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Synthesis of Novel Polyethers in a Geometrically Precise Conformation

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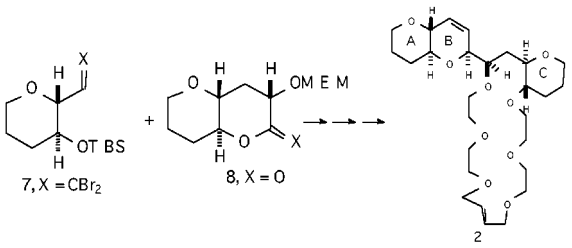
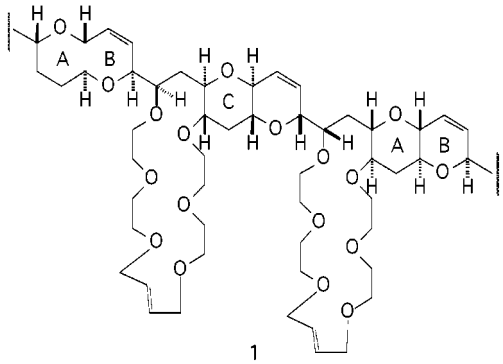
ABSTRACT



A convergent design for the preparation of a polyoxyethylene-based channel molecule is presented, and the synthesis of the key unit 2 required for the projected construction is described. The essential elements of the design included face to face oriented macrorings spaced by rigid *trans*-fused oxanes. The strategy combines conformational predictability of C-linked oxanyl systems and ring-closing metathesis for the synthesis of crown ethers with engineerable ion-binding abilities.

Effective conformation design to attain a monoconformational situation in large polyoxyethylene backbones would offer a good strategy for selective cation transport.[1,2] In our unimolecular model **1**, the essential elements of the design included face to face oriented cyclic ethers spaced by rigid *trans*-fused oxacycles.



Here, as a first step toward the synthesis[3] of **1**, we describe the synthesis of the oxane-linked subunit **2** and report on its conformational behavior.[4]

The purpose of the present communication is also to show how our model may be applied to simulate the dynamics of

(1) Incorporation of macromolecular polyether derivatives into lipids has been shown to result in cation transport rates comparable to those ion channels formed by natural and synthetic oligopeptides or antifungal macrolides: (a) Fyles, T. M.; Loock, D.; Zhou, X. *J. Am. Chem. Soc.* **1998**, *120*, 2997−3003. (b) Meillon, J.-C.; Voyer, N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 967−968. (c) Pechulis, A. D.; Thompson, R. J.; Fojtik, J. P.; Schwartz, H. M.; Lisek, C. A.; Frye, L. L. *Bioorg. Med. Chem.* **1997**, *5*, 1893−1901. (d) Maguire, G. E. M.; Meadows, E. S.; Murray, C. L.; Gokel, G. W. *Tetrahedron Lett.* **1997**, *38*, 6339−6342. (e) Abel, E.; Meadows, E. S.; Suzuki, I.; Jin, T.; Gokel, G. W. *J. Chem. Soc., Chem. Commun.* **1997**, 1145−1146. (f) Murray, C. L.; Meadows, E. S.; Murillo, O.; Gokel, G. W. *J. Am. Chem. Soc.* **1997**, *119*, 7887−7888. (g) Murillo, O.; Suzuki, I.; Abel, E.; Murray, C. L.; Meadows, E. S.; Jin, T.; Gokel, G. W. *J. Am. Chem. Soc.* **1997**, *119*, 5540−5549. (h) Wagner, H.; Harms, K.; Koert, U.; Meder, S.; Boheim, G. *Angew. Chem.* **1996**, *108*, 2836−2839; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2643−2646. (i) Stadler, E.; Dedek, P.; Yamashita, K.; Regen, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 6677−6682.

(2) Remarkably, the recently reported crystal structure of the potassium ion (K^+) channel reveals that the main chain atoms create a structurally constrained stack of oxygen atoms that tightly coordinate K^+ ions but not smaller Na^+ ions: (a) Doyle, D. A.; Morais-Cabral, J.; Pfuetzner, R. A.; Kuo, A.; Gulbis, J. M.; Cohen, S. L.; Chait, B. T.; MacKinnon, R. *Science* **1998**, *280*, 69−77. (b) MacKinnon, R.; Cohen, S. L.; Kuo, A.; Lee, A.; Chait, B. T. *Science* **1998**, *280*, 106−109. (c) Kreusch, A.; Pfaffinger, P. J.; Stevens, C. F.; Choe, S. *Nature* **1998**, *392*, 945−948.

