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THE "CHUNDLE" APPROACH TO MOLECULAR CHANNELS
SYNTHESIS OF A MACROCYCLE-BASED MOLECULAR BUNDLE

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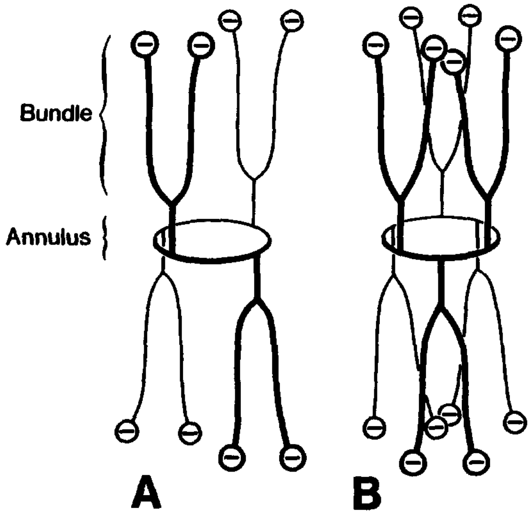
A molecular sheaf **7** *formed by bundles of oligo(oxyethylene) chains grafted on a macrocyclic polyether has been synthesized; its structural features characterize an approach to the design of transmembrane molecular channels.*

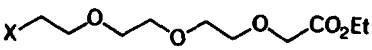
The regulation of membrane permeability is of fundamental importance in biology and of great potential in chemical systems. Selective transport and coupling of substrate flow to chemical and physical potentials may be induced either by mobile carrier molecules or by transmembrane channels. The design of such effectors and of transport processes represents one of the basic features of supramolecular chemistry[1,2].

The chemistry of carrier mediated transport processes has been extensively investigated in recent years thanks to the development of artificial receptor molecules that could be used to transfer the selectively bound substrate(s) through membrane barriers[1,2]. The design of transmembrane channels has been much less explored, probably because of the inherently larger molecular structures involved, despite the fact that biological transport is thought to occur principally via such channels.

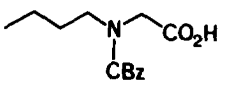
Several types of structures may serve as frameworks for channel design. 1) transmembrane molecules containing a continuous internal void defining a pore as may be the case in peptides and in proteins[3] (such as gramicidin A[4] or synthetic helical molecules[5,6]), 2) molecular tubes formed by the stacking of macrocyclic rings held in place by either connection to a polymeric chain[7], organisation in a tubular mesophase[8] or synthetic bridging into an axial polymacrocyclic unit[9,10], 3) bundles of transmembrane molecular chains that define a central channel, formed either by the spontaneous association of individual molecules (as in the polymolecular peptide channel of alamethicin[11]) or by grafting several chains onto a supporting unit such as a polyfunctional macrocyclic molecule which constitutes the organizing core. The latter case may be schematically depicted by structures **A**, **B**[12] and considered to represent the chundle approach (channel + bundle) to a transmembrane channel. Such an entity should present three main features - 1) two bundles of chains long enough to span half a membrane bilayer, grafted on, - 2) a central annulus serving both as support maintaining the two bundles of chains and as substrate selective site, - 3) terminal polar groups for anchoring the molecule to each interface in a transmembrane fashion. We here describe the synthesis and properties of a molecule displaying the structural features of such a "chundle" species[13-15].

Dedicated to the memory of Professor Yuri Ovchinnikov.





1a X = OH
1b X = OTs
1c X = N_3
1d X = NH_2



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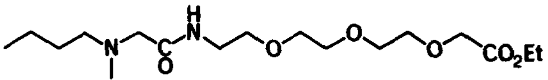
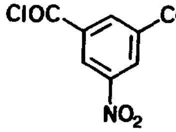


3a R = CBz
3b R = H



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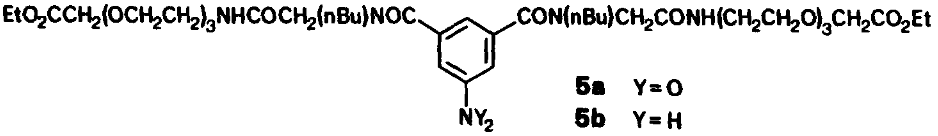


5a Y = O
5b Y = H

Synthesis of the "chundle" molecule 7

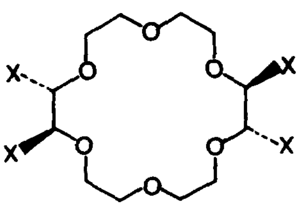
Treatment of triethyleneglycol in tenfold excess with ethyldiazoacetate in presence of BF_3: Et_2O (CH_2Cl_2, r.t.) gave the ester alcohol 1a (colourless liquid, 70% yield). Tosylation of 1a (TsCl, Py, 0-4°C) gave 1b (pale yellow liquid, 90% yield) which was converted to the azide 1c (pale yellow liquid, 95% yield) by reaction with NaN_3 (DMF, 60°C). Hydrogenation of 1c (H_2, Pd/C 10%, CH_2Cl_2, r.t.) gave the aminoester 1d (pale yellow liquid, 95% yield).

Carboxybenzylation of N-butylglycine[16] with benzylchloroformate (NaOH 4N, 0°C) gave the protected aminoacid 2 (CBz = $C_6H_5CH_2OCO$) (colourless viscous syrup, 80% yield).

