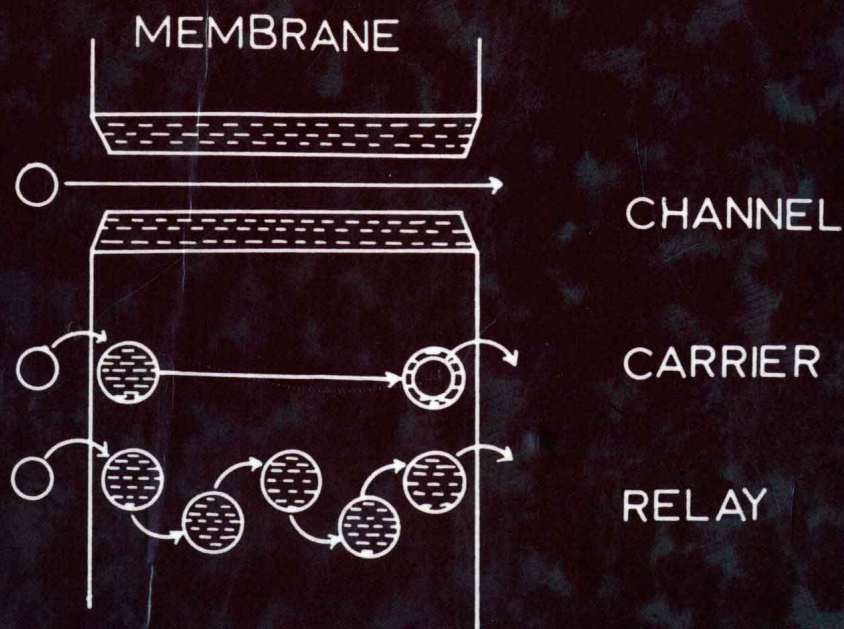

TOPICS IN INCLUSION SCIENCE

T. Osa and J. L. Atwood
Editors

INCLUSION ASPECTS OF MEMBRANE CHEMISTRY



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INCLUSION ASPECTS OF MEMBRANE CHEMISTRY

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INCLUSION ASPECTS OF MEMBRANE CHEMISTRY

TOPICS IN INCLUSION SCIENCE

VOLUME 2

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Ion Extraction and Transport by Proton-Ionizable Crown Ethers

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1. Introduction.

Interest in macrocyclic polyethers as complexing agents has grown exponentially since Pedersen's original description [1] of the ability of these compounds to lipophilize metal and ammonium cations. Such ligands have been used to complex about half the metals on the periodic table [2], to act as selective agents for metal extractions [3], to serve as phase transfer catalysts [4], to carry metal ions across hydrophobic barriers [5], and to emulate biological binding sites [6]. In view of their widespread applications, macrocycles have

been synthesized which provide a variety of ligand donor atoms for the ionophoric cavity [2]. Many structural variations have also appeared, so that macrocycles, macropolycycles (cryptands) [7], speleands [8], spherands [9], and torands [10] are frequently mentioned in the chemical literature. These variations on the theme of lipophilic host molecules form the basis for an ever-widening circle of interest in host-guest chemistry and separation science using synthetically prepared ionophoric molecules.

The use of macrocycles as extraction agents has also led to the development of molecules in which the lipophilicity has been increased by the addition of aryl or alkyl substituents to the outer surfaces of the macrocyclic ring structures [1,11]. A natural extension of such structural modification was the addition of extra ligand sites in side chains [11] in an effort to increase the stability and selectivity of complexes formed by these molecules. A further outgrowth was the addition of proton-ionizable moieties [12] in the side chains to increase their complexing abilities by providing the requisite anion(s) for complexation.