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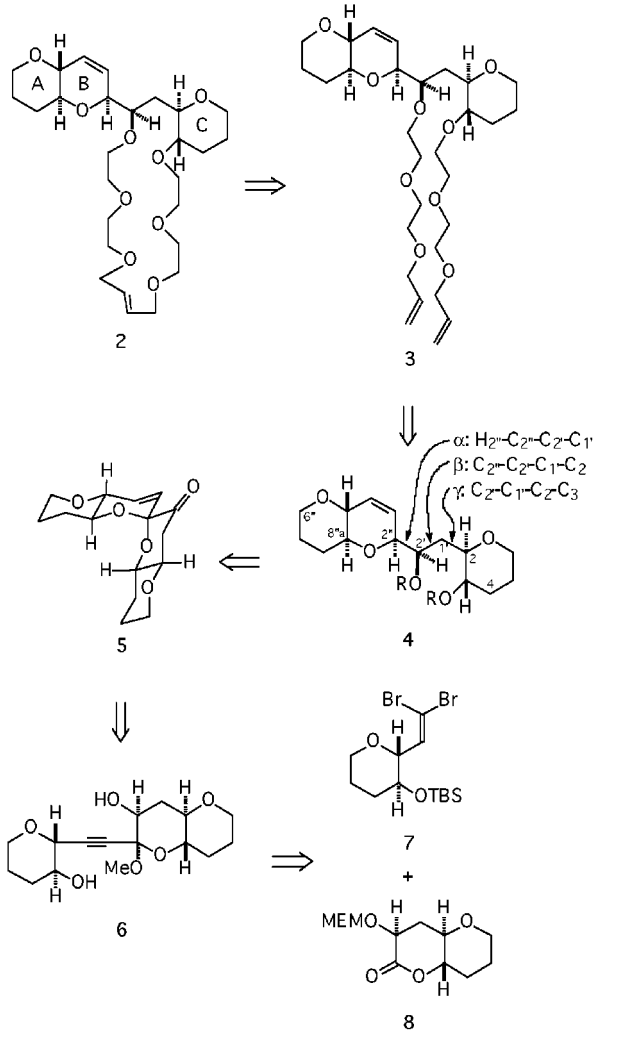
channel organization. The strategy for the synthesis of **2** is outlined in Scheme 1.

Scheme 1. Retrosynthesis of the Tetracyclic Polyether **2**



It was anticipated that the macrocyclic ring in **2** could be obtained by ring-closing metathesis (RCM)[5] of the bis(allyl) podand **3** derived from the basic diol **4** (R = H), which in turn could be obtained by silane double reduction of the spiroacetal **5**. This latter system was envisioned to arise via the acetylene **6** by partial reduction to the *cis*-olefin and spirocyclization.

Both precursors, dibromoolefin **7** and lactone **8**,[6] can be readily prepared from **9**[7] by standard methodologies (Scheme 2). Coupling of lactone **8** with the acetylene anion generated in situ from dibromide **7** gave the hemiacetal **21**, which was further treated with CSA/MeOH to produce the acetal **6** (62% yield, over two steps). Partial hydrogenation of **6** and treatment of the resulting olefin with $BF_3{\cdot}Et_2O$/MeCN gave the spiroketal **23**[8] (84% yield), which was then oxidized with TPAP−NMO[9] (for abbreviations see ref 23) to furnish ketone **5** (88% yield). Reduction of **5** using $BF_3{\cdot}Et_2O$ and Et_3SiH resulted in the desired diol **4** (R = H) (84% yield).[10] Compound **3** was prepared in 64% yield by treatment of **4** (R = H) with *t*-BuOK (2.2 equiv) and excess allyl diethylene glycol toluene-*p*-sulfonate in THF at 25 °C. Finally, reaction **3** in CH_2Cl_2 (0.005 M) with 10 mol % of bis(tricyclohexylphosphine)benzylideneruthenium dichloride, at 25 °C for 5 h, provided 81% of the macrocycle **2**.[5]

We have studied the conformational behavior of **4** (R = Ac) by NMR methods coupled with force-field computation.[11,12] Averaged $^1H-^1H$ coupling constants over the calculated whole set of conformers[13] gave a 500 MHz simulated ^1H NMR spectrum[14] fully in agreement with the experimental one. Calculated interproton distances obtained from 2D-NOESY[15] and those corresponding to each conformer exhibit a very good agreement, showing that, in solution, 93% of the conformer population is covered by two major conformations: $\alpha = \beta = \gamma = 180°$ (66%, 86%, and 80%, respectively) and $\alpha = 55°$ (18%), $\beta = \gamma = 180°$ (86% and 80%).

