Thermodynamic and Kinetic Data for Macrocycle Interaction with Cations, Anions, and Neutral Molecules

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Contents

I. Introduction

Cation–macrocycle interaction was treated in three earlier *Chemical Reviews* articles (1974,[1] 1985,[2] and 1991[3]), anion–macrocycle interaction was treated in 1991,[3] and neutral molecule–macrocycle interaction was treated in 1992.[4] The present review updates this material and includes data which were inadvertently omitted earlier. In general, this review does not repeat the data included in the earlier reviews. As in the past reviews, particular effort has been made to include literature from countries of the former USSR, Eastern Europe, and the Peoples Republic of China.

As with the earlier reviews, the most important part of this review is considered by the authors to be the data compilation. The complete data compilation will be available only in the supporting information via the Internet. Thermodynamic and kinetic data are brought together to provide a quantitative base for understanding the effect of macrocycle and guest parameters on the thermodynamic and kinetic stabilities of the resulting complexes. In turn, this understanding can lead to the intelligent design of new macrocycles and to predictions of their effectiveness in forming complexes of desired stabilities with guest species. It is apparent from the increase in the data available since the 1985 review,[2] which was featured as a Classic Citation,[5] that these data are valuable to workers in the field.

Several reviews containing compilations of some thermodynamic and/or kinetic data for macrocycle

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Reed M. Izatt was born in Logan, UT. He received his B.S. degree at Utah State University in 1951 and his Ph.D. degree in 1954 with Professor W. Conard Fernelius in coordination chemistry at The Pennsylvania State University. After two years of postdoctoral work at Carnegie-Mellon University, he joined the Brigham Young University Chemistry Department in 1956. He is the Charles E. Maw Professor of Chemistry, Emeritus, at BYU. He delivered the Annual Sigma Xi lecture at BYU in 1966 and the Annual BYU Faculty Lecture in 1970. He was BYU Teacher of the Month in October 1974. He received the BYU Karl G. Maeser Research and Creative Arts Award in 1967 and was the recipient of an NIH Career Development Award (1967–1972), the Utah Award (American Chemical Society) in 1971, the Huffman Award (Calorimetry Conference) in 1983, the Willard Gardner Award of the Utah Academy of Sciences, Arts, and Letters in 1985, the State of Utah Governor's Medal in Science in 1990 and the American Chemical Society Award in Separation Science and Technology for 1996. He is a Fellow of the American Association for the Advancement of Science and is Chairman of the Organizing Committee for the annual International Symposium on Macrocyclic Chemistry. His research interests include the design of novel molecular recognition systems for the selective separation of cations, anions, and neutral species; calorimetry applied to metal–ligand and nonelectrolyte interactions, particularly at elevated temperatures and pressures; and the compilation of thermodynamic data.

Jerald S. Bradshaw, Reed M. Izatt Professor of Chemistry, was born in Cedar City, UT, and received a B.A. degree in chemistry at the University of Utah in 1955. After four years as an officer in the U.S. Navy, he enrolled in a Ph.D. program at UCLA. He received the Ph.D. in 1963 with Professor Donald J. Cram on electrophilic substitution at saturated carbon. He received an NSF postdoctoral fellowship for the 1962–1963 academic year to work with Professor George S. Hammond at the California Institute of Technology. After three years as a research chemist at Chevron Research in Richmond, CA, he joined the faculty at Brigham Young University in 1966. He was named Professor of the Year at BYU in 1975. He was U.S. National Academy of Sciences Exchange Professor for the academic year of 1972–1973 and the Summer of 1982, working with Professor Miha Tisler at the University of Ljubljana, Slovenia. He also was a visiting professor with Dr. J. F. Stoddart at the University of Sheffield, England, in 1978, and a National Science Foundation Cooperative Research Fellow with Dr. L. F. Lindoy at James Cook University, Townsville, Australia, in 1988. He is a member of the American Chemical Society. He received the 1989 Utah Award from the Salt Lake and Central Utah sections of the American Chemical Society and the American Chemical Society Award in Separation Science and Technology for 1996. He received the State of Utah Governor's Medal in Science in 1991. In 1992, he presented the Annual Faculty Lecture at BYU. His research interests include the synthesis and cation complexation properties of macrocyclic multidentate compounds, the photochemical reactions of heterocyclic compounds, and the preparation of new polysiloxanes for chromatography uses.

Krystyna Pawlak was born in Poland and received her M.D. degree at the Medical Academy in Gdansk, Poland, in 1964. She obtained her specialization in psychiatry at the Medical Academy in Gdansk and at the Institute of Neurology and Psychiatry in Warsaw. After five years of practicing medicine at the State Psychiatric Hospital, she served as a Director of the Outpatient Clinic for Alcoholics and Drug Addicts in Gdansk where she did research on pharmacodynamics of drugs used in the treatment of alcoholics. From 1973 to 1986, she was a consultant in the Outpatient Psychiatric Clinic in Gdynia and a sworn expert for the court. She was a member of the Polish Psychiatric Society. From 1981 to 1982, she was an observer in The Tower Hospital in Leicester, England. In 1986, she joined the chemistry research group at Brigham Young University. Her recent interests are in researching the known literature on the thermodynamics of macrocycle and amino acid interactions with cations, anions, and neutral molecules, and the compilation of thermodynamic data. In 1992 she became a member of Sigma Xi, the Scientific Research Society.

Ronald L. Bruening was born in Salt Lake City, UT, and received his B.S. degree in chemical engineering at Brigham Young University in 1985. He obtained his M.S. degree in chemistry in 1986 and his Ph.D. in chemistry with Professor R. M. Izatt in 1988 at BYU. He received the H. Tracy Hall Award as the outstanding graduating Ph.D. student in 1988 and Sigma Xi Outstanding Ph.D. Dissertation Award for the College of Physical and Mathematical Sciences in 1989. From 1986 to 1988 he was a research assistant at BYU. Since 1988, he has been Vice-President of Research, IBC Advanced Technologies, Inc., American Fork, UT, and a research associate at BYU. He is a member of the American Chemical Society, Sigma Xi, and Tau Beta Pi Honorary Engineering Society. His scientific interests involve macrocycle-mediated separations in both packed solid supported systems and in membrane formats.

interaction with cations, anions, and neutral molecules have been published since the 1991[3] and 1992[4] reviews. These reviews are now listed together with the major areas of emphasis in each case.

(1) A. Bencini, A. Bianchi, P. Paoletti, and P. Paoli, "Thermodynamic and structural aspects of transition metal compounds. Polynuclear complexes of azamacrocycles", 1992.[6] The authors of this review collect significant examples of equilibria in aqueous solution in which polynuclear transition metal complexes of azamacrocycles, and also of some ligands which behave as azamacrocycles, are formed. The authors also analyze the formation of these complexes from the thermodynamic and structural points of view. The review has many tables with thermodynamic data and 85 references.

(2) A. Bianchi, M. Micheloni, and P. Paoletti, "Thermodynamic Aspects of the Polyazacycloalkane Complexes with Cations and Anions", 1991.[7] This review is dedicated to the thermodynamics of the equilibria, in aqueous solution, between saturated polyazamacrocycles and metal cations or anions. Ligands included in this review range from the smallest triazamacrocycle (1,4,7-triazacyclononane) to the large polyazacycloalkane (1,4,7,10,13,16,19,-22,25,28,31,34-dodecaazacyclohexatriacontane). The review contains numerous tables with thermodynamic data and 217 references.

(3) S. R. Cooper, Ed., *Crown Compounds. Toward Future Applications*; 1992.[8] "Internationally prominent researchers were asked to survey their own areas briefly, speculate on where likely future applications might arise, and to identify the research (both basic and applied) necessary to bring their predictions to fruition." Four chapters of the book have tables with thermodynamic data for macrocycle interaction with cations and neutral molecules.

(4) Diederich, F., *Cyclophanes*, 1991.[9] This extensive review on macrocyclic cyclophane chemistry contains numerous tables with thermodynamic and kinetic data for cyclophane complexation with charged and uncharged organic guests.

(5) C. Detellier, H. Graves, and K. M. Brière, "Alkali Metal NMR Studies of Synthetic and Natural Ionophore Complexes", 1991.[10] Among other topics, the authors discuss microdynamics, thermodynamics, and kinetics of macrocycle interaction with alkali metals and cite many thermodynamic and kinetic data. The review contains 132 references.

(6) G. W. Gokel, *Crown Ethers and Cryptands*, 1991.[11] The book contains chapters on syntheses of title compounds, structural aspects, applications, and complexation. In the chapter on complexation, the author discusses the techniques for determining cation-binding constants, binding dynamics, cation transport, molecular complexation, complexation of organic cations, and complexation of anions. This chapter contains several tables with thermodynamic and kinetic data for macrocycle complexation with cations.

(7) G. W. Gokel, Ed. *Advances in Supramolecular Chemistry*, 1993.[12] French, Japanese, and American authors present their work in the supramolecular chemistry field. The book contains discussions on macrocyclic compounds such as calixarenes, cryptophane receptors for tetrahedral molecules, functionalized tetraazamacrocycles, synthetic receptors for molecular recognition of neutral molecules, and fluorescent chemosensors for metal and nonmetal cations. Thermodynamic data for the interaction of cations and neutral molecules with macrocycles are included.

(8) C. Seel and F. Vögtle, "Molecules with Large Cavities in Supramolecular Chemistry", 1992.[13] This is a review on the strategy for the design and synthesis of three-dimensional bridged cyclophanes and their complexation with metal cations, organic cations, and neutral molecules. There are thermodynamic data in the text. 159 references have been reviewed.

(9) V. P. Solov'ev, E. A. Vnuk, N. N. Strakhova, and O. A. Raevskii, *Complexation Thermodynamics of Alkali and Alkaline Earth Metal Salts with Cyclic Polyethers*, 1991 (Russian).[14] The authors analyze and tabulate thermodynamic data for the complexation of over 330 crown ethers (3500 entries) with alkali and alkaline earth metal cations. Sixteen tables, printed on 330 pages, contain metal salt and ligand formulas, salt and ligand concentrations, stoichiometry of complexes, log K values with conditions under which they have been studied (temperature, ionic strength, and medium), and methods used for data evaluation. In one of the tables, ΔH and ΔS values are given. The literature consists of 336 references.

(10) I. Tănase, A. M. Joşceanu, and C. Luca, *Complexes with Macrocyclic Ligands. Stability Constants and Thermodynamic Data*, 1991 (Rumanian).[15] The authors review macrocyclic compounds including their nomenclature, classification, synthesis, and complexation with cations of alkali, alkaline-earth, and some transition metals. The factors which influence complex formation in solution are discussed. The major part of the book consists of the collection of stability constants and thermodynamic data for macrocycle–cation interaction. The book cites 423 references published prior to January 1987.

(11) J. Vicens, and V. Böhmer, Eds., *Calixarenes: A Versatile Class of Macrocyclic Compounds*, 1991.[16] The book is a comprehensive survey on calixarene chemistry. It deals with the synthesis and chemical modification of calixarenes, the conformation of calixarenes and their derivatives in the solid state, the inclusion properties of calixarenes in solution and in the solid state, and existing and potential industrial applications of calixarenes. The book contains tables with thermodynamic data for calixarene interaction with charged and uncharged guests as well as thermodynamic data which are scattered in the text.

(12) M. W. Hosseini, "Preorganization of the Second Coordination Sphere", 1992.[17] This short review has 52 references and discusses coordination of protonated macrocyclic polyamines with complex anions and formation of super-complexes. Thermodynamic data are presented in one graph. The authors cite many references containing thermodynamic data.

Additional reviews are available on enantiomeric recognition of organic ammonium salts by chiral pyridino-18-crown-6 ligands;[18,19] on aza cages as "fast proton sponges";[20] on solvent effects in molecular recognition;[21] on chelate ring size and metal ion selection;[22] on the coordination chemistry of cryptand

interaction with alkali, alkaline-earth, radioactive, and toxic cations including selectivity ranges of cryptands for these cations;[23] on polyamine complexation;[24] on cation, anion, and neutral molecule interaction with a variety of macrocycles,[25] on macrocyclic fluorescent chemosensors;[26] on the usefulness of thermodynamic data;[27] and on macrocycle applications.[28] The book, *Studies in Organic Chemistry 45. Crown Ethers and Analogous Compounds*, edited by Hiraoka and issued in 1992 to the memory of Charles J. Pedersen, contains chapters on recent advances in syntheses of crown compounds, characteristics of new crown compounds, applications of crown ethers to analytical and separation chemistry, enzyme modeling with crown ethers, amine-selective color complexation with chromogenic "acerands", new developments in "switched-on" crown ethers, and on macrocyclic polyamine chemistry.[29]

The compilation of thermodynamic (log K, ΔH, ΔS, ΔC_p) and kinetic (k_f, k_d, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$) data is intended to be exhaustive. Included in the tables in the supporting information are data for the interaction of a wide variety of macrocycles with inorganic and organic cations, inorganic and organic anions, and neutral molecules. The reactions have been studied in a variety of solvents and under a variety of experimental conditions. The experimental conditions and some supplementary information are provided for each interaction listed. It is important to realize that the data are valid only at the specific conditions given. Few studies have been made at temperatures outside of the 20−30 °C range. The solvents used include H_2O (D_2O), various nonaqueous solvents, various solvent mixtures, and molten salts.[30] The abbreviations used in the tables in the supporting information can be understood by reference to the structures and names given in Charts I−LXXII (macrocycles), Charts LXXIII−LXXV (organic cations), Charts LXXV−LXXVI (organic anions), and Charts LXXVI−LXXVII (neutral molecules). The charts in which each macrocycle is located are indicated in the tables in the supporting information. The nomenclature used is defined in the charts. The set of charts is applicable only to tables in the supporting information.

The text of the review includes a separate set of drawings. In each drawing, the macrocycle under discussion is indicated by arabic numbers in bold. In each drawing, the macrocyle name and number are given in parentheses as they are used in the charts and in the tables in the supporting information, e.g., **5** (18C6-1, XIX). In this example, the macrocycle is designated by **5** in the text but in the tables and charts (supporting information) it is named 18C6-1 and its structure can be found in Chart XIX.

In this review, emphasis will be placed on the presentation of thermodynamic and kinetic data for the period from 1991−1993. Data will be included where appropriate. The complete data set is included in the supporting information.

II. Thermodynamics of Cation–Macrocycle Interaction

Table I (supporting information) contains log K, ΔH, and ΔS values for the interaction of macrocycles and related ligands with cations. The method used to determine log K is given in each case. The method used to determine ΔH is given only if it is different than that used to determine log K. In these cases, the method is placed in parentheses immediately after the ΔH value. The temperature of measurement, the medium (solvent, supporting electrolyte) used in each determination, some supplementary information (equation, short explanation), and the literature reference are given, also.

A. Old, Modified, and New Compounds

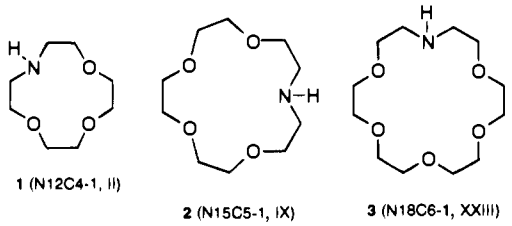
The review by Izatt et al. published in 1991[3] on cation interaction with macrocycles contains over 10 000 entries. The number of compounds listed in the 1991 review[3] exceeds the number in the 1985 review[2] by about 4-fold. Comparison of Table I in the supporting information with the 1985 and 1991 reviews shows that expansion of macrocycle chemistry continues unabated. Many more macrocycles have been synthesized than have been characterized with respect to their thermodynamic and kinetic properties. Table I (supporting information) lists only macrocycles for which quantitative thermodynamic data are given. These macrocycles consist of "old" compounds which have appeared in previous reviews, "old" compounds which have been modified with different side arms, donor atoms, etc. (majority of the entries), and new compounds. The major emphasis in the papers reviewed is the attempted design of macrocycles with selectivities for specific guests.

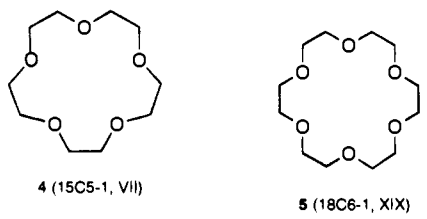
1. Crown Ethers

a. Old Crown Ethers with Oxygen or Mixed-Donor Atoms. Since the 1991 review,[3] there have been numerous studies on the complexation of cations with known crown ethers. These investigations represent the continuation of previous studies and/or studies under different conditions (with respect to cations, methods, temperature, pressure, solvents, etc.). Examples of these investigations are now presented.