The volume of macrocyclic polyether research conducted during the past two decades has been so great that several substantive reviews on macrocycles [2], cryptands [7] and lariat ethers [11] are available. These reviews cover topics as widely varied as synthesis [13], complexation chemistry [14], extraction [15] and transport behavior [5, 16, 17], analytical applications [18, 19] and complexation with neutral guest molecules [20]. Only in a very limited number of these compilations [2, 5, 7, 18, 19] are proton-ionizable crown ethers identified as an important class of macrocyclic polyethers. Since this class of compounds is now quite extensive and has unique advantages for applications in separation science, this review will concentrate on the synthesis, complexation behavior, use in solvent extraction, and utilization in membrane transport of proton-ionizable macrocyclic polyethers. The constraints of time and space dictate a restriction to only those compounds which have oxygen atoms as the most numerous electron donor atoms in the ring structure of the macrocycle. Thus, this review will not mention the extensive research being conducted with cyclams, lactams, porphyrins, and thiacrowns. Even within this restricted field, there is a wealth of valuable and interesting chemistry to be understood and applied to practical separation problems.

2. Syntheses of Proton-Ionizable Macrocyclic Compounds.

The publication frequency of papers dealing with the synthesis of crown ether compounds which contain ionizable moieties has been steadily increasing since the first such paper appeared in 1973 (Figure 1).

The topography of a molecule synthesized by a particular

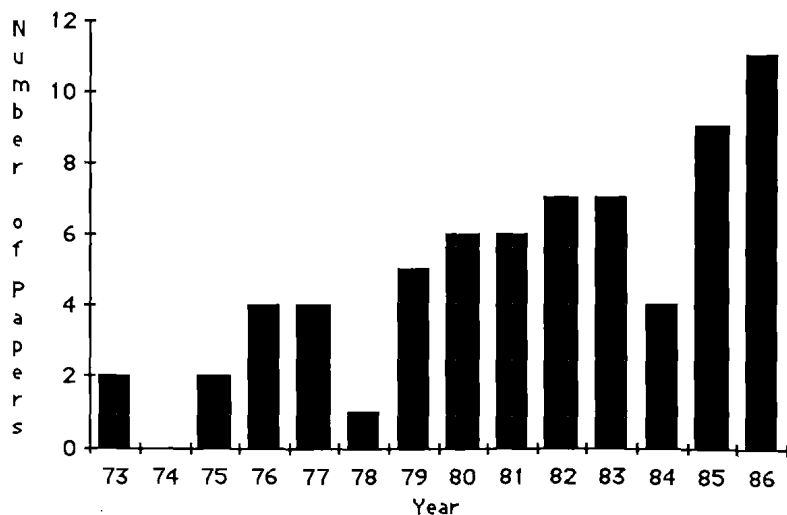
researcher is usually designed in direct response to a particular interest of that worker. This is particularly evident among the ligands designed with pendant side arms. Two major motivations for molecular design are the construction of ionophores which will; (1) mimic the catalytic or ion-specific sites of a biological molecule; and, (2) aid in the selective separation of metal ions from aqueous solutions.

A review of the literature reveals that three primary methods for incorporation of proton-ionizable moieties in macrocycles have evolved. These are:

- (1) attachment of a pendant side arm which includes or is terminated by an ionizable entity [7,12,21-66];
- (2) inclusion within the crown ether framework of a subunit which projects an ionizable entity, so that both the proton and the atom which bears it are within the cavity [67-75]; and
- (3) inclusion, as part of the crown ether framework, of a unit which places a heteroatom in a ligating position, with an attached proton projecting into the ring cavity [76-84].

The macrocyclic compounds in these three classes will be designated as macrocycles with ionizable pendant groups, ionizable intra-annular groups and ionizable ring atoms, respectively, throughout this chapter.

Figure 1: A histogram of publication frequency for journal articles dealing with proton-ionizable crown ether synthesis.



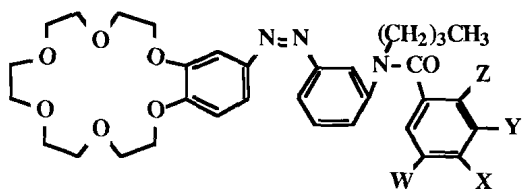
2.1 Ionizable Pendant Groups.