(3) Reviews related to synthetic models for transmembrane channels: (a) Gokel, G. W.; Murillo, O. *Acc. Chem. Res.* **1996**, *29*, 425−432. (b) Fyles, T. M.; Straaten-Nijenhuis, W. F. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNichol, D. D., Vögtle, F., Reinhoudt, D. N., Eds.; Pergamon: Oxford, U.K., 1996; Vol. 10, pp 53−77. (c) Voyer, N. *Top. Curr. Chem.* **1996**, *184*, 1−37. (d) Akerfeldt, K. S.; Lear, J. D.; Wasserman, Z. R.; Chung, L. A.; DeGrado, W. F. *Acc. Chem. Res.* **1993**, *26*, 191−197.

(4) The reason for using crown ether homologues as the pore-forming moieties is the fact that their binding ability can be engineered to specific needs. Thus, the cavity diameter 5.5(5.9)−7.8(7.6) Å of the selected macroring in **2** and its weaker binding efficiency in comparison with 18-crown-6 analogues (see the Supporting Information) should allow for the transport of a wide variety of metal ions.

(5) (a) Köning, B.; Horn, C. *Synlett* **1996**, 1013−1014. (b) Marsella, M. J.; Maynard, H. D.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1101−1103. (c) Mohr, B.; Weck, M.; Sauvege, J.-P.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1308−1310. (d) Delgado, M.; Martín, J. D. *Tetrahedron Lett.* **1997**, *38*, 8387−8390.

(6) For a different approach to the synthesis of lactone **8**, see: Zheng, W.; De Mattei, J. A.; Wu, J.-P.; Duan, J. J.-W.; Cook, L. R.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946−7968.

(7) Compound **9** was prepared from triacetyl-D-glucal according to the described procedure: Nicolaou, K. C.; Hwang, C.-K.; Marron, B. E.; De Frees, S. A.; Coulados, E. A.; Abe, Y.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040−3054.

(8) The exclusive selection of one of the possible conformations for spiroacetal **23** is a consequence of the stabilizing anomeric and *exo*-anomeric effects that direct both C−O bonds to axial positions on the respective rings. For a review, see: Perron, F.; Albizati, K. J. *Chem. Rev.* **1989**, *89*, 1617−1661.

(9) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.

(10) Applications involving reductive cleavage of the anomeric center in spiroacetals have only recently been recognized for their potential synthetic utility. For recent examples, see: (a) Crimmins, M. T.; Rafferty, S. W. *Tetrahedron Lett.* **1996**, *32*, 5649−5652. (b) Oikawa, M.; Veno, T.; Oikawa, H.; Ichihara, A. *J. Org. Chem.* **1995**, *60*, 5048−5068.

(11) This is done by minimizing the individual structures by an MM3* force field implemented in the MacroModel V6.0 program. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caulfield, C.; Chang, G.; Hendrikson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−447.