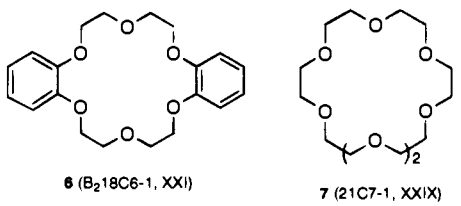
Gahan and co-workers have investigated the interaction of monoazapolyoxacrown ethers such as **1**−**3** with Pb^{2+}, Hg^{2+}, Cd^{2+}, and Zn^{2+} by potentiometry in methanol/water (95:5 v/v).[31,32] In earlier reviews, thermodynamic data for the interaction of these compounds with alkali metal, silver, and ammonium cations are given.[2,3] The azaoxacrown ethers are of interest because they are structurally similar to polyoxacrown ethers but, because of the presence of the nitrogen donor atom, are expected to form stronger complexes with heavy metal cations.[31] Indeed, in methanol/water (95:5 v/v) log K values for the reaction of Pb^{2+} with **2** (log K = 6.0)[32] and **3** (log K = 8.4)[32] are significantly higher than those for the reaction of Pb^{2+} with the cyclic polyoxa analogues, **4** (log K = 2.05−2.76 in water[3] and 3.36−3.92 in methanol[3]) and **5** (log K = 3.58−4.25 in water,[3] 6.99−7.7 in methanol,[3] and 6.5 in methanol/water (70:30 v/v).[2] Crystal X-ray structural analysis showed that in the case of the Pb−**2** complex, the Pb^{2+} is located noncentrosymmetrically with respect to the five potential donor atoms of the macrocycle and is 1.52 Å above the plane of the macrocycle ring.[32] Unlike the above case, the macrocyclic cavity of **3** can accommodate Pb^{2+}, but the bonding between the Pb^{2+}

and the donors in the ring is still unsymmetrical.[32] The unsymmetrical nature of the interaction suggests the presence of a stereochemically active lone pair of electrons on the Pb^{2+}.[32] Hg^{2+} forms more stable complexes in methanol/water (95:5 v/v) with **1**, **2**, and **3** (log K = >11, 10.3, and >12, respectively) than either Zn^{2+} (log K = 3.7, 4.1, and <4.0, respectively) or Cd^{2+} (log K = <4.5, <3.7, and 3.7, respectively), even though it does not sit in the cavity of **2**, while Cd^{2+} does.[31]

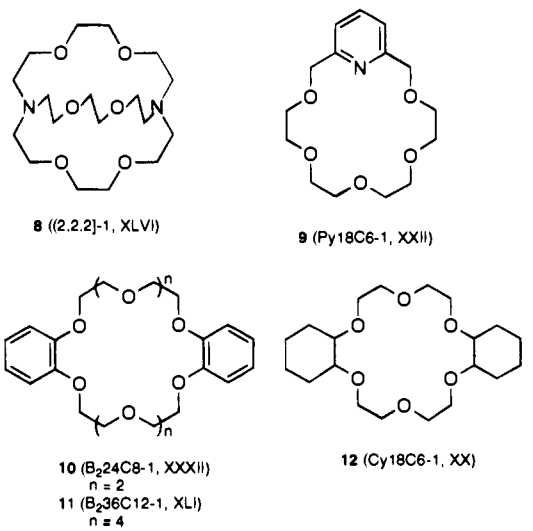




Mercury is one of the most hazardous materials in environmental pollution, but few studies have been reported of its interaction with crown ethers. Luis and co-workers determined log K values for the interaction of $Hg(CN)_2$ with the crown ethers **5**, **6**, and **7**, log K (CD_3COCD_3/$CDCl_3$, 1:0.8) = >4, >4, and 3.18, respectively.[33] They found that complexes with crowns of 18-membered ring sizes are most favorable except for HgX_2 compounds for which the size of X is larger than the macrocyclic ring, as is the case for X = CF_3.[33]



Danil de Namor and co-workers found no significant variations in the Gibbs energies of complexation of various protonated amino acids with **5** and the cryptand, **8**, in methanol or ethanol, due to remarkable enthalpy–entropy compensation effects, e.g., ΔG (CH_3OH) = −20.49, −19.52, −19.12, and −18.72 kJ mol^{-1} for the interaction of **5** with alanine, arginine, leucine, and valine, respectively.[34,35] Gokel and co-workers, using ion-selective electrode and fast-atom bombardment mass spectroscopy techniques, examined hydrogen-bonding interactions and found that all-oxygen crown ethers and their derivatives exhibit different complexation behavior with ammonium salts than do their various azacrown counterparts.[36] Izatt with co-workers have continued thermodynamic studies on alkylammonium cation complexation with **9** and its derivatives.[37,38] Recently, they synthesized a series of new chiral crown ethers[27,39,40] which will be discussed in the following section. Lee and co-workers have investigated the stabilities of complexes of **5** with a variety of methylanilinium ions in methanol. The magnitude of the log K values were found to be sensitive to steric interference caused by the positions and numbers of methyl groups, e.g., log K (CH_3OH) = 4.84, 3.47, 4.65, 3.52, and 4.64 for anilinium, 2-methylanilinium, 4-methylanilinium, 2,3-dimethylanilium, and 3,4-methylanilinium ions, respectively.[41,42] Todd and co-workers in studies on ruthenium ammine cation interactions with several crown ethers, e.g., **10**–**12**, etc., showed that second-sphere complexation is prevalent in nitromethane and that the stability constants of complexes can be varied by *ca.* 10^8-fold by modifying guest and host properties.[43] For guests, these binding constants increase with an increase of guest oxidation state and in the presence of strongly electron-withdrawing ancillary ligands, e.g., in the case of the $[(NH_3)_5Ru^{II}$-(4,4′-bipyridine)$Ru^{III}(NH_3)_5]^{5+}$ ion interaction with **10**, log K = 1.36 and 3.20 for $(NH_3)_5Ru^{II}$ and $(NH_3)_5Ru^{III}$, respectively.[43] For hosts, binding constants increase with an increase of host size (and therefore number of oxygen donor atoms) and flexibility, e.g., log K = 3.20 and 8.36 for the interaction of the $(NH_3)_5Ru^{III}$ moiety with **10** and **11**, respectively.[43]



The stabilities of crown ether complexes depend upon the type of solvent used. Kalinowski with co-workers, for example, extensively examined complexation of Tl^+ with **5** using polarography in a variety of nonaqueous solvents, binary nonaqueous–water mixed solvents, and binary alcohol–water mixed solvents.[44–46] They found that in nonaqueous aprotic solvents and in their solvent mixtures with water, the solvation of Tl^+ is mainly responsible for the magnitude of the stability constants of the complexes formed.[44,46] Many experimental techniques have been used to study cation–macrocycle interaction. However, since the experimental conditions often vary, a direct comparison may not be possible. Buschmann has studied complexation reactions of crown ethers and cryptands with cations in several solvents by different experimental techniques including direct and competitive potentiometry, calorimetry, and conductometry.[47–55] The stability constants obtained by the different experimental methods were in good agreement and agreed well with literature data.[47,49]

Calorimetric measurements are advantageous because the stability constants together with the reac-

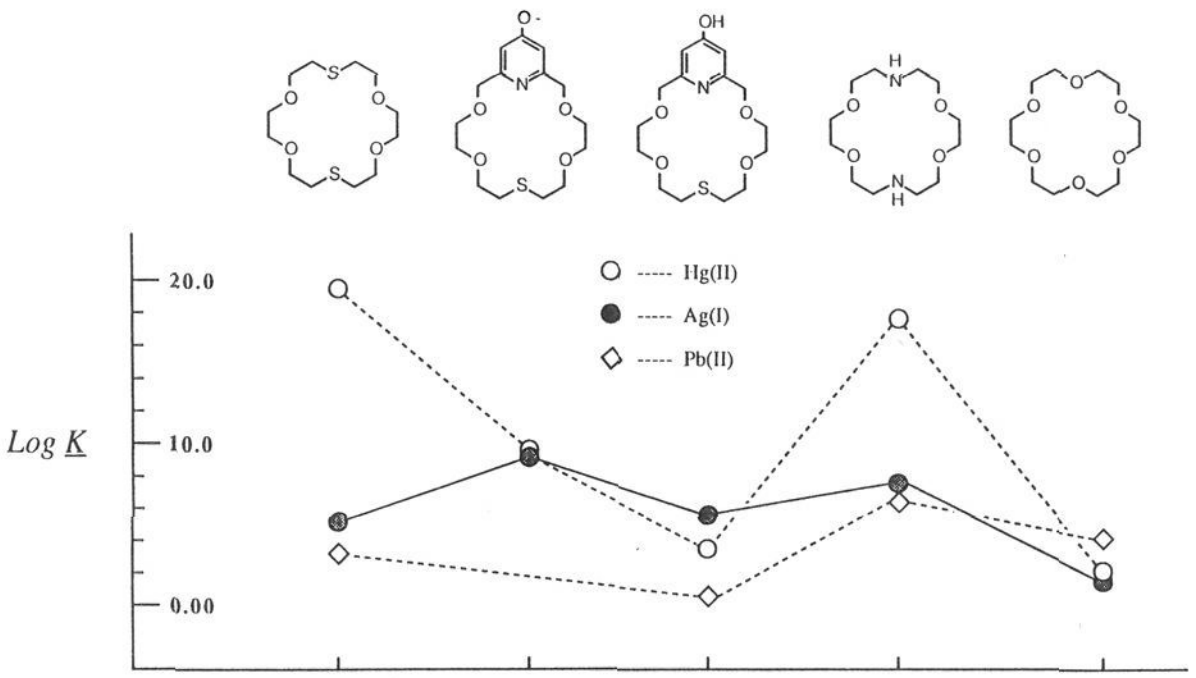
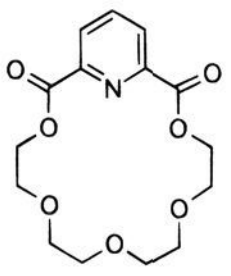


Figure 1. Plot of log K for Ag^+, Hg^{2+}, and Pb^{2+} macrocycle interaction vs macrocycle arranged in the order of decreasing overall donor atom softness.

tion enthalpies can be calculated from one experiment provided that the log K values lie within a certain range.[37,47] Calorimetry can also help in better understanding the relationship between structure and stability of the crown ether complexes and gives more information about the influence of solvents on complexation.[27,37,47,56] The ΔH values obtained, even with great care, from the variation of K with temperature using the van't Hoff equation are not as reliable as those obtained from calorimetric data. Izatt and co-workers compared results from calorimetric and direct ^{1}H NMR measurements of crown ether interactions with alkylammonium cations and found that the log K values determined by both methods are in good agreement, e.g., for the interaction of **13** with α-phenylethylammonium ion log K



13 (K_2Py18C6-1, XXIII)

($CDCl_3/CD_3OD$ or $CHCl_3/CH_3OH$, 1:1 v/v) values determined by ^{1}H NMR and calorimetry were 3.33 and 3.42, respectively.[37] However, the agreement of the ΔH values determined by the two methods was poor, differing by approximately 10 kJ mol^{-1} with the NMR method giving more negative values.[27,37] Interpretations based on the use of ΔH and ΔS values derived from K *vs* $1 \times T^{-1}$ data can result in inaccurate conclusions.[27] Fortunately, the number of thermodynamic data obtained by calorimetric measurements is increasing as we can conclude from Table I (supporting information).[57–73]

Simultaneous use of calorimetric and NMR measurements for the study of interactions between macrocycles and cations provide much more information about the complexation process than do calorimetric measurements alone. Calorimetric measurements give reliable log K and ΔH values for complexation reactions and NMR relaxation time and chemical shift measurements provide information on ligand conformation, binding strength, and binding

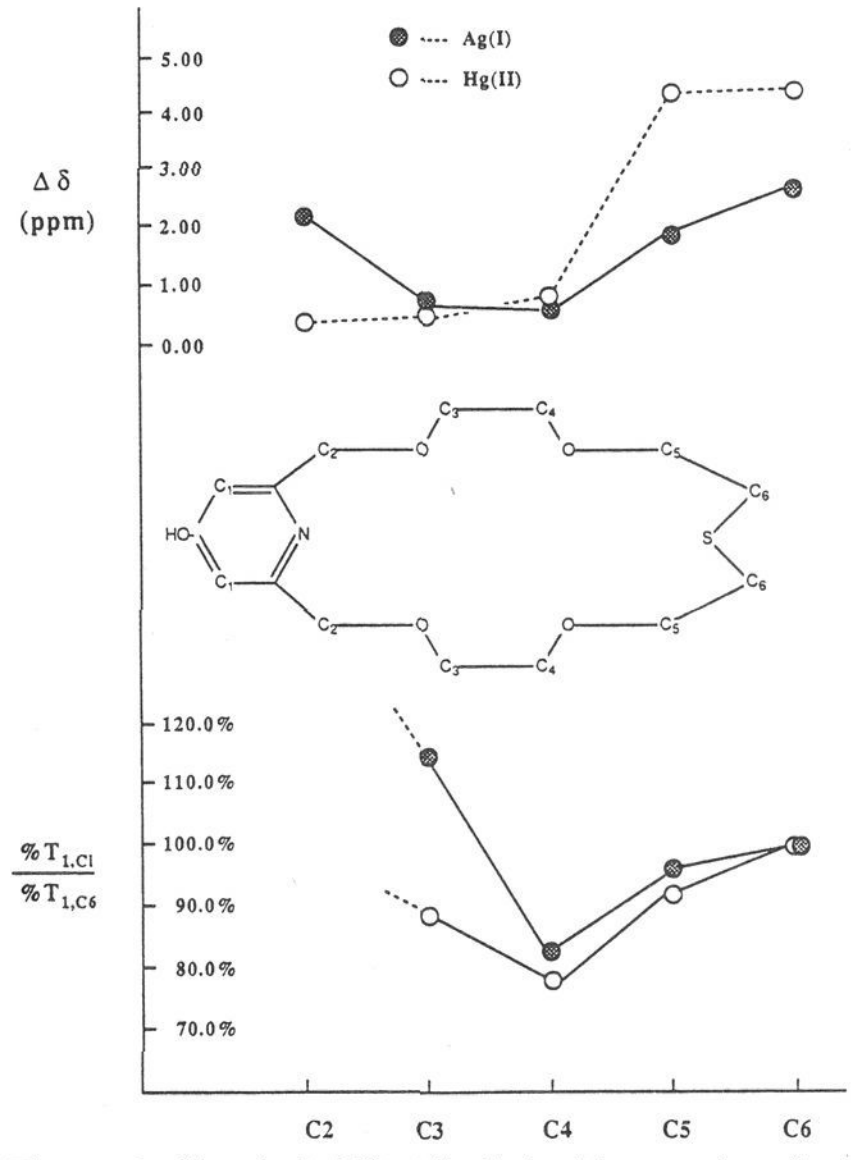


Figure 2. Chemical shift and relative T_1 percentage drop curves for various carbons in pyridonothia-18-crown-6 complexes with Ag^+ and Hg^{2+}.

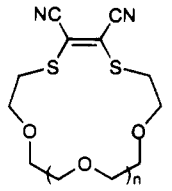
dynamics in solution. In one of their experiments, Izatt and co-workers used the different coordination geometries of Ag^+ and Hg^{2+} together with their relative affinities for various donor atoms to understand better why the macrocycle, pyridonothia-18-crown-6, displays a reversal of the normal Hg^{2+} over Ag^+ selectivity order.[3,74] Calorimetric and potentiometric titrations were used to measure the log K, ΔH, and ΔS values of complexation of Ag^+, Hg^{2+}, and Pb^{2+} with this macrocycle and, for comparison, with several others having donor atoms with varying degrees of softness (see Figure 1). ^{13}C NMR techniques were used to identify the metal-binding contributions of specific binding sites in different

portions of the multidentate pyridonothia-18-crown-6 system (see Figure 2).[3,74]

As seen in Figure 2, the pyridone half of the pyridonothia-18-crown-6 has low affinity for Hg^{2+}, but considerable affinity for Ag^+. This results in the higher overall log K value for the complex with Ag^+ and selectivity for Ag^+ over Hg^{2+}.[74]

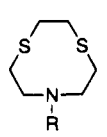
b. Modified and New Crown Ethers with Oxygen or Mixed-Donor Atoms. The number of new and, especially, "old" modified crown ethers, since the 1991 review,[3] has shown a marked increase. Complexation properties of several of these ligands are now presented.

Holdt synthesized dithiacrown compounds, **14**–**16**, in which sulfur atoms are integral parts of the rigid 1,2-dicyano-1,2-dithioethene unit.[75] He observed a direct proportionality between extraction constants from chloroform to water and related complex stability constants valid in methanol, e.g., log K (CH_3OH) = 6.2 and 3.9, and log K_{ext} ($CHCl_3/H_2O$) = 7.8 and 5.9 for the interaction of $PdCl_2$ with **14** and **15**, respectively. Comparison of the crystal structures of the free **14** and its $PdCl_2$ complex suggests that hardly any change of the ligand conformation occurs upon complexation.[75]

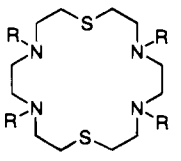


14 ($S_2$12C4-ene-1, III)
n = 0
15 ($S_2$15C5-ene-1, X)
n = 1
16 ($S_2$18C6-ene-1, XXVI)
n = 2

Interest in ^{111}Ag-based immunotherapy lead Parker and co-workers to synthesize azathiacrown ethers, e.g., **17**–**20**.[76] The complexation behavior of Ag^+ with these crown ethers in water and methanol was studied and it was found that N-alkyl derivatives (e.g., **20**) show enhanced enthalpies of complexation, ΔH (CH_3OH) = −102.1 kJ mol^{-1}, but exhibit unfavorable entropies of complexation, ΔS (CH_3OH) = −62.8 J mol^{-1} K^{-1}. Unfortunately, although the Ag^+ complexes of **19** and **20** show reasonable stability even at low pH, log K (CH_3OH) = 14.1 and 14.6 and log K (H_2O) = 10.4 and 9.47, respectively, it is doubtful that they have sufficient kinetic stability over the physiological pH range for *in vivo* application.[76]

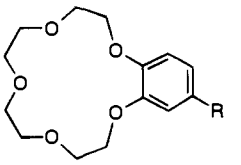


17 ($S_2N_9C_3$-1, I)
R = H
18 ($S_2N_9C_3$-2, I)
R = CH_3

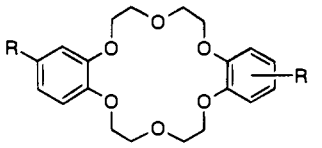


19 ($S_2N_4$18C6-1, XXVI)
R = H
20 ($S_2N_4$18C6-2, XXVI)
R = CH_3

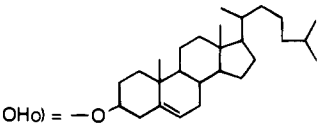
He and co-workers synthesized five new cholesteric liquid crystal crown ethers, e.g., **21**–**23**, and studied their complexation with K^+ in acetonitrile/chloroform mixtures.[77,78] The complexation was shown to depend on the cavity diameter of the crown ethers.[77,78]



21 (B15C5-17, VIII)



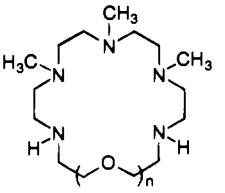
22 ($B_2$18C6-15, XXI)
(cis)
23 ($B_2$18C6-16, XXI)
(trans)



OHo) = —O

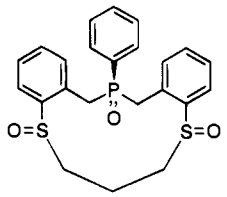
R = NHC(O)OHo)

New large crown ethers, **24** and **25**, with two different binding sites (one N_5 grouping with three methylated nitrogen atoms and another grouping of O_2 or O_3) located at opposite sides of the same macrocycle were synthesized by Bianchi and coworkers.[79] The presence of three tertiary amino groups affects the protonation behavior of such receptors, lowering their basicity.[79] NMR measurements showed that the first protonation steps involve at least one of the nitrogens bearing a methyl group.[79] Thermodynamic and structural data for the complexes of these macrocycles with Cu^{2+}, log K (H_2O) = 17.66 and 17.30 for **24** and **25**, respectively, indicated that all nitrogen donors are coordinated to the metal ion in the complex, while oxygens remain unbonded.[79]