Side arms have been attached to the perimeters of macrocyclic

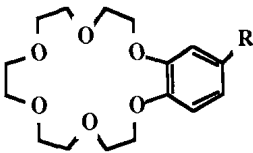
ring structures by substitution on the aryl groups of benzo (**I-XVIII**), biphenyl (**XIX-XXVII**) and binaphthyl (**XXVIII-XXXIII**) crown ethers, by the addition of substituents directly to carbon atoms of the macrocyclic framework (**XXXIV-CXLVII**), and by substitution at the nitrogen atom of a monoazacrown (**CXLVIII-CLVIII**) or both nitrogen atoms of a diazacrown (**CLIX-CLXXXVIII**). The resultant side arms include ionizable sites either to provide a specific binding site for biomimetic experiments, or to eliminate the need for inorganic anions to accompany extracted cations during solvent extraction and membrane transport procedures.

When crown ethers with pendant side arms are considered, the intended application of a compound strongly influences the type of molecule that is constructed. Biomimetic molecules have side arms which, by virtue of either the length or the structure of the side arm (e.g., **XXVIII-XXXIII, CXXXIII, CXXXIV**), maintain relatively fixed steric locations in relation to the macrocyclic cavity. This is desirable in hosts which are designed to produce high chiral or structural recognition of proposed guest molecules. The success of the technique is illustrated by the ability of Cram and co-workers to separate racemates with suitable macrocyclic hosts [85].

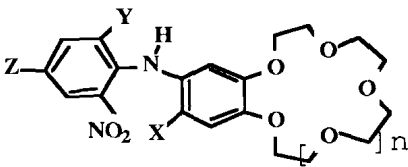
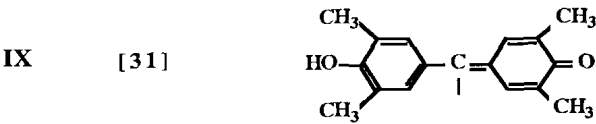
In contrast with these more rigid structures, molecules designed for metal ion separations tend to have side arms which are more flexible, to allow for arrangement of the molecule so that the charged unit of the ionized moiety can more easily approach a desirable ion-pairing position in relation to the cation sequestered within the cavity (e.g., **XXXIV-LVIII**). Other variations of side arms designed for metal ion complexation include the addition of chromophores for the colorimetric detection of complexed metals (e.g., **LXII, LXIII, LXXIV-LXXXIII**) [42, 57], and the addition of photo-responsive bonds [39] (**I-III**) which allow the use of light-switching to control the efficiency and selectivity of metal ion solvent extraction and liquid membrane transport.



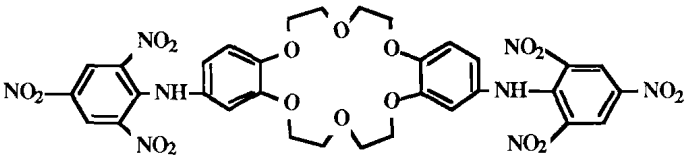
Cmpd	Ref	W	X	Y	Z
I	[39]	H	H	OH	H
II	[39]	H	OH	H	H
III	[39]	OH	H	H	NO ₂



Cmpd	Ref	R
IV	[31]	N=N-2-hydroxy-1-naphthyl
V	[31]	N=N-4-hydroxyphenyl
VI	[31]	N=N-3-t-butyl-4-hydroxyphenyl
VII	[31]	N=N-3-chloro-4-hydroxyphenyl
VIII	[22]	CONH(CH ₂) ₅ CO ₂ H