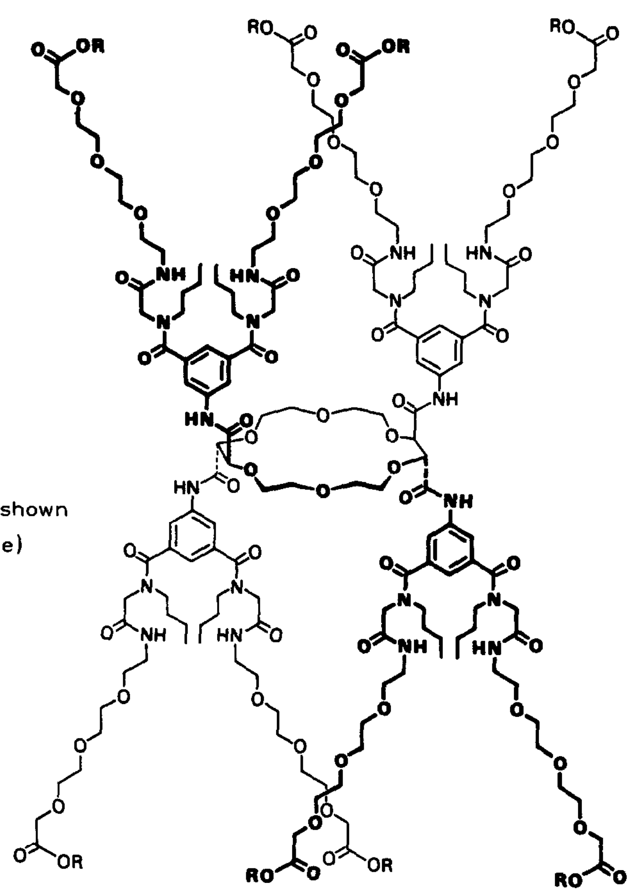
Condensation of the aminoester 1d with the aminoacid 2 (dicyclohexylcarbodiimide, p-dimethylaminopyridine, CH_2Cl_2, r.t.) afforded 3a (pale yellow liquid, 40% yield) which was deprotected to the aminoester 3b (H_2, Pd/C 10%, CH_2Cl_2, r.t., pale yellow liquid, 92% yield).

The synthesis of the desired side-chain was completed by condensing 3b with the diacid chloride 4[17] (NEt_3, CH_2Cl_2, r.t.) to give 5a (colourless viscous syrup, 80% yield), which was reduced to the amine 5b (H_2, Pd/C 10%, CH_2Cl_2, r.t., colourless viscous syrup, 95% yield).

The desired "chundle" molecule was obtained by reacting (N,N-dimethyl-acetamide, p-dimethylaminopyridine, r.t.) the doubly branched amine 5b with the tetra-chloride 6b[18] of the chiral 18-O_6 macrocyclic hexaether tetracarboxylic acid 6a (derived from L-tartaric acid)[18]. The product octaester 7 was isolated as a colourless wax in 30% yield after purification by chromatography (silica, elution by a CH_2Cl_2/MeOH gradient), it is soluble in organic solvents such as CH_2Cl_2 or MeOH.



6a X = CO_2H
6b X = COCl



7 R=Et
(The side-chains are shown in their extended state)

Properties and structural features of the "chundle" molecule 7

Compound 7 has a high molecular weight ($C_{176}H_{284}O_{66}N_{20}$ 3733.95), confirmed by FAB mass spectroscopy, which gave the expected ion distribution around 3759,8 ± 0.3 $(M+Na)^+$ (3-nitrobenzyl alcohol matrix) and 3737,8 ± 0.3 $(M+H)^+$, 3759,8 ± 0.3 $(M+Na)^+$ (glycerol/HCl matrix). It belongs to a class of large organic molecules, of size greater than mesomolecules[19] and comparable to the smaller biological macromolecules.

The 200 MHz proton NMR spectrum of 7 showed broad peaks at 293 K. A suitable spectrum, containing the expected signals, was obtained in $C_2D_2Cl_4$ at 364 K, where rotation around the tertiary amide bonds is fast. The 50.3 MHz carbon-13 NMR spectrum (in $C_2D_2Cl_4$, 383 K) gave sharp resonances at the required positions. Compound 7 possesses intense UV absorption with shoulders at 236 and 212 nm ($\log \varepsilon$ = 5.0 and 5.1 respectively, EtOH 95%), this should allow easy detection in membrane experiments.

The structural features of molecule 7 correspond to those desired for studies of "chundle" type molecular channels - 1) the functionalized 18-O_6 macrocyclic annulus possesses selective metal cation binding properties[20,21], - 2) it bears two axially oriented[21] bundles of four oxygen containing chains, which provide binding sites for metal cations[13,14], and are long enough for the molecule to span a typical lipid membrane; the overall length with the chains in an extended state may be estimated to lie in the 45-50 Å range, - 3) the eight terminal ester functions should yield, after hydrolysis, the carboxylate groups required for anchorage at water/ membrane interfaces and transmembrane orientation, as well as for eventual coupling to proton gradients, in addition, the rigid phenyl groups hinder back-bending of the chains and the N-butyl units confer lipophilicity facilitating membrane inclusion[23].

Whether molecule 7 will itself lead to a functional channel is not yet known and structural modifications may be required[22]. Nevertheless, it represents a prototype of the "chundle" approach to a molecular channel.

Finally, one may note that molecule 7 is of nanometer size and thus belongs to a class of molecular species, organized and functional nanostructures, that are synthetically constructed large molecules, possessing structural and functional features suitable for their incorporation in the design of molecular devices[1a]. In particular, molecules such as the "chundle" 7 are potential components of molecular ionic devices[1a].

Membrane incorporation, cation binding and cation transfer studies are underway[23] and further structural elaborations on the "chundle" principle are being investigated.

Mass spectral data for compound 7 were obtained by Drs S L Mullen and D. Gage at the Michigan State University Mass Spectrometry Laboratory.

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23 Preliminary experiments indicate that the octacarboxylate obtained by saponification of 7 may be incorporated into model bilayer membranes L Jullien, T Lazrak and J -M Lehn, work in progress.

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