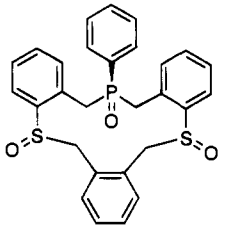


24 ($N_5$21C7-1, XXIX)
n = 2
25 ($N_5$24C8-1, XXXII)
n = 3

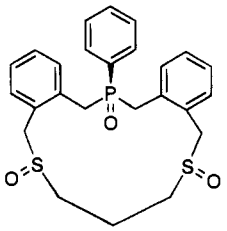
The complexation properties of macrocycles containing atoms such as sulfur and phosphorus have been less studied than corresponding macrocycles containing only oxygen and nitrogen.[80] Gellman and co-workers synthesized macrocycles with multiple sulfoxide and phosphine oxide groups, i.e., **26**–**31**.[80–82] These macrocycles are effective complexing agents for monoalkylammonium cations and protonated amino sugars in organic solvents, e.g., log K ($CDCl_3/CD_3OD$, 9:1 v/v) = 3.23 and 2.76 for the cyclohexylammonium ion interaction with **29** and **31**, respectively,[81,82] and for neutral molecules via multipoint hydrogen bonding.[80]



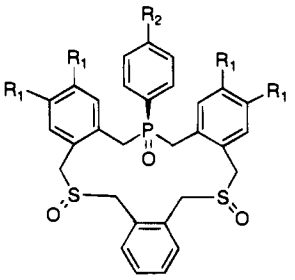
26 ($B_2PS_2$12C3-1, II)



27 ($B_3PS_2$13C3-1, IV)

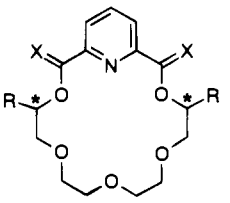


28 ($B_2PS_2$14C3-1, IV)

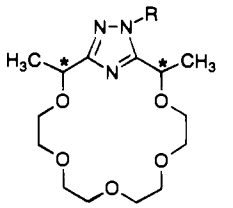


29 ($B_3PS_2$15C3-1, VII)
R_1, R_2 = H
30 ($B_3PS_2$15C3-1, VII)
R_1 = H; R_2 = t-C_4H_9
31 ($B_3PS_2$15C3-3, VII)
R_1 = CH_2OH; R_2 = C_4H_9

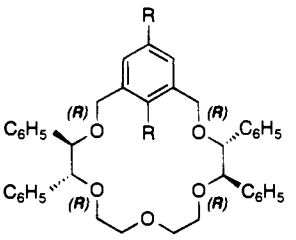
Many new chiral crown ethers for use in the enantiomeric recognition of organic ammonium cations have been prepared.[37,39,40,83,84] In the past decade, Izatt and Bradshaw and co-workers have been particularly interested in the interaction of chiral macrocycles containing pyridine units with organic ammonium cations. Recently, they synthesized a new series of chiral crown ethers based on symmetrically and asymmetrically substituted pyridino-18-crown-6 and examined their complexation abilities.[37,39,40] A high degree of chiral recognition (see section II.B) in methanol/chloroform mixtures or in methanol for the enantiomers of various chiral organic ammonium cations was shown by some diphenyl- and di-*tert*-butyl-substituted crown ethers.[39] For example, log K (CD_3OD/H_2O, 1:9 v/v) = 1.33 and 0.62 for interaction of chiral (*S*,*S*)-**32** with (*R*)- and (*S*)-α-(1-naphthylethyl)ammonium cations, respectively, and log K ($CD_3OD/CDCl_3$, 7:3 v/v) = 2.15 and <1.30 for the interaction of chiral (*S*,*S*)-**33** with the same cation isomers, respectively.[39] Substitution of one or two oxygen donor atoms in the ring of pyridino-18-crown-6 by nitrogen donor atom(s) results, in general, in moderate or no recognition for the enantiomers of the (1-naphthylethyl)ammonium cation.[40] Chiral crown ethers based on triazolo-18-crown-6, i.e., **34**–**36**, have been synthesized by Echegoyen and de Mendoza and co-workers.[83] Their results for chiral (*S*,*S*)-**35** show, in chloroform ($CDCl_3$), chiral recognition for the enantiomers of α-(1-naphthylethyl)ammonium cation (log K = 2.91 and 2.38 for the (*R*)- and (*S*)-enantiomers, respectively) and to a lesser extent, for the enantiomers of phenylethylammonium cation (log K = 2.67 and 2.21 for the (*R*)- and (*S*)-enantiomers, respectively).[83] Sawada and coworkers showed that in acetone chiral (*R*,*R*,*R*,*R*)-**37** favors the *R*-isomer of the (1-naphthylethyl)-ammonium cation (log K = 1.52) over the *S*-isomer (log K = 1.22).[84]



32 (Py18C6-6, XXII)
X = H_2
R = t-C_4H_9 (*S*, *S*)
33 (K_2Py18C6-6, XXIII)
X = O
R = C_6H_5 (*S*, *S*)

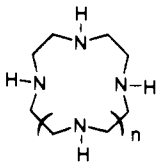


34 (Triazolo18C6-2, XXIII)
R = H (*S*, *S*)
35 (Triazolo18C6-3, XXIII)
R = $C_{12}H_{25}$ (*S*, *S*)
36 (Triazolo18C6-4, XXIII)
R = CH_2CO_2-cholesteryl (*S*, *S*)



37 ((1,3-B)18C5-7, XVIII)
R = OCH_3

c. Old, Modified, and New Crown Ethers with Nitrogen Donor Atoms. Azacrowns have been synthesized covering the range of 9-membered to 36-membered (**38**–**47**). These azacrowns become more flexible as the cavity dimensions increase. The larger azacrowns are able to form not only mono- but also polynuclear complexes with metal cations.[85] The large polyprotonated azacrowns, also called polyazacycloalkanes, can coordinate anions and are particularly useful as models for supramolecular catalysts such as enzymes, e.g., the phosphorylation of nucleotides like ATP.[85]

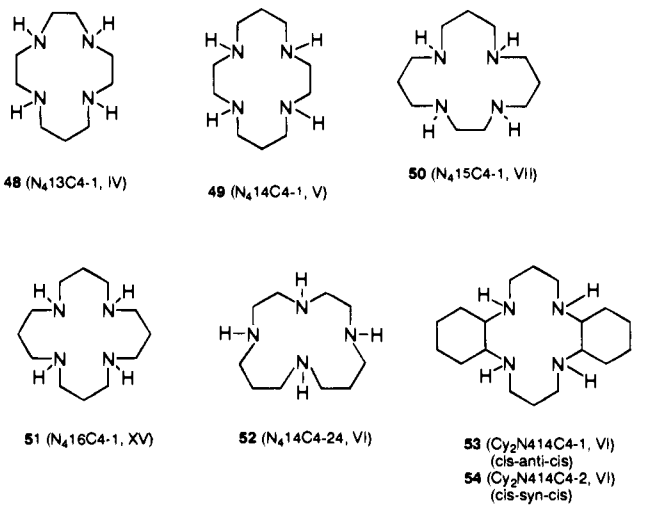


38 ($N_3$9C3-1, I)
n = 0
39 ($N_4$12C4-1, III)
n = 1
40 ($N_5$15C5-1, X)
n = 2
41 ($N_6$18C6-1, XXVI)
n = 3
42 ($N_7$21C7-1, XXX)
n = 4
43 ($N_8$24C8-1, XXXII)
n = 5
44 ($N_9$27C9-1, XXXIV)
n = 6
45 (N_{10}30C10-1, XXXVII)
n = 7
46 (N_{11}33C11-1, XXXIX)
n = 8
47 (N_{12}36C12-1, XLI)
n = 9

Bencini and colleagues have continued studies on large polyazacycloalkanes starting with 18-membered **41** which is intermediate between "small" and "large" polyazacycloalkanes.[7] Recently, they examined complexation abilities of large polyazacycloalkanes with a number of metal ions including Cu^{2+},[86] Ni^{2+},[86] Pd^{2+},[59,87,88] Mn^{2+},[86,89] and Fe^{2+}.[86] The stabilities of the mononuclear complexes increase from the smaller triaza ligand **38** to the pentaaza **40** with Mn^{2+}, Cu^{2+}, and Zn^{2+}, and to the hexaaza **41** with Co^{2+} and Ni^{2+}; then, a general decrease in stability is observed with larger polyazacycloalkanes, e.g., log K (H_2O) = 10.50, 9.79, and 6.27 for the interaction

of Mn^{2+} with **41**, **42**, and **43** respectively.[7,86] The metal cations Cu^{2+} and Ni^{2+}, like previously examined Zn^{2+}, Co^{2+}, and Cd^{2+},[3] form both mono- and dinuclear complexes with the larger polyazacycloalkanes in aqueous solution.[85,86] The ligand **42** is the smallest of the series able to form dinuclear complexes with Cu^{2+}, while **43** is required to form dinuclear complexes with Ni^{2+} and Zn^{2+}, and **44** with Co^{2+}.[86] Apart from these ligands, which can produce with the indicated metal ions both mono- and dinuclear complexes, polyazacycloalkanes larger than **44** form only dinuclear species. Trinuclear complexes of Cu^{2+} were identified in aqueous solutions containing the ligands **46** and **47**.[85] Complexes of Mn^{2+} with polyazacycloalkanes are the least stable in comparison with other examined metal ions.[85] However, all of these complexes have high stability. For example, the complex with **42** preserves Mn^{2+} from air oxidation even in alkaline solution.[86,89] Single-crystal X-ray analysis of the Mn^{2+} complex with **42** revealed an irregular polyhedron with all seven nitrogen atoms bound to the metal cation.[85] This can explain the lack of protonated complexes formed by **42** (and also **40** and **41**) with Mn^{2+} in aqueous solution.[85,86] Only a few complexes of Fe^{2+} with larger polyazacycloalkanes have been studied, but it was observed that the Fe^{2+} complex with **42**, $\log K(H_2O) = 12.09$, is about 100 times more stable than the analogous Mn^{2+} complex, $\log K(H_2O) = 9.79$.[85,86,89] The complexes of Pd^{II} are of particular interest since few thermodynamic quantities for the formation of these complexes have been reported.[85] Ligands **41** and **42** form both mono- and dinuclear complexes with Pd^{II}, while **42** forms also a trinuclear complex in which one nitrogen atom is deprotonated and this negatively charged atom acts as a bridge between two palladium atoms.[59,85,87,88] For **43** only a dinuclear complex with Pd^{II} has been observed.[59] All of these complexes are very stable due to favorable enthalpic and entropic contributions.[59] Bencini and colleagues have studied complexation of Pb^{2+} by large polyazacycloalkanes. The results show that as the ring size increases, the number of Pb^{2+} cations bound to the complex increases from one to three.[85] Only mononuclear complexes are formed in the reaction of Pb^{2+} with **41** and **42**, both mono- and dinuclear complexes are formed with **43**–**45**, and di- and trinuclear complexes are formed with **46** and **47**.[90]

Recently, Hancock and co-workers studied in aqueous solution complexation of small tetraazamacrocycles ranging from 12- to 16-membered rings with Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+} and confirmed that the overall stability pattern of their complexes is not in accord with the idea of a size–match selectivity, e.g., $\log K(H_2O) = 12.71$, 11.23, 12.10, and 12.65 for the interaction of Cd^{2+} with **48**–**51**, respectively.[91] When the coordinated metal ion lies out of the plane of the macrocycle, the factors controlling selectivity are the same as those for open-chain ligands.[91] The authors also observed that $\log K(H_2O)$ values for the isocyclam, **52** complexes with Cu^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+} ($\log K$ = 27.3, 15.44, 11.84, and 10.86, respectively) are almost identical to those of the cyclam (**49**) complexes ($\log K$ = 26.5, 15.5, 11.23, and 10.83, respectively).[91] This suggests, contrary to what has generally been believed, that the ring sequence in isocyclam does not have an unfavorable effect on the stability of its complexes.[91] This group of scientists searching for a selective ionophore for Bi^{3+} studied its complexation with the tetraazamacrocycle **50** and observed high Bi^{3+} affinity for nitrogen-donor ligands in aqueous solution ($\log K = 23.5$).[92] Bismuth, as ^{212}-Bi, is promising in cancer therapy when attached via complexing ligands to monoclonal antibodies, and Bi^{3+} complexes are of interest in the treatment of gastric ulcers.[92] Complexation of other small azacrowns, e.g., **38**, **53**, and **54** with metal ions was also studied.[93,94]



Azacrowns containing pyridine,[95–98] furan,[97] phenanthroline,[96] or piperazine[96] units incorporated into the macrocycle frame have been synthesized. Complexation abilities of most of them with protons or metal cations have been examined.

Azacrowns containing side arms are presented in the following section.

d. Lariat Ethers. Lariat ethers form probably the majority of old and modified "old" crown ethers. Gokel and co-workers began a search for more effective membrane transport carriers in the early 1980s. Their studies attempted to mimic valinomycin which is a natural and almost ideal carrier for K^+.[99] Their endeavors resulted in exploring crown ethers having side arms because it was apparent that the cryptands had the required three dimensionality to form stable complexes but lacked dynamics and the crown ethers were dynamic but lacked the capability to envelop the cation and lacked sufficient binding strength, especially in water.[99] In general, each side arm containing one or more donor atoms provides a third dimension of solvation to a ring-bound cation. They suggested the name lariat for these crown ethers after the word lasso which was used in the American west to "rope and tie" an animal. The complexation process involving the pendent arms containing donor atoms reminds one of this cowboy operation[99] (Figure 3).

There are two basic groups of lariat ethers. One of these has a side arm attached to the carbon in the polyoxy ring (*C*-pivot) and the second one has a side arm attached to the nitrogen donor in the ring (*N*-pivot).[99]

Lariat Ethers with Oxygen or Mixed-Donor Atoms in the Ring. Gokel with co-workers have synthesized mono-, di-, and tribrachial lariat ethers and studied

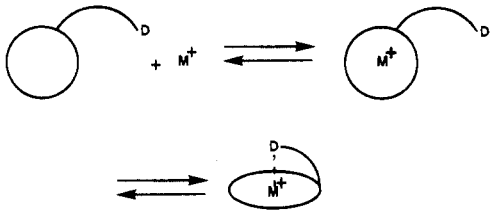
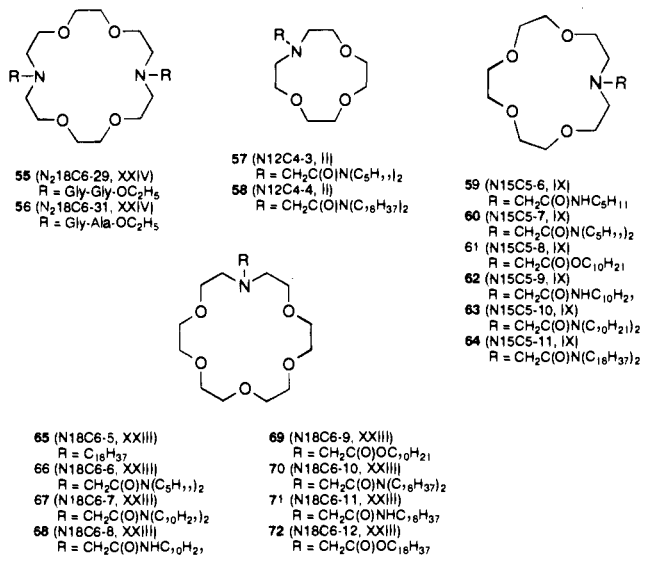
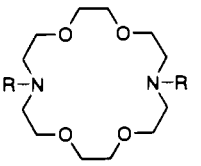


Figure 3. Schematic of the lariat ether complexation process. (Reproduced by permission from the article by Gokel, G. W. published in *Chem. Soc. Rev.* **1992**, 39–47. Copyright 1992 Royal Society of Chemistry.)