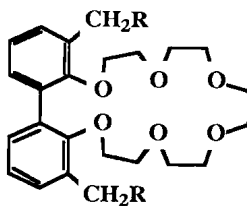


Cmpd	Ref	n	X	Y	Z
X	[31]	2	H	NO ₂	NO ₂
XI	[31]	2	NO ₂	NO ₂	NO ₂
XII	[25]	1	H	NO ₂	NO ₂
XIII	[25]	1	Br	NO ₂	NO ₂
XIV	[25]	1	NO ₂	NO ₂	NO ₂
XV	[32]	1	H	NO ₂	CN
XVI	[34]	1	H	NO ₂	CF ₃
XVII	[34]	1	H	CF ₃	NO ₂

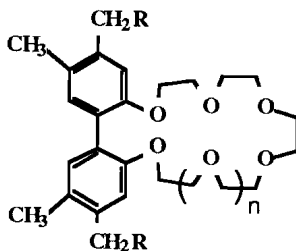


Cmpd
XVIII

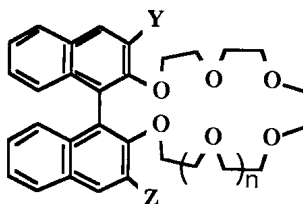
Ref
[31]



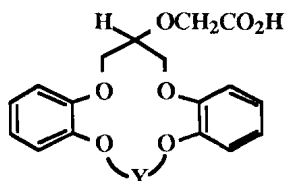
Cmpd	Ref	R	Cmpd	Ref	R
XIX	[36]	$\text{SCH}_2\text{CO}_2\text{H}$	XXI	[36]	SO_3M
XX	[36]	OSO_3M	XXII	[36]	$\text{PO}(\text{OH})_2$



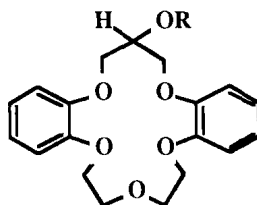
Cmpd	Ref	n	R	Cmpd	Ref	n	R
XXIII	[36]	1	$\text{SCH}_2\text{CO}_2\text{H}$	XXVI	[36]	2	$\text{S}(\text{CH}_2)_3\text{CO}_2\text{H}$
XXIV	[36]	1	$\text{S}(\text{CH}_2)_2\text{CO}_2\text{H}$	XXVII	[36]	1	$\text{O}(\text{CH}_2)_2\text{OSO}_3\text{M}$
XXV	[36]	2	$\text{S}(\text{CH}_2)_2\text{CO}_2\text{H}$				



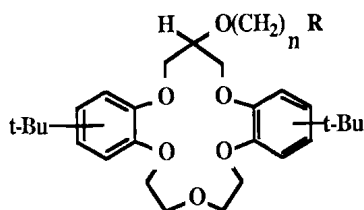
Cmpd	Ref	n	Y	Z
XXVIII	[12]	1	H	$\text{CH}_2\text{OCH}_2\text{CO}_2\text{H}$
XXIX	[12]	1	$\text{CH}_2\text{OCH}_2\text{CO}_2\text{H}$	$\text{CH}_2\text{OCH}_2\text{CO}_2\text{H}$
XXX	[12]	0	$\text{CH}_2\text{OCH}_2\text{CO}_2\text{H}$	$\text{CH}_2\text{OCH}_2\text{CO}_2\text{H}$
XXXI	[12]	2	$\text{CH}_2\text{OCH}_2\text{CO}_2\text{H}$	$\text{CH}_2\text{OCH}_2\text{CO}_2\text{H}$
XXXII	[24]	1	CO_2H	CO_2H
XXXIII	[24]	2	$\text{PO}(\text{OEt})_2$	$\text{PO}(\text{OEt})_2$



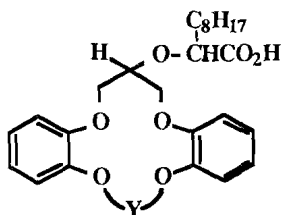
Cmpd	Ref	Y	Cmpd	Ref	Y
XXXIV	[38]	CH ₂ CH ₂	XXXVI	[38]	CH ₂ CH ₂ OCH ₂ CH ₂
XXXV	[38]	CH ₂ CH ₂ CH ₂	XXXVII	[38]	CH ₂ (CH ₂ OCH ₂) ₂ CH ₂