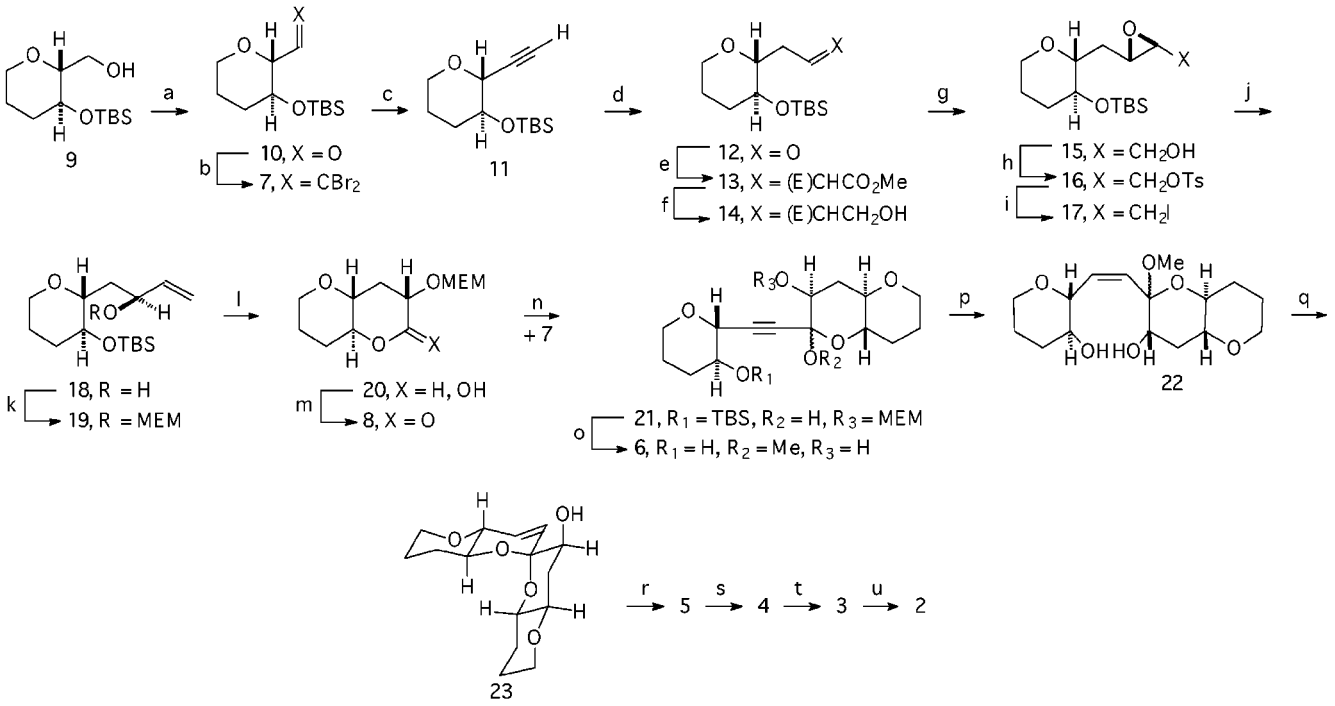
(12) Calculated coupling constants for diacetate **4** (R = Ac) gave better agreement with the experimental values than did those constants for free hydroxyl groups: Haasnot, C. A. G.; De Leeuw, F. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783−2792.

(13) Monte Carlo calculations were made, yielding a set of 192 conformers (see the Supporting Information).

(14) Simulations were done using gNMR 6.3.5 from Cherwell Scientific Publishing Ltd., The Magdalen Centre, Oxford Science Park, Oxford OX4 4GA, U.K.

(15) Analysis of the spectra were made using TRIAD 6.3 as part of the package SYBYL 6.3 from Tripos Inc. (Supporting Information).

Scheme 2. Synthesis of the Tetracyclic Polyether **2**[a]