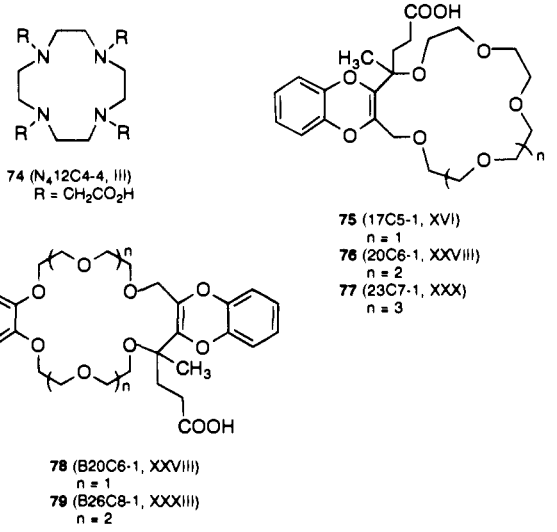
the thermodynamics of their cation complexation.[100–103] They found the highest Ca^{2+} binding constants and Ca^{2+}/Na^{+} selectivities ever observed in aqueous solution for neutral crown derivatives. These crowns, **55** and **56** had dipeptide, Gly-Gly-OC_2H_5 or Gly-Ala-OC_2H_5 side arms (log K = 2.2 and 6.6 for the **55** interaction with Na^{+} and Ca^{2+}, respectively, and log K = 2.2 and 7.8 for the **56** interaction with the same cations, respectively).[101] They also found that alkali metal cation transport by a family of new monoaza lipophilic 12-, 15-, and 18-membered ester and amide-side-armed lariat ethers, i.e., **57–72**, in a bulk H_2O–$CHCl_3$–H_2O liquid membrane, correlates well with both log K determined in methanol and with picrate extraction constants determined in the membrane solvent mixture.[100]



New lariat ethers with sterically hindered alkyl and pyridyl groups were prepared.[104–106] Hancock and co-workers studied steric and inductive effects of these side arms on complex stability and found that these two effects are delicately balanced making it difficult to predict the overall effect on complex stability.[104,105] The steric effects are often more important for the stability of complexes with small as compared to large metal ions.[104] Tsukube and co-workers observed that pyridyl-armed crown ethers, e.g., **73** effectively transported not only Na^{+} and Ca^{2+} but Cu^{2+} and Zn^{2+} as well. The authors state that to the best of their knowledge, this is the first example of the use of synthetic ionophores having lariat ether structures for transition metal ion transport.[106]



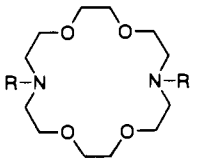
It is known that carboxyl groups attached to the macrocyclic ring can significantly enhance the stability of the complexes of these ligands with cations, e.g., **74** (DOTA) forms the most stable lanthanide complexes studied so far, log K (H_2O) = 22.86–29.2.[3] Macrocycles with carboxyl side arms continue to be of interest to many chemists because of their exceptional complexation properties. Juillard and co-workers synthesized several new polyoxa macrocycles, i.e., **75–79** incorporating a benzodioxinic unit with a carboxyl side arm on the carbon next to this unit.[107] The complexation of Na^{+} and K^{+} by anionic



forms of these ligands was found to be more efficient than the complexation either by acid forms of these ligands or by analogous macrocycles without carboxyl groups.[107] For example, the anionic form of **75** binds Na^{+} and K^{+} with log K (CH_3OH) = 2.41 and 2.60, respectively, while the acid form of this ligand binds the same cations with log K (CH_3OH) = 1.26 and 1.30, respectively.[107]

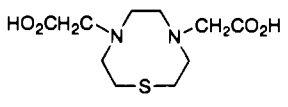
Brücher and co-workers found that 1,10-diaza-18-crown-6 with malonate pendants, **80**, shows unusual complexing properties toward cations.[108] First, the trend in stability constants for the formation of the complexes in aqueous solution is unexpected. In the case of alkaline earth cations, the stability increases in the order $Mg^{2+} < Ca^{2+} < Sr^{2+} \approx Ba^{2+}$ (log K = 2.53, 7.54, 9.79, and 9.76, respectively). The stability order for the lanthanide ions is $Lu^{3+} < Ce^{3+}$ (log K = 10.74 and 16.15, respectively), and for transition metal ions and lead is $Zn^{2+} < Mn^{2+} < Cd^{2+} < Pb^{2+}$ (log K = 6.28, 7.40, 10.27, and 13.03, respectively).[108] Second, the macrocycle displays high selectivity for large metal cations. This high selectivity can probably be explained by the better "size-match", by the ability of larger metal ions to coordinate more carboxyl oxygens, and by interaction with more donor atoms which leads to larger stability constants and

higher selectivities for the large metal cations over the smaller ones.[108] The high Sr^{2+}/Ca^{2+} and Pb^{2+}/Zn^{2+} selectivities suggest that macrocycle **80** could be useful in mobilizing freshly incorporated radioactive strontium and as a chelating agent needed in the therapy of lead poisoning.[108]

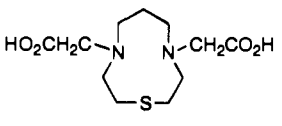


80 ($N_2$18C6-9, XXIV)
R = $CH(CO_2^-)_2$

Herman and co-workers studied complexation of carboxyl derivatives of macrocycles having two nitrogen atoms and one sulfur atom in the rings, **81** and **82**.[109,110] They found that the sulfur atom particularly enhances covalent bonding with Cu^{2+} as indicated by a higher heat of complexation, e.g., ΔH (H_2O) = −46.0 kJ mol for **81**, more favorable entropy changes, e.g., ΔS (H_2O) = 214 J K^{-1} mol^{-1} for **81**, and a stronger ligand field strength.[109]



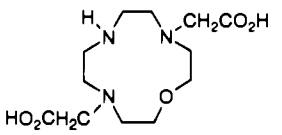
81 ($SN_2$9C3-2, I)



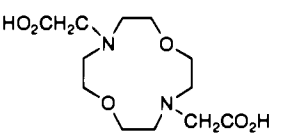
82 ($SN_2$10C3-2, I)

Delgado and Fraústo da Silva and co-workers have done extensive studies on macrocycles containing both oxygen and nitrogen donor atoms.[111−116] For example, studies are reported on carboxyl derivatives of some 9- to 14-membered oxaazamacrocycles and their complexation with divalent metal cations in aqueous solution.[111−113,115,116] The results show that the replacement of one nitrogen by an oxygen atom in the macrocyclic ring has considerable effect both on the kinetics of the complexation (faster equilibration) and on the stability of the complexes.[113] They found a considerable decrease in the stability of the complexes with the first series transition metal cations (e.g., for Zn^{2+} and Cd^{2+} from 1.7 to 5.0 log K units) and a small increase in the stability of the alkaline earth metal cations (e.g., for Ca^{2+} and Sr^{2+} the increase is 0.38 and 1.08 log K units when comparing **83** and **84**).[112] The complexes formed with the 12-membered ligands are generally more stable, but the 14-membered ligands are more selective toward the same series of metal cations.[112] For example, log K (H_2O) = 12.737, 8.12, 16.80, 17.17, 17.85, 16.12, 16.362, and 15.66 for the interaction of **83** with Ca^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+}, respectively, and log K (H_2O) = 7.08, 2.1, 11.81, 14.7, 17.62, 12.597, 11.55, and 8.01 for the interaction of **85** with the same cations, respectively.[112,115]

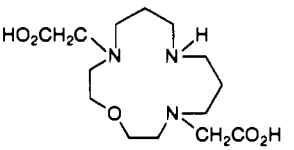
Delgado together with Martell and his group investigated complexation behavior of macrocyclic triaza triacetic acid **86** (NOTA) and oxygen−nitrogen mixed donor macrocyclic triaza triacetic acids, i.e., **87**−**89**, with divalent and trivalent metal cations.[117] They found that in aqueous solution these ligands form, in general, stable complexes with trivalent metal cations.[117] The ligand **87** forms a very stable



83 ($N_3$12C4-3, III)

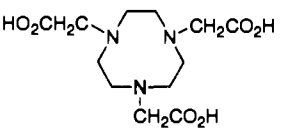


84 ($N_2$12C4-2, III)

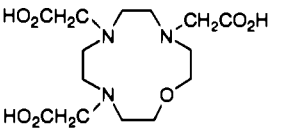


85 ($N_3$14C4-3, V)

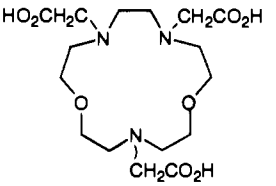
complex with In^{3+} (log K = 25.48), with the stability constant higher than that of the macrocyclic tetraaza tetraacetic acid DOTA (**74**; log K = 23.9),[118] and forms a Ga^{3+} complex with the stability (log K = 21.3) the same as that of DOTA (**74**, log K = 21.33[118]).[117] When the ring size of the above macrocycles increases, all the stability constants decrease, but the decrease is larger for the 15-membered macrocycle than for the 18-membered, except for the In^{3+} complex where the situation is reversed.[117]



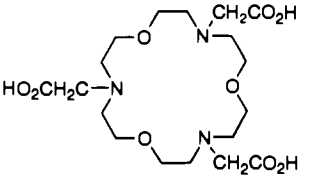
86 ($N_3$9C3-5, I)



87 ($N_3$12C4-4, III)



88 ($N_3$15C5-2, X)

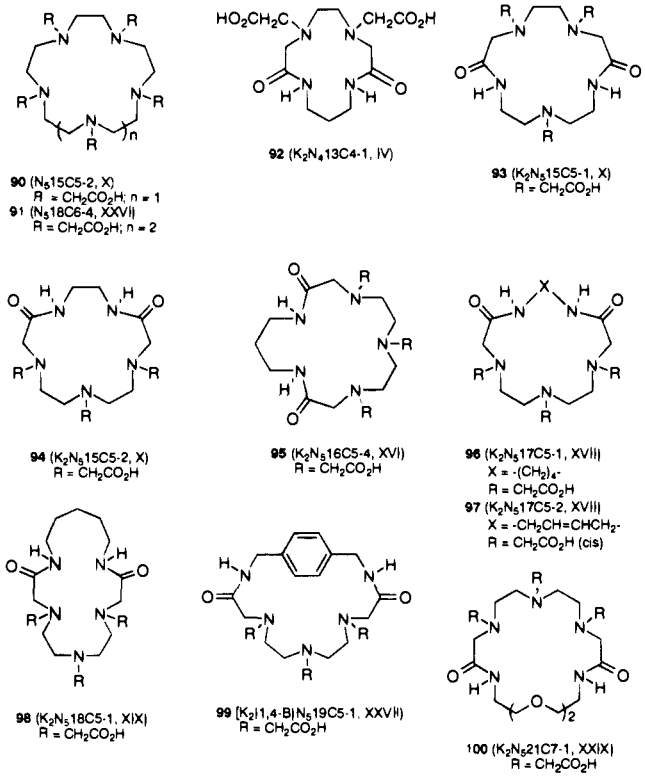


89 ($N_3$18C6-6, XXV)

Lariat Ethers with Nitrogen Donor Atoms in the Ring. Carboxyl derivatives of macrocycles having all nitrogen donor atoms in the ring continue to attract the attention of a large number of chemists. Recent investigations of complexation properties of macrocyclic carboxyl derivatives having all nitrogen donors and 9- to 14-membered rings confirmed previous studies that these ligands form very stable complexes with lanthanide metal cations.[118−132] Kodama and co-workers first synthesized macrocyclic carboxylate derivatives of larger size, **90** and **91**.[133,134] They examined complexation of these ligands with lanthanide metal cations and found that the complexation by these new macrocycles was much more rapid than that by DOTA (**74**), while maintaining extraordinary thermodynamic stabilities, i.e., log K (H_2O) = 24.0,[118] 15.88, and 22.95 for the interaction of Gd^{3+} with **74**, **90**, and **91**, respectively.[133]

Another series of new macrocyclic carboxylate derivatives was synthesized by Chang with co-workers[123] and Zhang with co-workers.[135,136] Complexation behavior of these new macrocycles which are bis(amide) derivatives of DTPA and EDTA, i.e., **92**−**100** was studied.[123,136] Macrocycle **96** exhibits in aqueous solution the highest selectivity for Gd^{3+} over

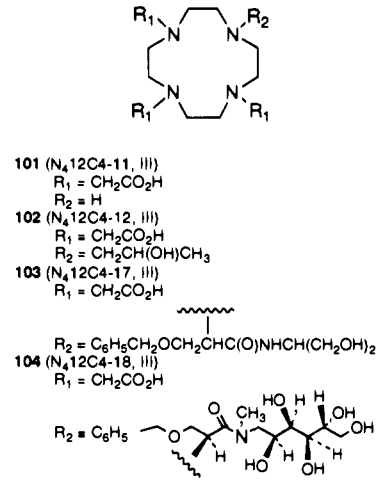
Zn^{2+} among known polyamino polycarboxylates, log K = 15.14 and 9.03, respectively.[123]



In search of effective agents for magnetic resonance imaging which is a powerful diagnostic tool in clinical practice, numerous studies have been performed. Replacement of one carboxyl group by hydrogen, **101**, or $CH_2CH(OH)CH_3$, **102**, lowers in water the complex stability with Gd^{3+} and other lanthanide cations in comparison with **74** (DOTA), e.g., log K = 21.0 and 23.8 for the interaction of Gd^{3+} with **101** and **102**, respectively, while for **74** log K = 25.3.[129,137,138] Aime and co-workers synthesized two DOTA-like macrocycles in which they transform one carboxyl group into an amide group, **103** and **104**.[139] Study of the interaction of these macrocycles with Gd^{3+} in aqueous solution revealed that the amide group does not alter their coordination capabilities, as evidenced by the high formation constants (log K = 25.9 and 26.4 for **103** and **104**, respectively, while for **74** log K = 27.0).[139] These large constants support the hypothesis of a direct involvement of the amide functionality in the coordination cage. The X-ray structure of **103** shows that, inside the square antiprismatic coordination cage, the Gd−O bond distances are quite similar for the carboxyl and carboxamide groups.[139]

Some of the macrocyclic carboxyl derivatives described above are of potential interest in medical applications, such as the removal of Fe^{3+} from the body in cases of iron overload,[117,118] the treatment of Al^{3+} intoxication,[117] use of $^{111}In^{3+}$ and $^{67,68}Ga^{3+}$ complexes as radiopharmaceutical agents enhancing diagnostic images through γ-ray detection,[118,126] use of lanthanide complexes as NMR shift probes for biological systems,[128] and as radiolabeled monoclonal antibodies (^{90}Y complexes)[119,140] or as magnetic resonance imaging agents (especially Gd^{3+} complexes).[117,118,124,128]

Macrocyclic phosphonic and phosphinic acid derivatives have attracted considerable interest because

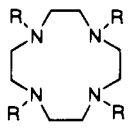


their lanthanide complexes can be used as shift reagents for biological systems and as potential contrast agents in MRI.[141] The pentavalency of phosphorus in the phosphinic acids means that the alkyl (or aryl) substituent on the phosphorus atom may be used to allow further ligand functionalization.[142] Phosphinic acid is usually more acidic than the corresponding carboxylic acid.[140,142] In addition, a phosphinic acid oxygen donor is a better σ donor than a carboxylate for cations of high charge density.[140]

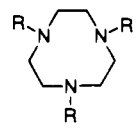
A series of macrocycles bearing phosphinic acid donors has been synthesized and their protonation constants and metal ion binding abilities have been determined.[140−146] In general, macrocyclic phosphinate derivatives form less stable complexes with the alkaline earth metal cations, Cu^{2+}, Zn^{2+}, and Cd^{2+}, and the trivalent lanthanides than do their macrocyclic carboxylate analogues which is largely due to the lower basicity of the nitrogen and oxygen donor atoms.[145] However, there are some exceptions, e.g., the stabilities of the complexes formed in the reaction of **105** with Yb^{3+} and Mg^{2+}, log K (H_2O) = 25.1 and 13.0, respectively,[140] are slightly higher than those reported for **74** (DOTA), log K (H_2O) = 24.9 and 11.9, respectively.[3] One of these macrocycles, **107**, exhibits marked selectivities for Mg^{2+} over Ca^{2+} in aqueous solution, log K = 11.78 and 6.14, respectively.[144]

A phosphonic acid derivative **106** forms a very stable complex with Fe^{3+}, log K (H_2O) = 29.6.[143] Another phosphonic acid derivative, **108**, which was synthesized and analyzed by Sherry and co-workers for use as a ^{31}P NMR indicator of intracellular Mg^{2+} and Zn^{2+} concentrations, has in physiological conditions (pH = 7.4 and 37 °C) a 10-fold higher affinity for Mg^{2+} than for Ca^{2+} (log K = 2.33 and 1.32, respectively) and also binds strongly with Zn^{2+} (estimated log K = 11).[146] This macrocycle is readily loaded into red blood cells in the presence of Mg^{2+}. The resonances of **108** and its Mg^{2+} complex do not overlap with the phosphorus-containing metabolites in tissue.[146]

Table I (supporting information) contains thermodynamic data for many additional *N*-pivot- and *C*-pivot-type lariat azacrown ethers. *N*-Pivot-type lariats include those bearing the following side arms: 3,5-dimethyl-2-hydroxybenzyl (**110**)[147] and 3-hydroxy-6-methyl-2-pyridylmethyl (**111**),[148,149] which form the most stable known complexes with Fe^{3+} (log

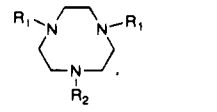


105 ($N_4$12C4-6, III)
R = $CH_2P(O)(CH_3)OH$

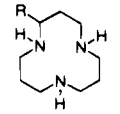


106 ($N_3$9C3-8, I)
R = $CH_2PO_3H_2$
107 ($N_3$9C3-9, I)
R = $CH_2P(O)(CH_3)OH$
108 ($N_3$9C3-10, I)
R = $CH_2P(O)(C_2H_5)O^-$

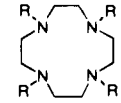
K (C_2H_5OH/H_2O, 75:25 v/v) = 51.3 and log K (H_2O) = 49.98, respectively); 2-hydroxyethyl (**113**);[150] 2-methoxyethyl (**114**);[151] 2-hydroxyalkyl (**115**),[152,153] which lowers the pK_a values of nitrogen donors allowing the formation of a very stable complex with UO_2^{2+} in water;[153] 2-aminoethyl (**116**),[154,155] which makes possible the formation of aquated bimetallic species with transition metal cations and which complexes anions; 2,2′-bipyridyl-6-ylmethyl (**109** and **117**);[156] and 2-cyanoethyl (**122**).[157] *C*-Pivot-type lariats include those bearing the side arms imidazole (**112**);[158] pyridine-*N* (**118**);[159] pyridinolate-*O*$^-$ (**119**);[159] and NH_2 (**120**[160] or **121**[161]).