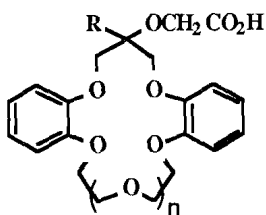
Cmpd	Ref	R	Cmpd	Ref	R
XXXVIII	[38]	CH(C ₂ H ₅)CO ₂ H	XLII	[38]	(CH ₂) ₂ CO ₂ H
XXXIX	[38]	CH(C ₄ H ₉)CO ₂ H	XLIII	[38]	(CH ₂) ₄ CO ₂ H
XL	[38]	CH(C ₆ H ₁₃)CO ₂ H	XLIV	[61]	(CH ₂) ₃ SO ₃ H
XLI	[38]	CH(C ₈ H ₁₇)CO ₂ H	XLV	[61]	(CH ₂)PO(OH)(OEt)



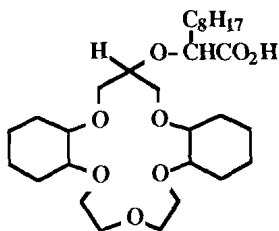
Cmpd	Ref	n	R
XLVI	[62]	1	PO(OH)(OEt)
XLVII	[62]	2	PO(OH)(OEt)
XLVIII	[62]	3	PO(OH)(OEt)
IL	[62]	4	PO(OH)(OEt)
L	[40]	1	CO ₂ H



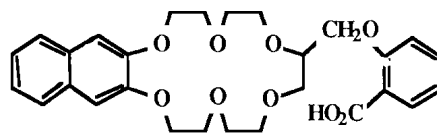
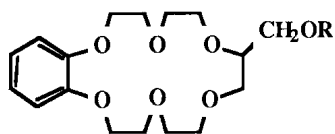
Cmpd	Ref	Y
LI	[46]	CH ₂ CH ₂ CH ₂
LII	[46]	CH ₂ (CH ₂ OCH ₂) ₂ CH ₂
LIII	[46]	CH ₂ (CH ₂ OCH ₂) ₃ CH ₂



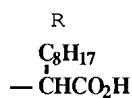
Cmpd	Ref	n	R
LIV	[46]	1	C ₄ H ₉
LV	[46]	1	C ₈ H ₁₇
LVI	[46]	1	C ₁₄ H ₂₉
LVII	[46]	2	C ₈ H ₁₇



Cmpd	Ref
LVIII	[46]

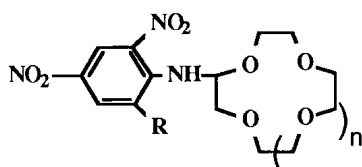
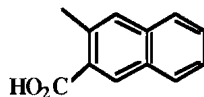


Cmpd Ref
LIX [48]

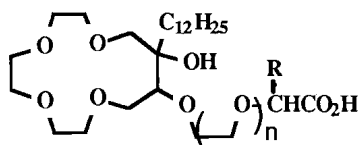


Cmpd Ref
LXI [47]

LX [48]

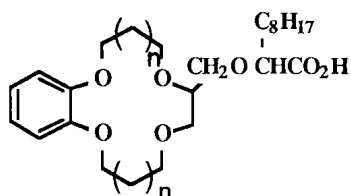


Cmpd	Ref	n	R
LXII	[54]	1	CF ₃
LXIII	[54]	2	NO ₂

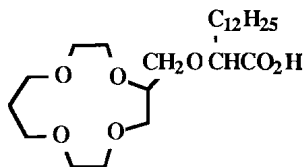


Cmpd	Ref	n	R
LXIV	[55]	0	H
LXV	[55]	1	H
LXVI	[55]	2	H
LXVII	[55]	3	H

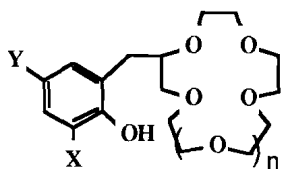
Cmpd	Ref	n	R
LXVIII	[55]	1	C ₆ H ₁₃
LXIX	[55]	2	C ₆ H ₁₃
LXX	[55]	3	C ₆ H ₁₃