[a] Reagents and conditions: (a) 5.0 equiv of SO_3·pyr, 5.0 equiv of Et_3N, CH_2Cl_2−DMSO (6:1), 25 °C, 4 h, 75%; (b) 4.0 equiv of Ph_3P, 2.0 equiv of CBr_4, CH_2Cl_2, 0 °C, 20 min, 83%; (c) 2.0 equiv of *n*-BuLi, THF, −78 °C, 20 min, then H_2O, 82%; (d) 2.0 equiv of $(Sia)_2BH$, THF, 0 °C, 12 h, then 10 equiv of 3 N NaOH, 20 equiv of 30% H_2O_2, 0 °C, 2 h, 88%; (e) 1.3 equiv of NaH, 1.2 equiv of $(MeO)_2POCH_2CO_2Me$, benzene, 25 °C, 15 min, then add **11**, 25 °C, 15 min, 88%; (f) 5.0 equiv of DIBALH, Et_2O, 0 °C, 1 h; quench with NaOH−H_2O, 98%; (g) 0.3 equiv of Ti(O-*i*-Pr)$_4$, 0.4 equiv of (+)-diethyl tartrate, 1.8 equiv of *t*-BuOOH (5−6 N in decane), 4 Å MS, CH_2Cl_2, −20 °C, 12 h, 95%; (h) 1.1 equiv of TsCl, 0.05 equiv of 4-DMAP, 2.5 equiv of Et_3N, CH_2Cl_2, 25 °C, 8 h, 93%; (i) 2.3 equiv of NaI, 2.0 equiv of $NaHCO_3$, butanone, 60 °C, 1 h, 97%; (j) 2.0 equiv of *t*-BuLi, Et_2O, −78 °C, 2 h, 99%; (k) 2.0 equiv of MEMCl, 4.0 equiv of $(i\text{-Pr})_2EtN$, 0.1 equiv of 4-DMAP, CH_2Cl_2, 25 °C, 5 h, 95%; (l) (i) 3.0 equiv of NMO, OsO_4 catalyst, THF−H_2O−acetone (1:1:1), 25 °C, 12 h, 75%, (ii) 1.2 equiv of TBAF, THF, 25 °C, 6 h, (iii) 2.5 equiv of $(n\text{-Bu})_4NIO_4$, MeOH−H_2O (4:1), 20 °C, 3 h, 81% for two steps; (m) 1.5 equiv of PCC, 0.2 equiv of NaOAc, CH_2Cl_2, 25 °C, 12 h, 66%; (n) 2.0 equiv of *n*-BuLi, THF, −78 °C, then add 1.0 equiv of **7**, −78 to 0 °C, then add 1.0 equiv of **8**, −35 °C, 30 min, 77%; (o) 0.2 equiv of CSA, MeOH, 25 °C, 24 h, 80%; (p) 10 wt % of 10% Pd−$CaCO_3$, 0.07 equiv of quinoline, H_2, EtOAc, 25 °C, 10 h, 95%; (q) 1.1 equiv of BF_3·Et_2O, MeCN, −30 °C, 20 min, 88%; (r) 0.1 equiv of TPAP, 1.5 equiv of NMO, CH_2Cl_2, 25 °C, 2 h, 88%; (s) 8.0 equiv of Et_3SiH, 5.0 equiv of BF_3·Et_2O, MeCN, −15 °C, 20 min, 84%; (t) 2.2 equiv of allyl diethylene glycol toluene-*p*-sulfonate, 2.2 equiv of *t*-BuOK, THF, 50 °C, 4 h, 64%; (u) **3**, 0.005 M in CH_2Cl_2, 10 mol % $[(PCy_3)_2RuCHPh]Cl_2$, 25 °C, 12 h, 81%. For abbreviations see ref 23.

Since the conformational behavior of cyclized ether **2** is identical with that of the acyclic precursor **3**,[16] we can expect mid-plane oxane systems in **2** to be perpendicular to the ring plane of the crown ether moiety, a situation which is ideal for channel formation (Figure 1).[17] Molecular dynamic studies were carried out over the macrocyclic unit **2** and a simulated three-unit oligomer, using a continuum solvent model. In the model $\epsilon = 4.0$ ($CHCl_3$), which is the one expected to simulate the interior environment of mem-

(16) The NMR characteristic observed for **2** and **3** were virtually superimposable on those of the relevant protons and carbons.

(17) As is the case for all ring-forming reactions, the RCM of polyoxyethylene rings is determined by several factors, including the kinetics of ring closing, ring strain, and competing metathesis-based polymerization. In the case of compound **3** (2*R*,3*S*,2′*R*,2″*S*,4″a*R*,8″a*S*) the RCM to give **2** occurs due to the favored preorganization of the C-linked oxanyl system, which allows close proximity of the terminal olefins. All attempts to prepare diastereomers of **2** by RCM of diastereomers of **3**, **3a** (2*R*,3*S*,2′*S*,2″*S*,4″a*R*,8″a*S*), **3b** (2*S*,3*R*,2′*R*,2″*S*,4″a*R*,8″a*S*), and **3c** (2*S*,3*R*,2′*S*,2″*S*,4″a*R*,8″a*S*), were unsuccessful. This gathered information was of crucial importance in the selection of the target unit subject of the present communication.

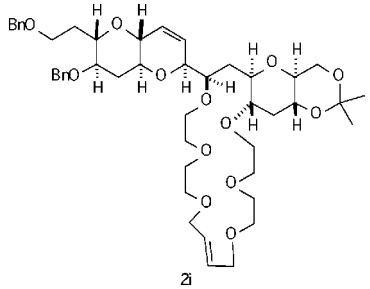
(18) Coveney, P. V.; Emerton, A. N.; Boghosian, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 10719−10724.

(19) Although this computer modeling was the basis for the selection of the "building block" **2**, rigorous testing will be required to determine whether the design lives up to its expectations as an ion channel agent.

(20) HOLE suite of programs. Smart, O. S.; Goodfellow, J. M.; Wallace, B. A. *Biophys. J.* **1993**, *65*, 2455−2460.

(21) Calculations were done by fixing the backbone of the oligomer, allowing only the movement of the atoms forming the cyclic ether ring. MMFF 94 was used with our standard conditions (Supporting Information).