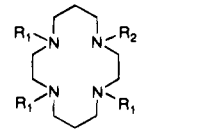
109 ($N_3$9C3-3, I)
R_1 = H, R_2 = CH_2-6-(2,2′-bipyridyl)
110 ($N_3$9C3-12, I)
R_1, R_2 = CH_2-[2-OH-3,5-$(CH_3)_2C_6H_2$]
111 ($N_3$9C3-13, I)
R_1, R_2 = 2-(3-OH-6-CH_3Py)



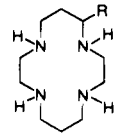
112 ($N_3$12C3-4, II)
R = 4-imidazole



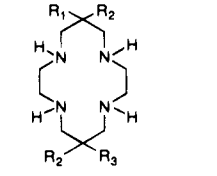
113 ($N_4$12C4-2, III)
R = CH_2CH_2OH
114 ($N_4$12C4-3, III)
R = $CH_2CH_2OCH_3$



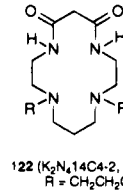
115 ($N_4$14C4-6, V)
R_1, R_2 = CH_2CH_2OH
116 ($N_4$14C4-8, V)
R_1, R_2 = $CH_2CH_2NH_2$
117 ($N_4$14C4-9, V)
R_1 = H, R_2 = CH_2-6-(2,2′-bipyridyl)



118 ($N_4$14C4-12, V)
R = 2-Py
119 ($N_4$14C4-13, V)
R = 2-(3-OHPy)

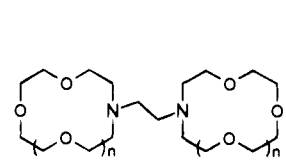


120 ($N_4$14C4-14, V)
R_1 = NH_2; R_2, R_3 = H
121 ($N_4$14C4-15, V)
R_1, R_3 = CH_3; R_2 = NH_2

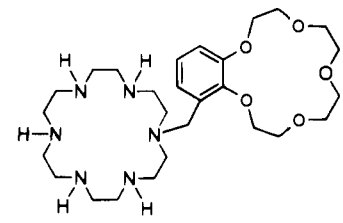


122 ($K_2N_4$14C4-2, VII)
R = CH_2CH_2CN

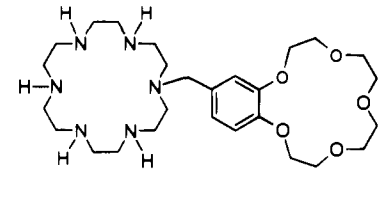
e. Bis- and Polycrown Ethers. Table I (supporting information) contains some thermodynamic data for cation complexation with bis- and polycrown ethers. These macrocycles exhibit somewhat different cation-complexing properties than the corresponding monocyclic analogues. The ability of biscrowns to form intramolecular sandwich complexes, in which both adjacent crown units cooperate, is one of these properties.[162] This phenomenon contributes to the observed, sometimes high, selectivity of biscrowns toward some cations.[162] In the series of homologous bis(monoazacrown ether)s connected by alkyl bridges, Závada and co-workers noted that not only the macrocyclic ring size but the bridge length as well has remarkable influence on ligand selectivities toward alkali metal cations.[162] In methanol/water (99:1), the biscrown **123** with the shortest $-(CH_2)_2-$ bridge appeared to be the most selective for Na^+ over K^+ (log K = 8.18 and 4.21, respectively) and the biscrown **124** with the same bridge length formed the most selective complexes with K^+ over Na^+ (log K = 7.10 and 4.62, respectively).[162] Introduction of a (benzyloxy)methyl, (1-naphthyloxy)methyl, or hydroxymethyl substituent into the $-(CH_2)_2-$ alkyl bridge gives a surprisingly large destabilizing effect due to symmetry violation.[163] Table I (supporting information) also has data for cation complexes with the following: biscrowns consisting of one polyether and one polyazacrown unit (**125** and **126**);[164] a biscrown (**127**), which easily solubilizes urinary calculi in an acidic region;[165] a biscrown with an anthracene bridge (**128**), which can be used as a fluorescent sensor for protons;[166] a biscrown (**129**), which acts as a host for Ag^+;[76] and a triscrown (**130**), which shows marked selectivity for K^+ with respect to Na^+.[167] There are also metal complexation data for several polycrown-substituted porphyrins[168–170] and crown-substituted calixarenes.[171,172]



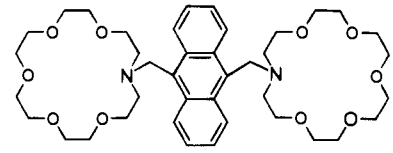
123 ((N12C4)$_2$-1, XLIII]
n = 1
124 ((N15C5)$_2$-1, XLIII]
n = 2



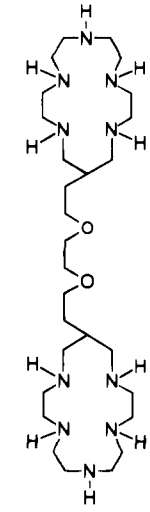
125 ((B15C5)($N_6$18C6)-1, XLIII]



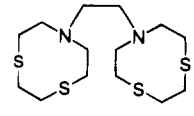
126 [B15C5)($N_6$18C6)-2, XLIII)



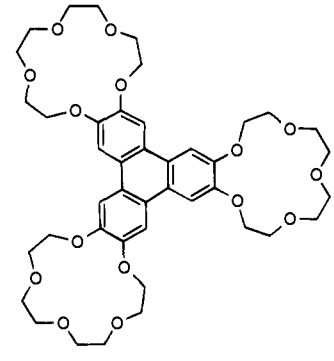
128 [(N18C6)$_2$-9, XLIV]



127 ((N$_5$16C5)$_2$-1, XLIV]



129)S_2N9C3)$_2$-1, XLIII)



130)(B15C5)$_3$-1, XLV]

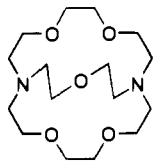
2. Cryptands and Polycyclic Compounds

Cryptands are macrobicycles capable of ion encapsulation due to their cagelike structures. Generally, the metal ion whose ionic crystal radius best matches the radius of the cryptand cavity will form the most stable complex. The correspondence between cavity size and complex stability is more pronounced with the cryptands than with the coronands. The selectivity and stability of cryptates are also influenced by the cryptand structural flexibility, the number and type of cryptand donor atoms, and the solvation energy of the metal ion.[173]

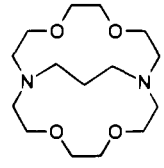
Since the 1991 review,[3] many new articles on cryptand complexation with metal ions have been published. Part of them deal with cryptands whose structures have been known before.

Complexation of these cryptands with a variety of metal ions, in many different solvents, and by several different methods has been examined.[47,51,52,173–186]

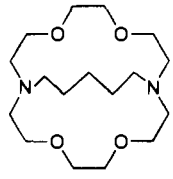
Lincoln and co-workers considered the cryptands, **131–133**, as modifications of 1,10-diaza-18-crown-6, **134**, in which the amine hydrogens have been replaced by $-(CH_2)_2O(CH_2)_2-$, $-(CH_2)_5-$, and $-(CH_2)_2-$ bridges, respectively, between the two nitrogen atoms.[173,175,187] The overall effect of these bridges is to decrease the ring flexibility in comparison to that of **134**, and to produce more stable complexes of **132** and **133** with metal ions than those of **134** which has the same number of donor atoms.[173] These bridges prevent the solvent from approaching one side of the metal cation in the cryptates formed.[173] The structure and relative inflexibility of these cryptands increase stability constants by comparison with that of **134**, whose structure and greater flexibility render the metal ion more accessible to the solvent, e.g., $\log K$ (CH_3OH) = 6.6, 5.41, and 2.04 for the interaction of K^+ with **132**, **133**, and **134**, respectively.[173]



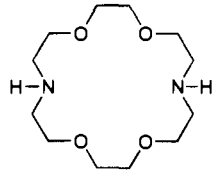
131 ([2.2.1]-1, XLVI)



132 (2.2.C_2)-1, XLVI)

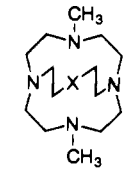


133 ([2.2.C_5]-1, XLVI)



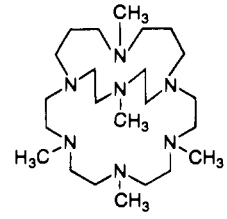
134 ($N_2$18C6-1, XXIV)

Micheloni and colleagues have continued synthesis of a variety of new small aza cages and have studied their ligation properties.[188–192] Small aza cages are highly preorganized molecules which possess a tridimensional cavity of fixed dimensions.[189] All of them are rather strong bases, at least in the first protonation step.[189] Few of them behave as "fast proton sponges" which means that they are stronger bases than OH^- in aqueous solution and cannot be deprotonated.[189,190] Their preorganized small cavities allow selective encapsulation of metal ions of appropriate size. Especially strong and selective binding of Li^+ among alkali metal ions is a remarkable feature of some of these compounds, e.g., $\log K$ (H_2O) = 5.5 and 3.0 for **135** and **136**, respectively.[190,191]

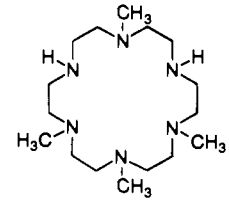


135 (N_3(1.1.1]-1, XLVI)
X = NCH_3
136 (N_3(1.1.1]-3, XLVI)
X = $NCH_2C_6H_5$

Micheloni and co-workers have used the synthetic pathway employed for the synthesis of the small aza cages described above to obtain larger cages containing seven nitrogen atoms, **137**.[193,194] This new cryptand, **137**, has reduced stability in aqueous solution toward Cu^{2+}, Zn^{2+}, and Cd^{2+} ($\log K$ = 16.02, 9.36, and 14.22, respectively) with respect to its macromonocyclic analogue, **138** ($\log K$ = 20.49, 13.29, and 16.75, respectively). The reduced stability could be ascribed to a low number of donor atoms of the cryptand involved in the formation of metal complexes in solution; the "cryptate effect" is absent.[193] Formation of the stable hydroxy complexes of **137** with Cu^{2+}, Zn^{2+}, and Cd^{2+} also suggests a low number of nitrogen atoms involved in the coordination.[193] The crystal structure of the Zn–**137** complex shows that the metal ion is not completely embedded inside the cavity but emerges from the ligand by at least one coordination site and this arrangement allows for coordination to a further ligand.[193] In this light, complexes of **137** with transition metal ions are promising receptors for substrate molecules and anions.[193]



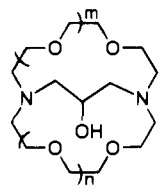
137 (N_5(3.1.1)-1, XLVIII)



138 ($N_6$18C6-2, XXVI)

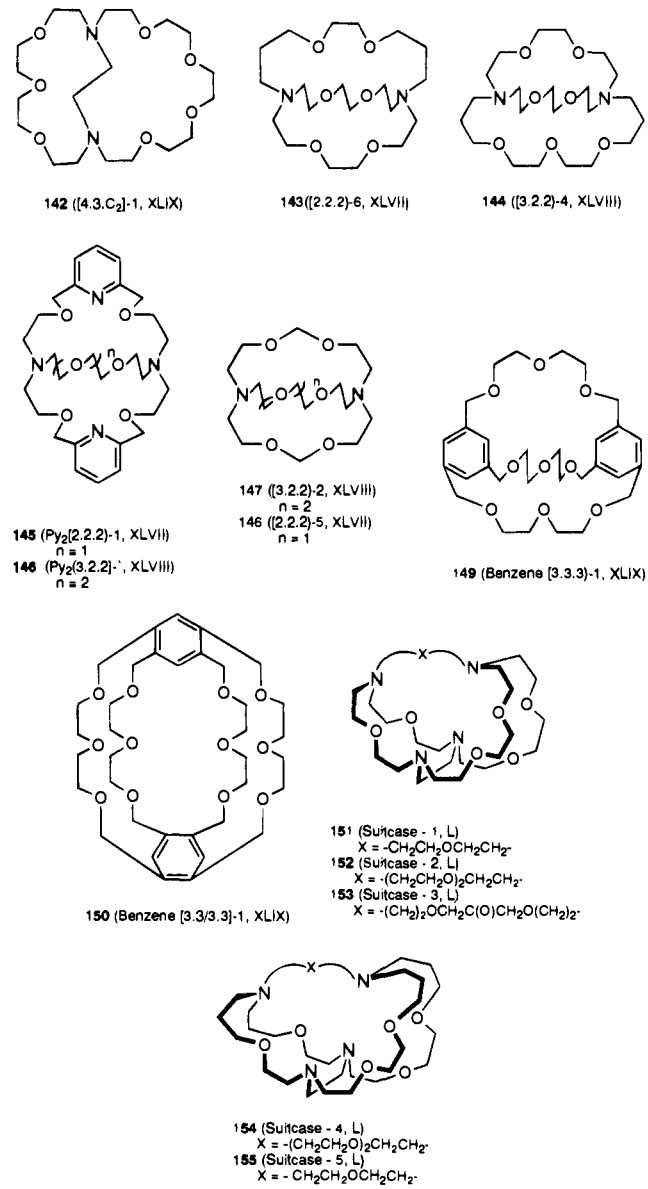
New types of functionalized cryptand-like ionophores prepared from appropriate diazacrown ethers and epichlorohydrin have been reported by Závada and co-workers.[195] All of these cryptands, **139–141**, have nitrogen bridgeheads connected by 2-hydroxy-1,3-propylene units and change their conformation and/or complexation pattern dramatically with the size of the macrocyclic ring. Studies on their complexation abilities toward alkali metal ions in methanol/water (99:1) revealed that **139** is selective toward Na^+ over K^+ ($\log K$ = 4.36 and 3.32, respectively), **140** shows little difference between Na^+ and K^+

complexation (log K = 3.07 and 3.16, respectively), and **141** forms only 2:1 (ligand/cation) complexes with all alkali metal ions. CPK models show that shallow tightly packed nestlike cavities of **139** and **140** are capable of spherical recognition contrary to the larger **141** which has the 12-crown-4-like arrangement that is known to form 2:1 complexes. To gain a deeper insight into the process of complexation, the authors performed a ^{13}C NMR relaxation time study of the cryptands and their sodium complexes. It was found that the hydroxy group is pointing inside the cavities of cryptands **139** and **140** prior to complexation. Upon complexation with Na^+, these cryptands change their conformation and the hydroxy group is pushed out of the cavity thus changing dramatically the magnetic environment of both methylene carbons and the mobility of the methine carbon on the hydroxypropylene unit.[195]



139 ((2.2.C_3]-1, XLVI)
n, m = 1
140 ((3.2.C_3]-1, XLVIII)
m = 1, n = 2
141 ((3.3.C_3]-1, XLVIII)
m, n = 2

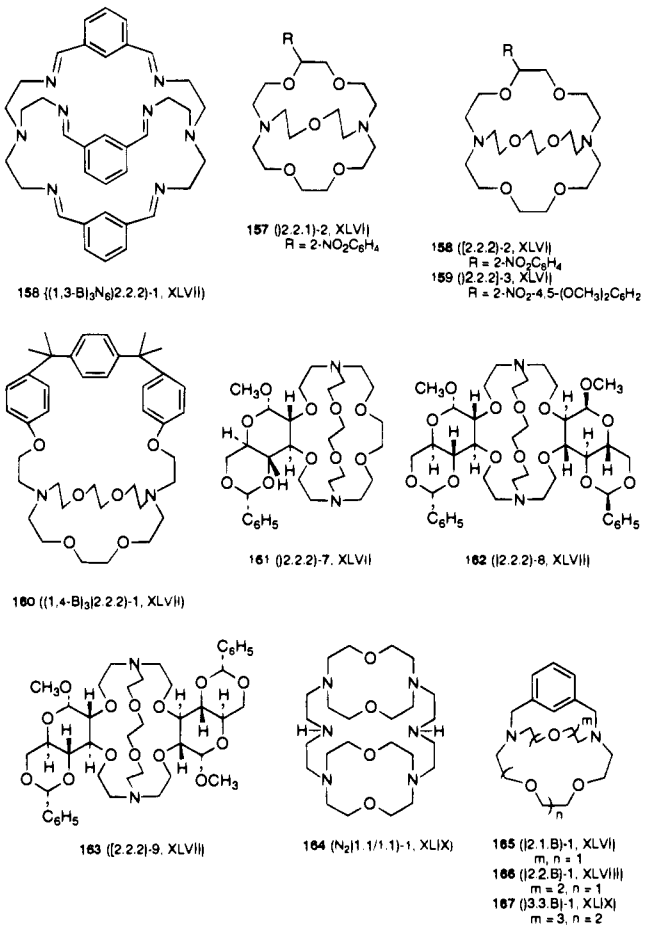
In order for a complexing agent to have practical use for separating metal ions, it must have high selectivity and labile kinetics, be inexpensive, and the complexed metal ions must be easily stripped at the end of the separation process. Recently, Bradshaw and Izatt with co-workers in a search for such agents prepared several series of new cryptands and examined their complexation abilities. In the series of 11 new macrobicyclic diptychands, one of them, **142**, exhibits a selectivity factor of 6.17 for K^+ over Na^+ which coupled with a pH complexation dependency and the simplified synthesis, make this ligand a possible candidate for practical use in metal separations chemistry.[60,196] In the series of five new cryptands containing two propylene units, interaction with various cations was much weaker than that of the corresponding cryptands with only ethylene units.[197] The most stable complexes of these new propylene-containing cryptands were those involving Ba^{2+} and Sr^{2+} ions, e.g., log K (H_2O) = 4.40 and 2.0, respectively, for **143**, and log K (H_2O) = 3.13 and 3.62, respectively, for **144**.[197] Another series consists of 12 novel unsymmetrical cryptands containing various units in each of the two bridges.[198] Complexation properties of nearly all of these cryptands with the alkali metal ions were studied by an NMR technique and some of the results were verified by a calorimetric titration technique. Cryptands **145** and **146**, containing 2,6-pyridinediyldimethylene units, and **147**, containing methylene units, showed high selectivity for K^+ over Na^+ by factors ranging from 40 to 200.[198] Dimethylene-containing cryptand **148** exhibited high selectivity for Na^+ over K^+ with a selectivity factor of over 1000.[198] Bradshaw and Izatt and coworkers also synthesized novel benzene-bridged macrobi- and macrotricyclic polyethers. Macrobicyclic **149** and macrotricyclic **150** are selective for Cs^+ over Na^+ and Pb^{2+}, log K (CH_3OH/H_2O, 8:2 v/v) = 2.20 and 3.50, respectively, for the interaction with Cs^+. Little or no reaction was found for these ligands with Na^+ and Pb^{2+}.[199] A series of 10 suitcase-shaped macrotricyclic polyethers, **151**–**156**, was prepared among which one (**151**) was selective for Pb^{2+}, log K (H_2O) = 12.90, while for Sr^{2+}, Eu^{3+}, and Cu^{2+} log K (H_2O) = 2.50, 3.60, and 6.32, respectively, and another (**154**) interacted strongly with Hg^{2+}, log K (H_2O) = 10.10.[200]



142 ([4.3.C_2]-1, XLIX)
143([2.2.2)-6, XLVII)
144 ([3.2.2)-4, XLVIII)
145 (Py_2[2.2.2)-1, XLVII)
n = 1
146 (Py_2(3.2.2]-', XLVIII)
n = 2
147 ([3.2.2)-2, XLVIII)
n = 2
146 ([2.2.2)-5, XLVII)
n = 1
149 (Benzene [3.3.3)-1, XLIX)
150 (Benzene [3.3/3.3]-1, XLIX)
151 (Suitcase - 1, L)
X = -$CH_2CH_2OCH_2CH_2$-
152 (Suitcase - 2, L)
X = -$(CH_2CH_2O)_2CH_2CH_2$-
153 (Suitcase - 3, L)
X = -$(CH_2)_2OCH_2C(O)CH_2O(CH_2)_2$-
154 (Suitcase - 4, L)
X = -$(CH_2CH_2O)_2CH_2CH_2$-
155 (Suitcase - 5, L)
X = - $CH_2CH_2OCH_2CH_2$-