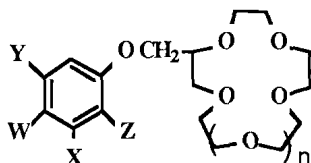
Cmpd	Ref	n
LXXI	[60]	0
LXXII	[60]	1



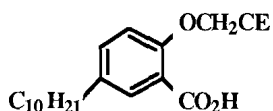
Cmpd	Ref
LXXIII	[60]



Cmpd	Ref	n	X	Y
LXXIV	[57]	1	NO ₂	NO ₂
LXXV	[57]	2	NO ₂	NO ₂
LXXVI	[57]	1	H	p-nitrophenylazo
LXXVII	[57]	2	H	p-nitrophenylazo
LXXVIII	[57]	1	p-nitrophenylazo	p-nitrophenylazo

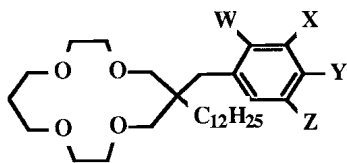


Cmpd	Ref	n	W	X	Y	Z
LXXIX	[57]	0	H	NO ₂	NO ₂	OH
LXXX	[42]	1	H	NO ₂	NO ₂	OH
LXXXI	[42]	2	H	NO ₂	NO ₂	OH
LXXXII	[42]	1	H	H	p-nitrophenylazo	OH
LXXXIII	[42]	2	H	H	p-nitrophenylazo	OH
LXXXIV	[51]	1	C ₁₀ H ₂₁	H	H	PO(OH)(OEt)
LXXXV	[51]	2	C ₁₀ H ₂₁	H	H	PO(OH)(OEt)
LXXXVI	[51]	3	C ₁₀ H ₂₁	H	H	PO(OH)(OEt)
LXXXVII	[51]	4	C ₁₀ H ₂₁	H	H	PO(OH)(OEt)
LXXXVIII	[59]	1	t-Bu	H	H	PO(OH)(OEt)

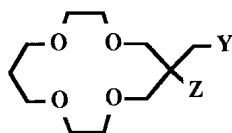


Cmpd	Ref	CE	Cmpd	Ref	CE
LXXXIX	[60]	12C4(2)*	XCVI	[60]	16C5(3)
XC	[60]	13C4(2)	XCVII	[60]	18C6
XCI	[60]	13C4(3)	XCVIII	[60]	19C6(2)
XCII	[60]	14C4(2)	IC	[60]	21C7
XCIII	[60]	14C4(3)	C	[60]	24C8
XCIV	[60]	15C4(3)	CI	[60]	27C9
XCV	[60]	15C5	CII	[60]	30C10

* (2) indicates the crown ether is attached to one of the carbon atoms in a two atom bridge; (3) indicates attachment is at the central carbon atom of a three carbon bridge.



Cmpd	Ref	W	X	Y	Z
CIII	[56]	OH	H	H	H
CIV	[56]	OH	H	H	NO ₂
CV	[56]	OH	NO ₂	H	H
CVI	[56]	OH	NO ₂	H	NO ₂
CVII	[66]	H	NO ₂	OH	NO ₂
CVIII	[66]	OH	H	H	p-(N,N-dimethyl-sulfonamido)phenylazo
CIX	[66]	OH	H	H	p-nitrophenylazo
CX	[66]	OH	p-nitrophenylazo	H	H
CXI	[66]	OH	p-nitrophenylazo	H	p-nitrophenylazo
CXII	[66]	OH	NO ₂	H	p-nitrophenylazo



Cmpd	Ref	Y	Z
CXIII	[66]		H
CXIV	[66]		H
CXV	[66]		CH ₃
CXVI	[66]		CH ₃