in the base strength of crown ether oxygen atoms will cause a reduction in the ion transporting efficiency [6].

Selectivity patterns are observed. In general these patterns are more or less

those expected on the basis of the relative cation to cavity diameter ratios, although this is not a universal relationship from the data obtained. Initial experiments suggested that the silacrowns needed an extra oxygen atom for optimum transport when compared to the regular crown ethers, i.e. Si-C-7 transported K^+ better than Si-C-6 [20]. However, these experiments were performed with the earlier samples of Si-C-6 which were later found to contain Si-C-12 as discussed in the experimental portion. With pure samples this relationship is not found, indeed the Si-C-6 is a particularly effective catalyst for K^+ transport, and the selectivity pattern for this ionophore $Na^+ \ll K^+ > Rb^+ > Cs^+$ is completely in accord with the size ratio effect. A similar relationship is observed for the transporting capacity of the larger Si-C-7, i.e. $Na^+ < K^+ < Rb^+ > Cs^+$.

The substituted silacrown ether, phenylmethylsilacrown-5, differs very little in the rate of transport of Na^+ and K^+ ions when compared with the dimethyl derivative.

For the specific transport of Na^+, the generally low rates increase progressively as more oxygen atoms are available within the macrocycle, a pattern that is also observed for Rb^+ and Cs^+ transport; for all three ions the selectivity is Si-C-4 < Si-C-5 < Si-C-6 < Si-C-7. Only in the case of K^+ transport is there a clear selectivity pattern, Si-C-4 < Si-C-5 < Si-C6 > Si-C-7, and the rate of transport of the K^+ ion is the greatest of all the combinations of ionophore and metal ion we have studied.

The transport rates using the ethyleneoxy glycols are much slower than the silacrowns, but not negligible. From the pre-equilibration studies it is clear that if these materials have the opportunity to partition out of the hydrophobic phase into an aqueous phase they do so efficiently. This is in direct contrast to the silacrowns and regular crown ethers which maintain their concentration levels within the chloroform phase. The ability of the glycols to partition results in non-linear transport, i.e. plots of A vs t slowly level out, and the rates reported are rates of metal ion transported over a 60-min time period to provide some idea of the relative efficiency of these materials as compared with the silacrown precursors.

Since it has been shown that the silacrowns readily hydrolyse, and their hydrolysis products partition out of hydrophobic phases into adjacent aqueous environments, it is tempting to suggest that this attribute is a major feature of their future development. It is established that they are relatively non-toxic, and for example do not cause testicular atrophy in laboratory animals [16]. Within a hydrophobic phase of a membrane there is a limited amount of water. Thus, gradual hydrolysis of the silacrowns will lead to progressive depletion of ion-carrying species, until no ionophoric capacity remains. This contrasts the regular crown ethers, and other non-destructible ionophores, where there will be no such diminution of ionophore character and hence a constant ion leakage

can produce a possible permanent state of abnormality in the physiological condition.

Thus, as short-term transporters, the silacrowns have the advantage of efficient ionophoric behaviour with a potential for lack of long-term side effects. Since certain ionophores have been proposed as potential anti-hypertensive pharmaceuticals [14,15], it seems appropriate to suggest that judicious positioning of a siloxy group within the macrocycle backbone may be useful. This would permit active ionophore behaviour *and* hydrolytic instability with respect to ionophorically non-active, and excretable, materials. The synthesis of such molecules is an attractive goal for the synthetic pharmacological chemist.