Table I (supporting information) contains data for cation complexes with many other new macrobi- and macropolycyclic compounds. These include an octaaza cryptand, **156**.[201] The dicopper(II) cryptate formed from this cryptand has hydroxide bridging in solution and carbonate bridging in the solid state.[201] There are also data for photocleavable cryptands, i.e., **157**–**159** suitable to perform Na^+ and K^+ concentration jumps;[202,203] for a ditopic cryptand, **160**, designed to complex alkylammonium cations;[204] for the first cryptands containing sugar moieties, i.e., **161**–**163**;[205] for a new macrotricyclic ligand, **164**, which can also bind anions;[206] and for new cryptands, i.e., **165**–**167**

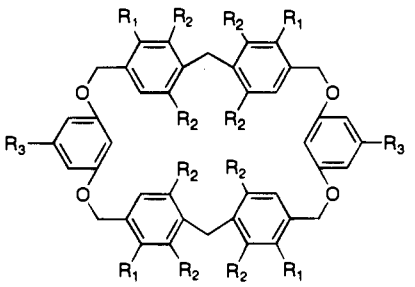
designed to bind post-transition metal ions.[207]

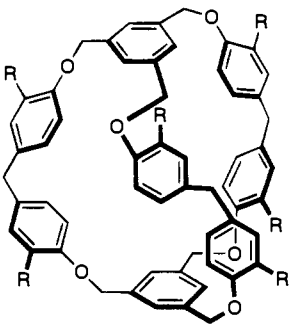


3. Cyclophane-type Macrocycles

Water-soluble cyclophane-type macrocycles, containing *p*-phenylene units as an integral part of the macrocycle, have a hydrophobic cavity of definite shape and dimensions.[208] Molecular recognition studies of cyclophane-type macrocycles in aqueous media have revealed hydrophobic and electrostatic interactions as two major binding forces.[209,210] Electrostatic effects can be illustrated by the increase in stability from monoammonium to diammonium cations while lipophilic effects are indicated by the increase of stability for cations containing bulkier organic groups.[211]

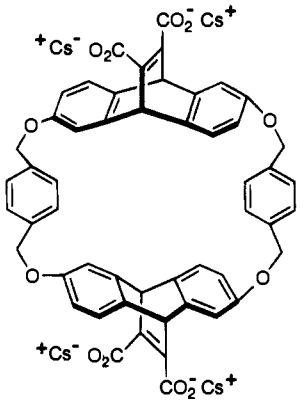
Several newly synthesized cyclophane-type macrocycles have the diphenylmethane units as the skeleton and negative charges located near the cavity, e.g., **168** and **169**.[209–213] They are all selective binders of quaternary ammonium cations at high pH.[209,212,213] Synthesis of one of them, macrobicyclic **170**, was a result of the interest of Lehn and coworkers in complexation of the neurotransmitter acetylcholine and the neuropharmacological properties of numerous quaternary ammonium compounds.[211] Hexacarboxylic **170** forms remarkably stable 1:1 complexes, log K (D_2O) ranging from 3.0 to 6.9, with various quaternary ammonium guests even at physiological pH.[211] Both electrostatic and hydrophobic effects contribute to the stability. Cyclophane **170**, in its fully extended form, has C_3 symmetry and delineates a large spheroidal cavity that was confirmed by an X-ray study.[211] It exhibits also a "macrobicyclic effect" in its complexation reactions; the monocyclic analogue of cyclophane **170**, **168**, formed weaker complexes than **170** with quaternary ammonium cations, e.g., log K (D_2O) = 3.0 and 4.1 for the interaction of **168** and **170**, respectively, with $C_6H_5CH_2NMe_3^+$ ion.[211] One additional binding force, "cation-π" or "π-stacking" effects, also influences stabilization of the above described complexes. These effects were observed by Lehn and co-workers[211] and also by Dougherty and coworkers.[214–216] This kind of donor–acceptor interaction exists between electron-rich aromatic receptors and electron-deficient aromatic guests like, in this case, quaternary ammonium cations.[211,214]





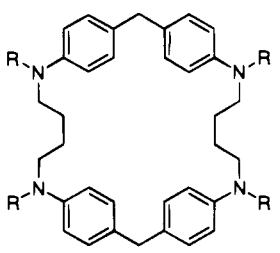
Dougherty and co-workers have extensively studied noncovalent binding interactions in aqueous media, especially the "cation-π" effects. Their studies included binding a variety of neutral and positively charged organic guests by a series of cyclophane-type macrocycles synthesized from ethenoanthracene units.[214–216] Ethenoanthracene units, which provide a concave, rigid, hydrophobic surface for binding, were linked by *p*-, *m*-, and o-xylyl, alkyl, cyclohexyl, and other groups. One of the macrocycles, **171**, binds acetylcholine in an aqueous buffer with log K = 4.30, a value comparable to those of biological recognition sites.[214] Sulfonium and guanidinium guests were also found to have substantial "cation-π" interactions with certain of these macrocycles.[215] It was found that "cation-π" effects are predominantly of enthalpic origin, and that this kind of interaction is observed in organic as well as aqueous media.[216]

The cyclophane-type macrocycle **172**, which bears four pH-sensitive L-aspartate moieties attached to nitrogen donor atoms, has charged units remote from the cavity.[217] Its guest-binding abilities are largely dependent on the pH of the medium. For cationic guests, log K (H_2O) values at pH 1.0 are much lower [1.00 for 2,6-bis[(trimethylammonio)methyl]-

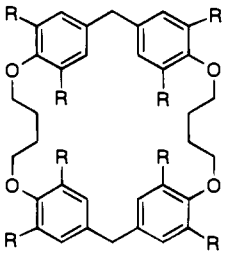


171 (Ethenoanthra-16, L)

naphthalene cation] than those at pH 11.0 (2.90 for the same cation).[217] The opposite pH-responsive binding was observed for anionic guests.[217] This macrocycle may be an excellent pH-responsive carrier for water-soluble organic molecules.[217] Macrocycle **173**, with eight carboxyl groups also attached remotely from the cavity via spacers ($-CHSCH_2-$) to the diphenylmethane units, appears to work as a nonselective host for cationic, anionic, and neutral guests in D_2O at pH 7.9.[208]

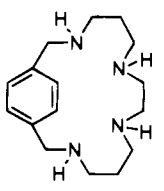


172 ((1,4-B)$_4$N$_4$30C4-5, XXXVI)
R = C(O)CH(NH$_2$)CH$_2$CO$_2$H



173 ((1,4-B)$_4$30C4-2, XXXVI)
R = CH$_2$SCH$_2$CO$_2$H

Several cyclophane-type macrocycles bind inorganic cations. One of them, **174**, contains a single *p*-phenylene moiety which could induce catalytic effects. At the same time, the number of nitrogen atoms and the dimensions of the cavity permit this macrocycle to act as a receptor for Cu^{2+} and Zn^{2+}, while the presence of propylene rather than ethylene units results in higher pK values. Thus the extent of protonation is higher at a given pH and effective coordination of anions is possible.[218] The effect of propylene units on pK_a values was observed earlier.[3,98] Cyclophanes with catechol segments[219] which form very stable complexes with Fe^{3+} will be described in section II.A.7.



174 ((1,4-B)N$_4$18C4-1, XVIII)

4. Calixarenes

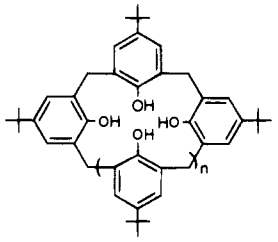
Calixarenes are cavity-shaped cyclic oligomers made up of phenol units. They offer many interesting possibilities in supramolecular chemistry, particularly in ion complexation. What makes them even more attractive is the ease with which they can be synthesized on a large scale in simple one-pot procedures from inexpensive starting materials. In addition, they are readily accessible for chemical modification on both "lower" and "upper" rims by attachment of a wide range of potential ligating groups. The variation of their cavity dimensions according to the requirements of different guests is possible.

Values of pK_a for calixarenes are important but few have been determined. The pK_a value for the dissociation of the first "super acidic" proton of conventional calix[4]arene tetrols, e.g., **175**, is very low.[220,221] This unusual pK_a value is attributed to the existence of strong circular intramolecular hydrogen bonds between the phenolic groups appended on the lower rim of the calixarene cavity.[220,222] The presence of such a "super-acidic" proton was also supported by X-ray crystallographic studies.[223]

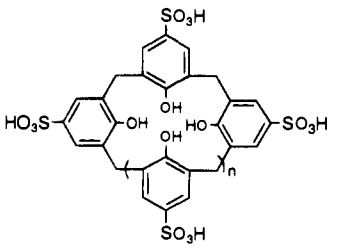
Shinkai and colleagues have noted that estimation of pK values is indispensable to an understanding of conformational and host–guest properties of calixarenes because these properties often play a decisive role in the stabilization of a cone conformation and in guest selectivity.[220] These workers described the first systematic estimation of apparent acid dissociation constants for *p-tert*-butylcalixarenes, i.e., **175**–**177** and their acyclic analogue *p-tert*-butylphenol in tetrahydrofuran (these compounds are insoluble in water).[220] The apparent pK_a values for these calixarenes in tetrahydrofuran were lower by at least four pK units from that of *p-tert*-butylphenol which confirms the existence of strong intramolecular hydrogen bonds between calixarene phenolic groups.[220] Substitution of two or more phenolic groups in the calixarene by methyl or amine groups weakens this specific hydrogen-bonding network.[220,221] Estimation of pK_a values in aqueous solution by several investigators for calixarenes bearing phenol hydroxy groups on the lower rim and various groups, e.g., SO_3H,[222,224–226] *p*-[4-(methylammonio)phenyl]azo,[227] NO_2,[228] and others,[228] on the upper rim resulted in similar conclusions to those drawn by Shinkai regarding *p-tert*-butylcalixarenes in tetrahydrofuran solution.[220] Recent thermodynamic investigation of calixarene protonation using potentiometric and calorimetric titration by Arena and co-workers revealed a significant discrepancy between their results and those reported in the literature.[224] They studied protonation of calix[4]arene-*p*-tetrasulfonate **178** in aqueous solution in the pH range 2.5–11 and detected only two titrable protons, having pK_a values equal to 11.5 and 3.34, respectively.[224] Their attempts to detect the proton ionization site, which according to the literature data should correspond to pK_a = 4,[3,229] failed. The first calorimetric measurements of protonation of **178** showed that formation of the species having pK_a = 11.5 is both enthalpy and entropy favored, while the species having pK_a = 3.34 is only entropy favored.[224]

Scharff and colleagues studied the protonation of **178**, and its larger analogues **179** and **180** in aqueous solution, and observed that in going from the smallest to the largest ring the hydroxyl groups became less acidic. In **178**, the first pK_a value is <1.[230] In **179**

and **180**, there are two ionizable protons in the pH region below 11 with pK_a values of 3.5 and 5.0, and 7.5 and 9.0, respectively.[230] The same phenomenon was observed for sulfonic groups.[230]

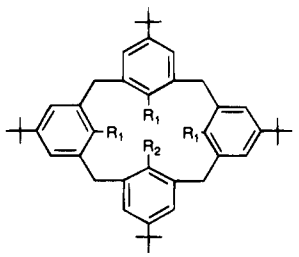


175 (Calix4-16C-1, XI)
n = 1
176 (Calix6-24C-1, XXXI)
n = 3
177 (Calix8-32C-1, XXXVII)
n = 5

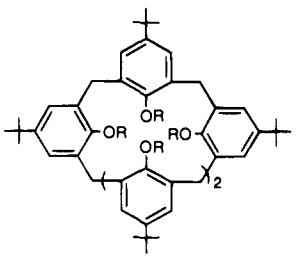


178 (Calix4-16C-3, XI)
n = 1
179 (Calix6-24C-2, XXXI)
n = 3
180 (Calix8-32C-6, XXXVII)
n = 5

Calixarenes, which are structurally preorganized, have more in common with spherands than with crown ethers.[231] Their selectivities toward cations are mainly a function of the cavity dimensions and the nature of the binding groups as is the case with spherands. In general, derivatives of the tetramers show a high selectivity for Na^+ over the other alkali metal cations and for Ca^{2+} over the other alkaline earth metal cations, e.g., for the **181** interaction with Li^+, Na^+, K^+, Rb^+, Cs^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+}, log K (CH_3OH) = 3.47, 5.71, 4.91, 3.15, 2.56, 3.88, 5.85, 4.5, and 3.87, respectively.[232–234] The ionic radii of Na^+ and Ca^{2+} are similar.[234] Derivatives of the pentamers and hexamers prefer larger cations such as K^+, Rb^+ or Cs^+, e.g., for the **182**, interaction with Li^+, Na^+, K^+, Rb^+, and Cs^+, log K (CH_3OH) = 1.0, 4.4, 5.3, 5.6, and 5.5, respectively, but their selectivity is less pronounced, and derivatives of octamers are usually less efficient ionophores.[234,235]

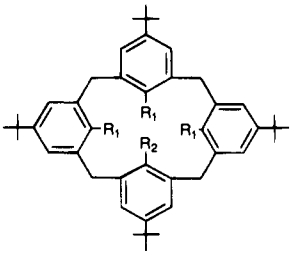


181 (Calix4-16C-33, XII)
R_1 = $OCH_2CO_2C_2H_5$
R_2 = OCH_2CO_2H



182 (Calix5-20C-3, XXVII)
R = $CH_2CO_2C_2H_5$

Arnaud-Neu, Schwing-Weill, and their colleagues have done extensive studies on transport, extraction, and complexation abilities of various calixarenes. Their recent efforts resulted in numerous new thermodynamic data for calixarene complexation with metal ions. For example, in the tetraphenols and tetraesters, the stepwise substitution of functional groups by carboxyl groups leads to an enhancement of the stability of the resulting complexes with alkali and alkaline-earth metal ions. However, the selectivity of Na^+ over K^+ decreases.[233] Selectivity of Ca^{2+} over Mg^{2+} is large, 11.41 log K units in methanol, for the tetraacid **183**.[233] The highest Ca^{2+}/Mg^{2+} selectivity ever recorded for neutral ligands is exhibited by the tetraamide **184** (≥7.8 log K units in methanol).[236] The monoacid triesters, **181** and **185**, form rather strong complexes with alkaline-earth metal ions, e.g., log K (CH_3OH) values for Ca^{2+} are 5.85 and 6.25, respectively.[233] This result is of interest because calixarene tetraesters do not complex Ca^{2+}.[233] This complexation is due to the electrostatic interaction between one carboxyl group and Ca^{2+} ion.[233]

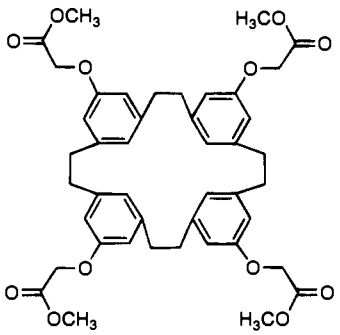


183 (Calix4-16C-16, XI)
R_1, R_2 = OCH_2CO_2H
184 (Calix4-16C-31, XI)
R_1, R_2 = $OCH_2CON(C_2H_5)_2$
185 (Calix4-16C-38, XII)
R_1 = $OCH_2CO_2(t\text{-}C_4H_9)$
R_2 = OCH_2CO_2H

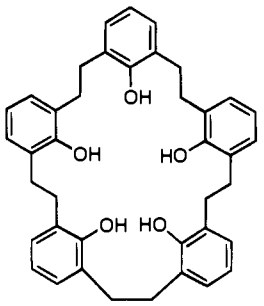
Further calixarene modification resulted in diooxocalix[4]arene[237] and homocalixarenes, two of which exhibit selectivity for Sr^{2+} over Ca^{2+}, e.g., for **186** log K (H_2O) = 2.70 and 0, respectively, and for **187** log K (H_2O) = 1.22 and 0, respectively;[238] bridged calixarenes;[234,239–242] double calix[4]arenes;[172,243] and crowned calix[4]arenes.[171,172] Crowned calix[4]arene, **188**, displays in acetonitrile a large selectivity (s) of K^+ over Na^+ (s = 1260) compared to **8**, **5**, and the natural antibiotic dinactin for which s = 40, 8, and 6, respectively.[171,172] The selectivity of **188** for Rb^+ over Cs^+ (s = 450) is also unusually high.[171] Studies suggest that K^+ and Rb^+ are included into the central cavity of **188**.[171] The stability of the K^+ complex with **188**, log K (CH_3CN) = 4.9, is comparable with that of the K^+ complex of **189**, log K (CH_3CN) = 4.5, which has the same number of oxygen donor atoms as the central cavity of **188**.[171] Bridges introduced into calix[4]arene rings have a drastic influence on stability constants for the complexes of these ligands with metal ions.[234,240] This observation may be useful in designing new compounds with desirable selectivities toward different metal ions. Recently, for example, calix[4]arene with a spherand bridge, **190**, was examined in a search for the hosts which can give kinetically stable complexes with radioactive Rb^+ isotopes for possible applications in organ imaging.[239]

Table I (supporting information) contains thermodynamic data for the interaction of calixarenes with uranyl ion;[244,245] cationic ferrocene derivatives;[246] silver ion;[232,235,236,247] lanthanide ions;[248] guanidinium ion, which is present in arginine residues and plays an important role in biological systems;[249,250] organic ammonium ions which, in comparison with alkali metal ions, exert large template effects on the conformation of water-soluble calixarenes;[251] and methylpyridinium ion whose complexation is an example of cation-π interaction.[252] This interaction is observed only for those hosts that can include the cation in the π-base cavity.[252] The π-base cavity is provided by calixarenes in the cone conformation.[252]

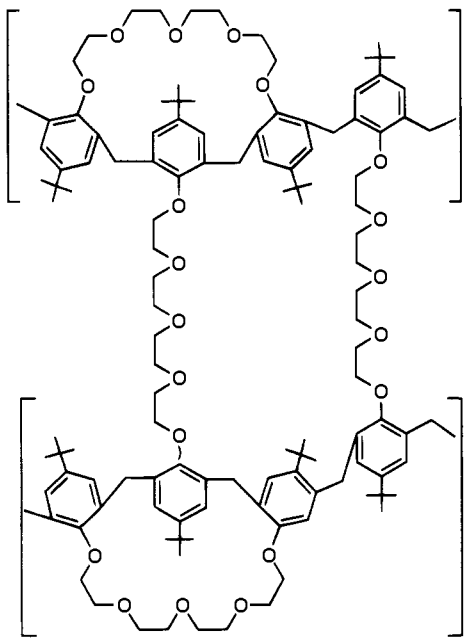
Potential and already existing possibilities of industrial applications of calixarenes are very broad: recovery of cesium from nuclear waste materials,