(22) The analogue **2i**, conveniently functionalized for coupling reactions following the synthetic sequence described in Scheme 1, has been prepared (to be submitted for publication):



2i

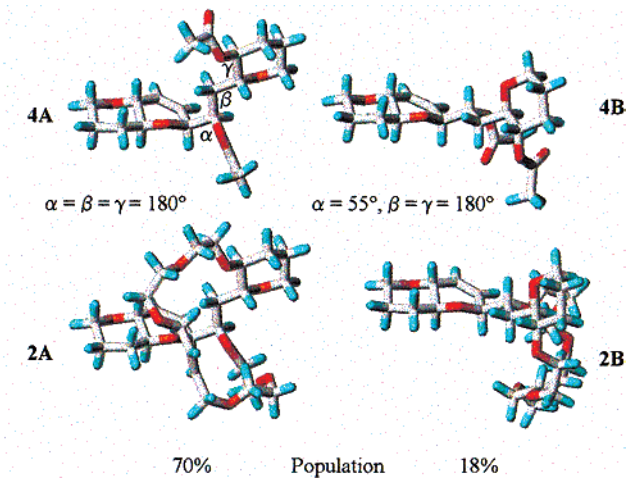


Figure 1. Preferred solution conformation of **4** (R = Ac) (top) and **2** (bottom). Monte Carlo studies in conjunction with distance calculations, from 2D-NOESY NMR experiments, over the A−B−C unit give us the two preferred conformers **2A** and **2B**, covering 88% of the overall population.

branes,[18] 100% of the sampled structures have $\alpha = \beta = \gamma = 180°$ conformation. This simulated model localizes crown ether residues face to face on the same side of the mid-plane which contains the oxanyl system, forming a channel for ions long enough (40 Å) to span a bilayer membrane, as illustrated in Figure 2 (left).[19]

A HOLE study of such channels shows the internal surface of the pore (Figure 2, right).[20] For this conformation, prediction of the conductance was carried out using the same suite of programs, combining the conductances of the individual rings. The expected conductance, in any case, is about 20 pS in 1 M KCl, about one-third that of gramicidin. However, calculations of the pore diameter after an MD run of 100 ps[21] shows that it ranges from 0.5 to 2.5 Å, allowing possible cation transfer through the membrane. Work is currently under way to prepare oligomers of **2**[22] and to elucidate their transport abilities.

(23) Abbreviations: TBS = *tert*-butyldimethylsilyl; MEM = methoxymethyl; DMSO = dimethyl sulfoxide; KHMDS = potassium bis(trimethylsilyl)amide; DIBALH = diisobutylaluminum hydride; MS = molecular sieves; 4-DMAP = 4-(dimethylamino)pyridine; NMO = 4-methylmorpholine *N*-oxide; TBAF = tetra-*n*-butylammonium fluoride; PCC = pyridinium chlorochromate; CSA = 10-camphorsulfonic acid; TPAP = tetra-*n*-propylammonium perruthenate.

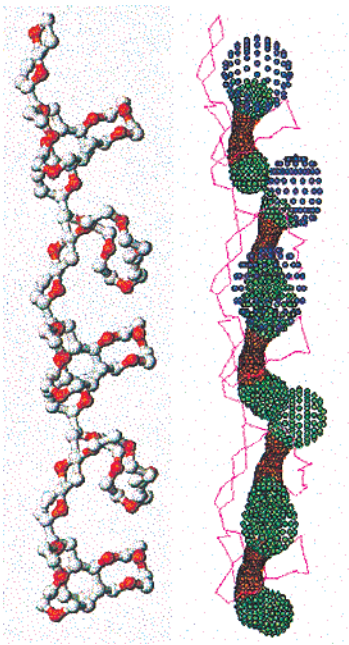


Figure 2. 3-D representation and HOLE analysis of the three A−B−C unit oligomer: (a, left) extended projection of the three-unit oligomer of **2**, generated by MD studies using a continuum solvent model with $\epsilon = 4.0$ ($CHCl_3$), 100%, $\alpha = \beta = \gamma = 180°$; (b, right) HOLE surface of the inside of the channel (red, diameter less than 1.15 Å; green, diameter between 1.15 and 2.3 Å; blue, diameter larger than 2.3 Å).

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Supporting Information Available: Experimental details and characterization data for compounds **2**−**23**, NMR studies, and calculation details. This material is available free of charge via the Internet at http://pubs.acs.org.

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