Acknowledgements

References

1 C.F. Reusch and E.L. Cussler, Selective membrane transport, AIChE J., 18 (1973) 736.
2 K.H. Wog, K. Yagi and J. Smid, Ion transport through liquid membrane facilitated by crown ethers and their polymers, J. Membrane Biol., 18 (1974) 379.
3 M. Kirsch and J.-M. Lehn, Selective transport of alkali metal cations through a liquid membrane by macrobicyclic carriers, Angew. Chem., Int. Ed. Engl., 14 (1975) 555.
4 J.J. Christensen, J.D. Lamb, S.R. Izatt, S.E. Starr, G.C. Weed, M.S. Astin, B.D. Stitt and R.M. Izatt, Effect of anion type on the rate of facilitated transport of cations across liquid membranes via neutral macrocyclic carriers, J. Amer. Chem. Soc., 100 (1978) 3219.
5 J.D. Lamb, J.J. Christensen, J.L. Oscarson, B.L. Nielson, B.W. Assay and R.M. Izatt, The relationship between complex stability constants and rates of cation transport through liquid membranes by macrocyclic carriers, J. Amer. Chem. Soc., 102 (1980) 6820.
6 K.H. Pannell, B.J. Rodriquez, S. Chiocca, L.P. Jones and J. Molinar, Dibenzo-crown facilitated transport across a $CHCl_3$ liquid membrane, J. Membrane Sci., 11 (1982) 169.
7 G. Eisenman, G. Szabo, S.G.A. McLaughlin and M. Ciani, Molecular basis for the action of macrocyclic carriers on passive translocation across lipid bilayer membranes, Bioenergetics, 4 (1973) 93.
8 M. Dobler, J.D. Dunitz and B.T. Kilbourn, The structure of KCNS-complexes of nonactin, Helv. Chim. Acta, 52 (1969) 2573.
9 M.M. Shemyakin, Yu A. Ovchinnikov, V.T. Ivanov, V.K. Antonov, E.I. Vinogradova, A.M. Shkrob, G.G. Malenkov, A.V. Evstratov, I.A. Laine, E.I. Melnik and I.D. Ryabova, Cyclodepsipeptides as chemical tools for stuyding ionic transport through a membrane, J. Membrane Biol., 1 (1969) 402.
10 J.D. Lamb, R.M. Izatt, J.J. Christensen and D.J. Eatough, in: G. Melson (Ed.), Coordination Chemistry of Macrocyclic Compounds, Plenum Press, New York, NY, 1979.
11 B. Leong, T.O. Tso and M.B. Chenoweth. Testicular atrophy from inhalation of ethylene oxide cyclic tetramer, Toxicol. Appl. Pharmacol., 27 (1974) 242.
12 R.D. Hendrixson, M.P. Mack, R.A. Palmer, A. Ottolenghi and R. Ghirardeli, Oral toxicity of the cyclic polyethers 12-crown-4, 15-crown-5, and 18-crown-6 in mice, Toxicol. Appl. Pharmacol., 44 (1978) 263.
13 S.C. Gad, W.J. Conroy, J.A. McKelvey and R.A. Turney, Behavioural and neuropharmacological toxicology of the macrocyclic ether 18-crown-6, Drug Chem. Toxicol., 1 (1978) 339.

14   M.W. Osborne, F. Kovzelove, M.R. Cohen and J.J. Wenger, Bromolasalocid (Ro 20-0006) antihypertensive ionophore, Fed. Proc., 42 (1983) 191.

15   N.T. Deguzman and B.C. Pressman, The ionotropic effects of the calcium ionophore X-574A in the anesthetized dog, Circulation, 49 (1974) 1072.

16   B. Arkles, K. King, R. Anderson and W. Peterson, Silacrowns: Phase transfer catalysts, Organometallic, 2 (1982) 454.

17   K.H. Pannell, C.K. La Neave, E. Rico and B. Arkles, Concerning the relative non-toxicity of silacrown ionophores, Pharmacol. Biochem. Behav., 21, Suppl. 1 (1983) 77.

18   C. Eaborn, Organosilicon Compounds, Academic Press, New York, NY, 1960, Chaps. 3 and 9.

19   J.C. Liu, Loctite Corp., Conn., U.S. Patent application 550411, 1985.

20   E. Rico, K.H. Pannell and B. Arkles, 38th Southwest and 6th Rocky Mountain Combined Regional Meeting of the American Chemical Society, El Paso, TX, Dec. 1-3, 1982, abstract 9.