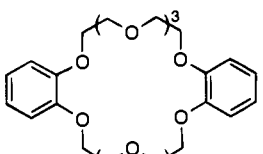
186 ((1,3-B)$_4$20C-1, XXVII)



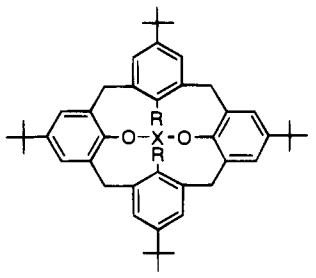
187 ((1,3-B)$_5$25C-1, XXXIII)



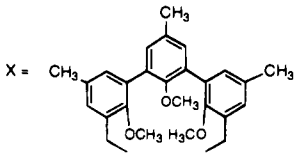
188 (Calixcrown-1, XLV)



189 (B$_2$30C10-1, XXXVII)



190 (Bridged Calix4-5, XIV)
R = OCH_3

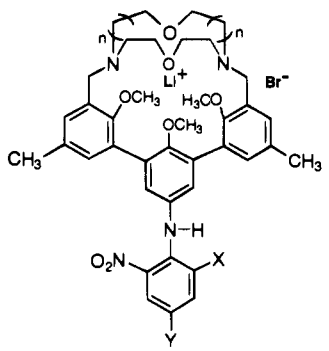


recovery of uranium, other ion sequestering possibilities, ion-selective electrodes and field-effect transistors (which are potentiometric sensors produced by combining semiconductors with ion selective membranes), phase-transfer agents, accelerators for instant adhesives, ion scavengers for electronic devices, stabilizers for organic polymers, separation of neutral organic molecules, and hydrolysis catalysts.[253]

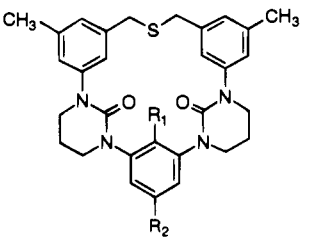
5. Other Preorganized Macrocycles

Cram has clarified the important role of *preorganization* and *complementarity* in determining the stabilities of cation complexes. The *principle of preorganization* in its original formulation states: "the smaller the changes in organization of host, guest, and solvent required for complexation, the stronger will be the binding".[254] This principle was experimentally demonstrated with the synthesis of spherands designed to complex selectively with Li^+ and Na^+.[255] Some of the macrocyclic compounds described earlier in this review fulfilled requirements for being preorganized, e.g., calixarenes and small aza cages.[188–190,194]

Additional preorganized macrocycles have been synthesized recently, and their cation complexation properties have been examined. New chromogenic cryptahemispherands, **191–193**, can effectively be used in determination of Na^+ in aqueous solution.[256] A new chromogenic spherand **194** exhibits selectivity for Na^+ over Li^+ in chloroform–water extraction.[257] This spherand has potential use for the colorimetric determination of Na^+ using an extraction procedure.[257] However, in homogeneous aqueous solutions it binds Li^+ better than Na^+ but the lack of adequate selectivity made it unsuitable for direct colorimetric determination of Li^+ in clinical samples.[257]



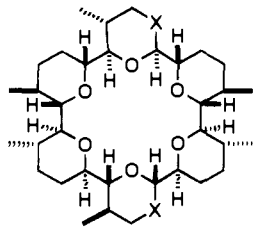
191 ((1.1.Spher]-1, XLVI)
X = CF_3; Y = NO_2; n = 1
192 ((1.1.Spher]-2, XLVI)
X = NO_2; Y = CF_3; n = 1
193 ([1.1.Spher]-3, XLVI)
X = CF_3; Y = NO_2; n = 3



194 (Spher-N_4S18C5-1, XIX)
R_1 = OCH_3
R_2 = NH-(2,4,6-$(NO_2)_3C_6H_2$)

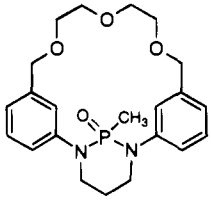
Rigid derivatives of **5**, acetal **195** and hemithioacetal **196**, have three-dimensional structures based on conformational locking mechanisms and are excellent hosts for K^+.[258] They show also very interesting features. Macrocycle **195** exhibits a 1000-fold increase over **5** in Na^+ binding, log K ($CDCl_3$) = 9.28 and 6.36, respectively, which is partially explained by its smaller ion-binding size. Macrocycle **196**, which differs from **195** by replacing two external oxygen atoms by sulfur in the dioxolane-like rings, binds Na^+ 100-fold less tightly than does **195**, log K ($CDCl_3$) = 7.40 and 9.28, respectively.[258] This phenomenon can suggest new ways to control ionophoric properties by structural modifications at locations which are remote from the binding sites.[258]

Complexation by additional new preorganized macrocycles was also examined including **197**, which imposes the inward orientation of a phosphorus moiety into the macrocyclic cavity;[259] a new macrocyclic diacid, **198**, with balanced conformational flexibility and preorganization;[260] a new macrocyclic

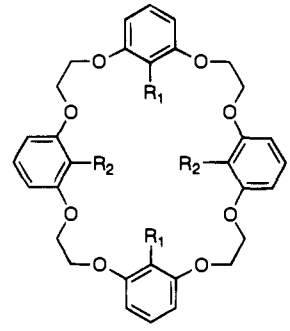


195 (18C6-25,XX)
X = O (diequatorial)
196 (18C6-28, XX)
X = S (diequatorial)

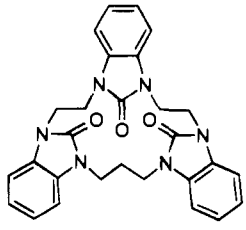
ligand, **199**, incorporating three benzimidazolin-2-one units;[261] two new spherands, **200** and **201**, each of which contains five meta-linked anisyl binding sites and which are examples of how preorganization overcomes the poor intrinsic ligating ability of aliphatic ethers by incorporating three adjacent anisyls into the host;[262] and a macrocycle, **202**, preorganized to bind benzamidinium ion, log K (CH_2Cl_2/C_2H_5OH, 95:5 v/v) = 5.70, through a network of convergent hydrogen bonds and/or π-stacking interactions.[263] The macrocycle **202** was designed to be a synthetic receptor capable of recognizing pentamidine isethionate, an important DNA-binding bis(benzamidine) drug used for treatment of *Pneumocystis carinii* in AIDS patients.[263]



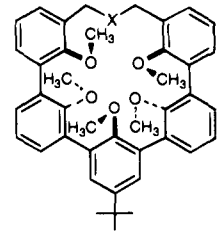
197 [(1,3-B)$_2$PN$_2$18C6-3, XXVII]



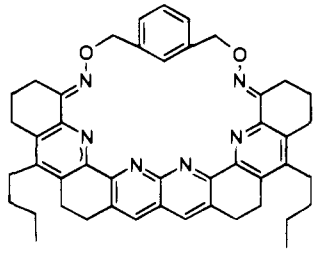
198 [(1,3-B)$_4$28C8-1, XXXIV]
R_1 = $CO_2C_2H_5$
R_2 = CO_2H



199 ($B_3N_6$18C6-1, XXVI)



200 (Spher-18C1-1, XVIII)
X = O
201 (Spher-S18C1-1, XVIII)
X = S

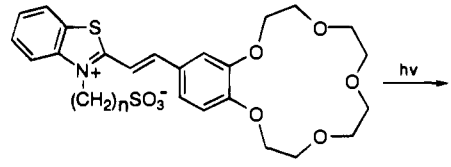


202 ($Py_4N_2$22C8-1, XXX)

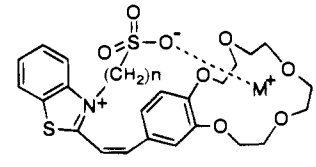
6. Switchable and Chromogenic Macrocycles

The basic idea of the "on/off" controlled ion-transport systems is very similar to that used in biological transport experiments. Among the chemical subspecies that have served as switches are azobenzene (photochemical switch), phenolic systems (pH switch), nitrobenzene and anthraquinone (neutral → anion redox switch), and ferrocene (neutral → cation redox switch).[264] The development of new molecular sensory devices has resulted in the synthesis of various responsive crown ethers which are used for the dynamic control of cation (and recently anion)[265] binding induced by changes in pH, redox potential, temperature, magnetic and electric field, and light.[3,266] When chromophores or fluorophores are linked to crown ethers, the resulting compounds can experience drastic changes in their photochemical and/or luminescent properties upon complexation with cations.[267,268] Such systems are of considerable interest especially for their potential applications to trace metal detection and determination.[267,268] Moreover, remote sensing is made possible by using optical fibers.[267]

a. Photoresponsive macrocycles, **203**–**208**, a styrene-containing dye, were prepared by Alfimov with co-workers.[266,269,270] The dye is highly sensitive to complexed metal cations and shows hypsochromic shifts of the long wavelength absorption and fluorescence bands, as well as a decrease in the fluorescence quantum yield upon complexation. The stability of these crown ether complexes with cations drastically changed after photoisomerization. The log K (CH_3CN) value (>9.15) for the reaction of Mg^{2+} with the "capped" cis-isomer **207** is much higher than the corresponding log K (CH_3CN) value (7.00) for the "uncapped" trans-isomer **204** due to the intramolecular interaction of the complexed cation with a tethered sulfonate anion.[266,269,270] The different stabilities of the isomer complexes can be used to expedite photoresponsive ion extraction and light-driven ion transport across membranes.



203 (B15C5-18, VIII)
n = 2 (trans)
204 (B15C5-19, VIII)
n = 3 (trans)
205 (B15C5-20, VIII)
n = 4 (trans)

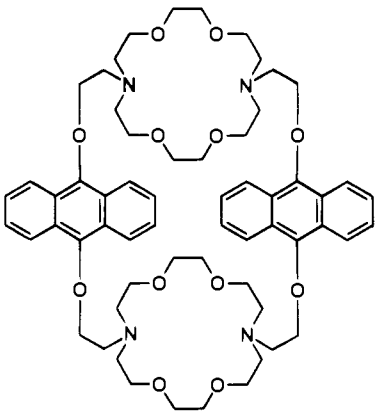


206 (B15C5-21, VIII)
n = 2 (cis)
207 (B15C5-22, VIII)
n = 3 (cis)
208 (B15C5-23, VIII)
n = 4 (cis)

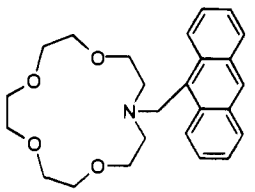
Photoresponsive macrocycles based on photochemical and photophysical properties of the anthracene ring have been synthesized by several groups of chemists. Bouas-Laurent with colleagues prepared bisanthracenyl macrotricycle **209** which combines photophysical properties of the anthracene ring and

the complexing ability of two face-to-face macrocycles toward bisalkylammonium cations.[267,271] This macrocycle was shown to encapsulate the $H_3N^+(CH_2)_7$-NH_3^+ cation with log K ($CHCl_3/CH_3OH$, 1:9 v/v) = 7.2.[267,271] This was the first example of optical detection of a linear molecular cation.[267,271]

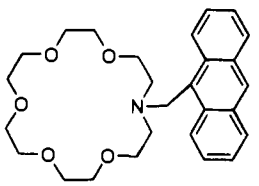
The macrocycles **210**, **211**, and biscrown **128** were examined for their ability to act as "switching on/off" fluorescent sensors for proton and alkali metal ions. They show pH-dependent fluorescence quantum yields while all other electronic spectral parameters remain essentially pH invariant.[166] Addition of Na^+ and K^+, but not Li^+, results in an enhancement of the fluorescence quantum yields by factors of ≤47.[272]



209 {(Anthra)$_2$[2.2/2.2]-1, XLIX}

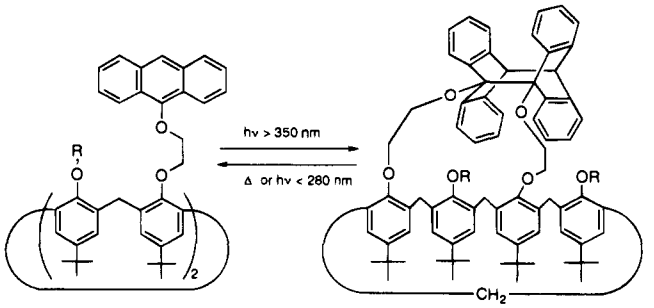


210 (N15C5-16, IX)



211 (N18C6-17, XXIII)

Shinkai and co-workers introduced two anthracenes near the metal-binding site of a calixarene. Isomer 1 (**212**) with an open ionophoric cavity showed poor ion affinity and selectivity, whereas isomer 2 (**213**) with a photochemically closed cavity showed much improved cation affinity and sharp Na^+ selectivity over other alkali metal ions, log K (THF) = 3.32 for Na^+ and <1.70 for other alkali metal ions.[273]



212 (Calix4-16C-61, XIII) R = $CH_2CH_2OC_2H_5$ (isomer 1)

213 (Calix4-16C-62, XIII) R = $CH_2CH_2OC_2H_5$ (isomer 2)

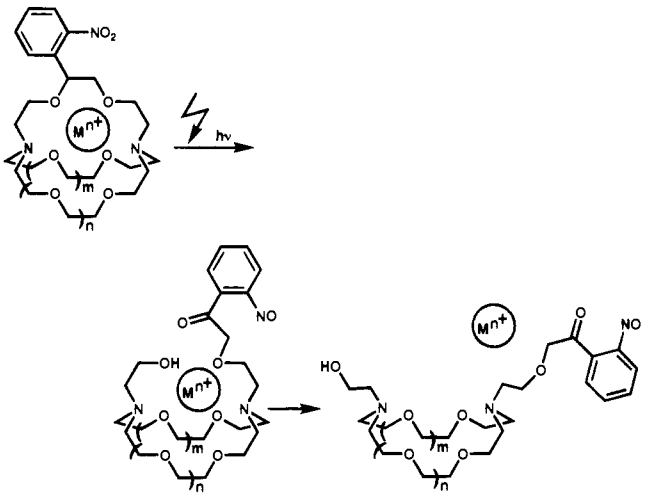
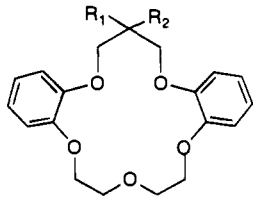


Figure 4. Light-induced release of a cation from a photocleavable cryptand (n = 1, m = 0, caged Na^+; n = m 1, caged K^+). (Reproduced by permission from the article by E. Grell and R. Warmuth published in *Pure Appl. Chem.* **1993**, *65*, 373–379. Copyright 1993 IUPAC Publications.)

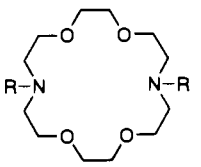
Lehn, Warmuth, and Grell searching for a new tool to perform Na^+ and K^+ cation concentration jumps which can be utilized in binding and transport studies prepared three photocleavable cryptands, **157–159**.[202,203] The binding properties of alkali metal cations and Ca^{2+} with these ligands in aqueous solution were examined and it was found that the cryptands exhibit high affinity for a cation of a given size (log K = 5.35, 3.8, and 6.3 for the interaction of **157** with Na^+, K^+, and Ca^{2+}, respectively, and log K = 3.8, 5.45, and 4.2 for the interaction of both ligands **158** and **159** with the same cations, respectively).[202,203]

As shown in Figure 4, a short UV light impulse cleaves the macrocyclic ring releasing the coordinated cation leading to the cation concentration jump.[202,203]

b. pH-responsive ionizable macrocyclic carriers which allow, by pH changes, the turning on/off of cation transport through liquid membranes continue to be of interest.[58,274] The ionizable proton can be attached either to a group exterior to the ring of donor atoms, to an atom that extends from the macrocycle as in the case of calixarenes, or to one of the ring donor atoms.[3] Proton-ionizable crown ethers have important advantages over neutral crown ethers in that the transfer of a metal ion into an organic medium in a separation process does not require concomitant transport of an aqueous phase anion.[58] This factor is of importance for potential practical applications in which hard, hydrophilic aqueous phase anions, such as chloride, nitrate, or sulfate, would be involved.[58] Bartsch with co-workers synthesized a series of proton-ionizable dibenzo-16-crown-5-oxyacetic acids, **214–220**[58] and Reinhoudt with co-workers prepared two proton-ionizable lipophilic diaza-18-crown-6 derivatives, **221** and **222**.[274] Macrocycle **221** was used to transport K^+ through supported liquid membranes.[274] A dramatic effect of pH of the receiving aqueous phase on the K^+ flux was observed.[274] The flux dropped significantly when the pH was decreased from 10 to 4. Below pH 4, almost no decrease in flux occurs on further pH lowering. Protonation of the carrier which takes place at pH 6 and lower can be responsible for inhibition of complexation and/or the partition of the carrier.[274]

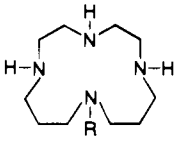


214 ($B_2$16C5-2, XV)
R_1 = H
R_2 = $OCH_2C(O)O^-$ $^+N(CH_3)_4$
215 ($B_2$16C5-3, XV)
R_1 = CH_3
R_2 = $OCH_2C(O)O^-$ $^+N(CH_3)_4$
216 ($B_2$16C5-4, XV)
R_1 = C_2H_5
R_2 = $OCH_2C(O)O^-$ $^+N(CH_3)_4$
217 (B216C5-5, XV)
R_1 = C_4H_9
R_2 = $OCH_2C(O)O^-$ $^+N(CH_3)_4$
218 (B216C5-6, XV)
R_1 = C_6H_{13}
R_2 = $OCH_2C(O)O^-$ $^+N(CH_3)_4$
219 (B216C5-7, XV)
R_1 = C_8H_{17}
R_2 = $OCH_2C(O)O^-$ $^+N(CH_3)_4$
220 (B216C5-8, XV)
R_1 = $C_{10}H_{21}$
R_2 = $OCH_2C(O)O^-$ $^+N(CH_3)_4$



221 ($N_2$18C6-6, XXIV)
R = $C_{10}H_{21}$
222 ($N_2$18C6-7, XXIV)
R = $C_{14}H_{29}$

An interesting behavior of tetraazamacrocycles carrying 3-aminopropyl side arms, isomers **223** and **224**, was observed by Kaden and co-workers.[275] Depending on the pH and on the age of the solution, each of these ligands forms different species with Cu^{2+}.[275] Each isomer is represented by both protonated and unprotonated forms. The amino group of the side arm of either isomer is coordinated to Cu^{2+} when present in the unprotonated form. However, the protonated side arm is not coordinated to Cu^{2+}. The authors state that to the best of their knowledge this is the first example in which the coordination of the donor group of the side chain not only modifies the coordination geometry of the metal ion, but also alters the configuration of the kinetically stable metal/macrocycle unit.[275]



223 ($N_4$14C4-25, VI)
R = $(CH_2)_3NH_2$
(isomer I)
224 ($N_4$14C4-26, VI)
R = $(CH_2)_3NH_2$
(isomer II)

c. Redox responsive macrocycles that contain active redox centers have the ability to switch complexation of cations or anions on/off when treated with redox reagents or electrochemical stimulation. The electrochemical switch is sometimes superior because it requires no additional reagents. Several workers have made use of these techniques to investigate on/off switching.

Beer has dedicated many of his publications to the synthesis and ion complexation of macrocycles containing ferrocene moieties (see ref 276 and references therein), but no log K values have been given. He found, for example, that when an equimolar mixture of Na^+/K^+ or $Na^+/K^+/Mg^{2+}$ is added to an electrochemical solution of ferrocene biscrown **225** (Figure 5) the ferrocene/ferricinium redox couple shifts anodically by an amount approximately the same as

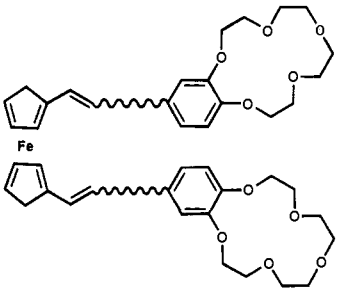
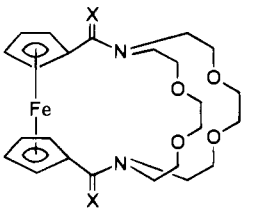


Figure 5. Ferrocene biscrown **225** (Reproduced by permission from the article by D. Beer published in *Endeavour* **1992**, *16*, 182–189. (Copyright 1992 Elsevier.)

that induced by the K^+ alone.[276] This observation, together with fast-atom bombardment mass spectrometry (FABMS) competition findings, suggests that this biscrown is a first generation prototype potassium-selective amperometric sensor, capable of detecting K^+ in the presence of Na^+ and Mg^{2+}.[276]

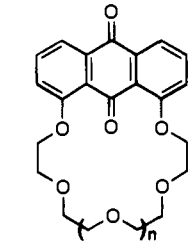
Gokel and Kaifer with co-workers prepared three novel ferrocene macrocycles and two of them, cryptands **226** and **227**, were characterized with respect to their thermodynamic properties.[264] The electrochemical behavior of **226** indicates that the cryptand acts as a redox-switchable ligand with several metal cations. The authors consider binding behavior in the group Na^+, K^+, and Ca^{2+} to be controlled by differences in charge density and to involve forces different than those that operate when Ag^+ is bound.[264] The large Ag^+ binding constant (log K = 8.35) in acetonitrile and electrochemistry both confirm a direct, stabilizing Ag–Fe interaction.[264] The authors state that **226** is the first reported ligand whose voltammetric behavior is greatly affected by alkali metal cations in relatively polar solvents, such as acetonitrile. Previous reports on other ferrocene-based, redox-active ligands demonstrated electrochemical behavior that changed appreciably in the presence of divalent or trivalent cations but was unaltered by the presence of monovalent cations.[264] Cryptand **226** acts as an effective redox-switchable ligand for Ag^+ not only in acetonitrile but in aqueous solution as well.[264] The authors state that to the best of their knowledge this is the first reported example of redox-switching of Ag^+ complexation and the first reported example of redox-switching ability by a ligand in aqueous medium.[264]



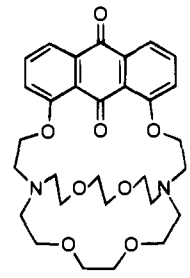
226 ((2.2.Ferrocene]-1, XLVIII)
X = H_2
227 (K_2[2.2.Ferrocene]-1, XLVIII)
X = O

Gokel and co-workers have synthesized many new podands, crown ethers, and lariat ethers containing the anthraquinone nucleus as the redox-active center. The authors produced thermodynamic data for some

of these macrocycles, e.g., **228–231**.[277,278] Electrochemical (or chemical) reduction of these ligands leads to excess negative charge which in turn enhances the binding of the cation.[277] Interaction of Li^+ with the cryptand **231** produced a 1:2 (ligand/cation) complex.[277] This is the first time that a 1:2 complex of this type has been detected by cyclic voltammetry.[277] The log K (CH_3CN) value for this 1:2 complex was 2.22, but this value was increased to 8.0 upon one-electron reduction, and to 13.1 upon two-electron reduction.[277]



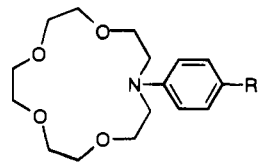
228 (Anthraquin18C5-1, XVIII)
n = 1
229 (Anthraquin21C6-1, XXIX)
n = 2
230 (Anthraquin24C7-1, XXXII)
n = 3



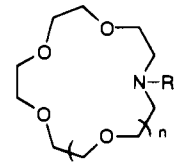
231 (Anthraquin(2.2.2)-1, XLVII)

d. Ion-responsive fluorescent macrocycles containing a variety of cation-responsive fluorescence moieties like coumarin,[279–281] merocyanine,[268,282,283] benzoxazinone,[284] pyrene,[285] and others[286] have been synthesized and their cation complexation abilities have been examined.

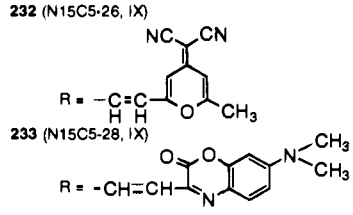
Valeur with co-workers synthesized a series of crown ethers linked to dyes.[268,279,280,282–284] Cation complexation in acetonitrile was followed by changes in absorption spectra. The complexation with metal ions of crown ethers linked to merocyanine, **232**,[268,282,283] and benzoxazinone, **233**,[284] had a different mechanism than in those cases where the crown ethers were linked to coumarin 153, **234–236**.[279,280] In the first case, the complexed cation attracts the lone pair of the nitrogen atom of the crown and thus reduces the electron-donating character of the nitrogen with regard to the rest of the molecule.[282] In the second case, changes are mainly controlled by the charge density of the cation that enhances the electron-withdrawing character of the carbonyl group of the coumarin via direct interaction.[280] In addition, thanks to participation of the carbonyl group of the coumarin, the log K (CH_3CN) values of the complexes of crowned coumarins with alkali and alkaline earth cations are much higher (e.g., log K = 5.10 and 6.75 for the **235** interaction with Na^+ and Ca^{2+}, respectively) [280] than those of the two other crowned dyes, **232** and **233** (e.g., log K = 1.98 and 3.79 for the interaction of **232** with Na^+ and Ca^{2+}, respectively, and log K = 2.23 and 4.41 for the interaction of **233** with the same cations, respectively).[268,282] Photoejection of Li^+ and Ca^{2+} from crowned merocyanine (**232**) was evidenced by ultrafast spectroscopy; ejection takes less than 5 and 20 ps for Li^+ and Ca^{2+} complexes, respectively.[283] The log K values for the formation of the complexes in the excited state are estimated to be 2 orders of magnitude lower than in the ground state, e.g., for the complex Ca–**232**, log K (CH_3CN) = 1.60 and 3.75, respectively.[283]



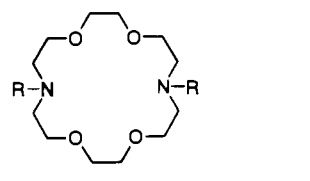
232 (N15C5-26, IX)



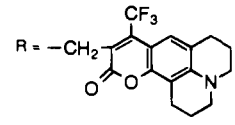
234 (N12C4-5, II)
n = 0
235 (N15C5-17, IX)
n = 1



233 (N15C5-28, IX)



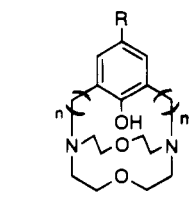
for **234**, **235**, and **236**



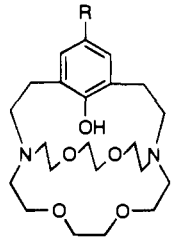
236 ($N_2$18C6-41, XXIV)

e. Chromogenic macrocycles formed by attaching synthetic chromophores to macrocycles give rise to specific color changes on complexation with metal cations. These macrocycles have been used as spectroscopic analytical reagents for the detection of specific cations. Bartsch and Czech with co-workers synthesized a series of new chromogenic macrocycles and studied their cation complexation abilities.[256,287–289] The cryptand **237** exhibits total selectivity for Li^+ over Na^+ in water/diethylene glycol monoethyl ether (90:10 v/v), (log K = 3.51 for Li^+, while log K for Na^+ and K^+ could not be obtained due to the lack of chromogenic response), the slightly larger **238** cryptand is highly selective for Li^+ in CH_2Cl_2/H_2O extractions but is inactive toward Li^+, Na^+, and K^+ in water/diethylene glycol monoethyl ether (90:10 v/v).[289] The largest among them, cryptand **239**, exhibits K^+ selectivity in aqueous media.[289] It has been demonstrated that Li^+ complexes with highly preorganized chromogenic cryptahemispherands, **191–193**, can be used in the determination of Na^+ in aqueous solution. Li^+ is loosely held in the cryptohemispherand cavity and is replaced by Na^+, which generates the observed response with the chromophore.[256] Synthesis of other chromogenic macrocycles was also reported.[287,290–292] Among them are optical sensors for Ca^{2+}.[287] A crown ether **240**, with three acetate groups which bears the 2,4,6-trinitroaniline chromophore, forms a rather weak 1:1 complex with Ca^{2+}, log K (H_2O, pH 7) = 2.98, but exhibits very high selectivity for Ca^{2+} over Mg^{2+} at pH 7.[287]

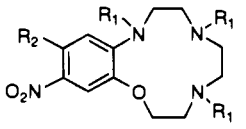
Kubo and co-workers designed the first chromogenic calixarene-type receptor **241** for Ca^{2+}.[291] This receptor, in ethanol/water (99:1), was more sensitive to Ca^{2+} than to Na^+, K^+, or Mg^{2+} (log K = 6.88, 4.57, 5.51, and 2.00, respectively) making it suitable for the colorimetric detection of Ca^{2+}.[291] Shinkai and co-



237 ([1.1.B]-1, XLVI)
n = 2; R = N=N-(4-$NO_2C_6H_4$)
238 ([1.1.B]-2, XLVI)
n = 3; R = N=N-(4-$NO_2C_6H_4$)

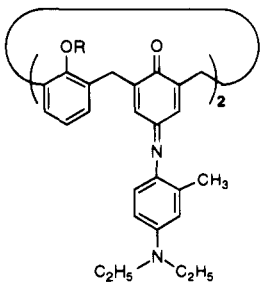


239 ([2.2.B]-2, XLVIII)
R = N=N-(4-$NO_2C_6H_4$)

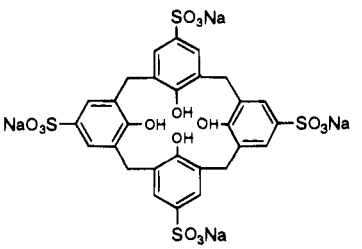


240 ($BN_3$12C4-1, III)
R_1 = CH_2CO_2H
R_2 = NH-(2,4,6-$(NO_2)_3C_6H_2$]

workers examined complexation of **242** with rare-earth cations and found that it acted in water as a specific chromogenic reagent for Ce^{3+} giving a pH dependent red-brown complex with absorption maximum at pH 11.7, while all other rare-earth ion complexes remained colorless.[248]



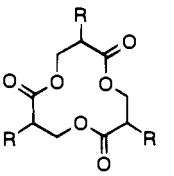
241 (Calix4-16C-63, XIII)
R = $CH_2CO_2C_2H_5$



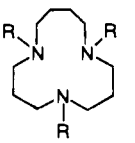
242 (Calix4-t6C-4, XI)

7. Siderophore-type Macrocycles

The siderophores are a class of microbially produced iron chelators that are powerful sequestering agents for Fe^{3+} (and other trivalent or tetravalent metal cations of similar charge to ionic radius ratios).[293] These chelators solubilize environmental ferric ion from normally very insoluble ferric hydroxide and facilitate its transport into the cell.[293,294] The siderophores generally can be divided into two classes: those based on hydroxamate chelating groups and those based on catechol groups.[295] It has been known for some time that enterobactin **243**, a catechol-based macrocyclic siderophore which can be isolated from several enteric bacteria, formed the most stable complex with Fe^{3+}.[294,295] The complex was octahedral and formed via coordination of the six catecholate oxygens.[294] The stability constant for this complex estimated by Raymond and co-workers at physiological pH was near 10^{52}. This value was almost 27 orders of magnitude higher than the stability constant for the Fe^{3+} complex with EDTA.[295] The more recent estimate by Raymond and co-workers of the stability constant of the Fe^{3+}–enterobactin complex, log K (H_2O) = 49, was based on use of MECAM [1,3,5-tris[[(dihydroxybenzoyl)amino]-methyl]benzene] as a model compound. This compound is a better protonation model than the previously used DMB (*N,N*-dimethyl-2,3-dihydroxybenzamide).[149,296] In search of synthetic high-affinity and highly selective chelating agents for Fe^{3+}, Raymond with co-workers prepared the two enterobactin analogues, CYCAM **244** and sulfonated CYCAM(S) **245**.[297,298] Both of these agents form stable complexes with Fe^{3+} (estimated log K = 40 and 38 for **244** and **245**, respectively). Unlike enterobactin, they are hydrolytically stable at physiological pH, and like enterobactin they are capable of removing iron from transferrin at a reasonable rate.[297,298]



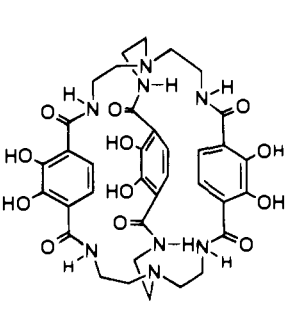
243 ($K_3$12C3-1, II)
(Enterobactin)
R = NHC(O)-[2,3- $(OH)_2$-C_6H_3]



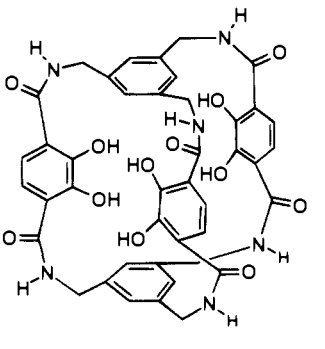
244 ($N_3$13C3-1, IV)
R = C(O)-[2,3-$(OH)_2C_6H_3$]
245 ($N_3$13C3-2, IV)
R = C(O)-[2,3-$(OH)_2$-5-$(SO_3^-)C_6H_2$]

Recently, macrocyclic siderophores more powerful than enterobactin at physiological pH (assuming the revised log K (H_2O) = 49 for the enterobactin complex with Fe^{3+}) were synthesized by Martell and co-workers.[147–149] Complexes of these macrocycles, **110** and **111**, with Fe^{3+} have log K values of 51.3 (ethanol/water, 75:25 v/v)[147] and 49.98 (water),[148,149] respectively. These macrocycles also form very stable complexes with In^{3+} and especially with Ga^{3+}, log K (C_2H_5OH/H_2O, 75:25 v/v) = 33.99 and 44.2, respectively, for interaction with **110**, and log K (H_2O) = 28.02 and 45.6 respectively, for interaction with **111**.[147,149] The high stabilities of the Fe^{3+} and Ga^{3+} complexes with **110** are due to the close fit of these hexacoordinated metal cations in the ligand cavity formed by the pseudo-octahedral arrangement of ligand donor atoms.[147]

Macrobicycles based on catecholate groups have been described by Raymond[299] and Vögtle[300] and co-workers. A macrobicycle prepared by Raymond and co-workers is bicapped TRENCAM **246** in which three catechol groups, connected together by capping groups derived from tris(2-aminoethyl)amine, are arranged to coordinate Fe^{3+}.[299] Vögtle and co-workers prepared a similar macrobicycle **247** but capped with mesitylene groups and have reported a preliminary stability constant of 10^{59},[300] which is more likely to be near 10^{43}.[149,299]

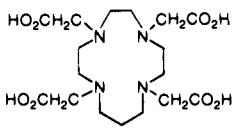


246 (Cyclophane-8, LII)

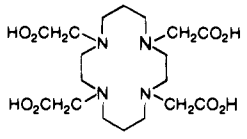


247 (Cyclophane-9, LII)

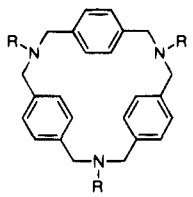
There are additional synthetic siderophore-type macrocycles which form stable complexes with Fe^{3+} but their stability constants are lower than those described above. Included in this group are triaza **86**,[126] **87**,[117] and **88**[117] with carboxyl side arms; tetraaza, **74**, **248**, and **249**, with carboxyl side arms;[118] triaza and tetraaza with $CH_2PO_3H_2$ side arms[143] (see also refs 71 and 171 in the 1991 review[3]); hexapus cyclophanes with catechol segments, e.g., **250** and **251**;[219] a polycatecholate macrocycle **252**;[293] catecholate and hydroxamate macrocycles (see refs 803 and 804 in the 1991 review[3]); and tris(hydroxamate) cryptand **253**.[301] Raymond and co-workers also reported a series of new macrocyclic hydroxamate-type siderophores which are produced by most of the actinomycetes and various other bacteria.[302]



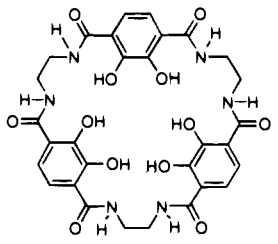
248 ($N_4$13C4-2, IV)



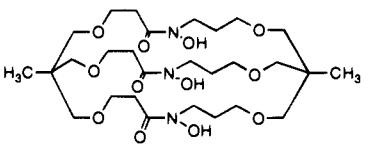
249 ($N_4$14C4-7, V)



260 I(1,4-B)$_3$N$_2$21C3-1, XXVIII)
R = -C(O)CH(CH$_3$)NHC(O)-[2,3-(OH)$_2$-4-C(O)N(CH$_3$)$_2$C$_6$H$_2$)
251 I(1,4-B)$_3$N$_2$21C3-2, XXVIII)
R = -C(O)-CH(CH$_3$)NHC(O)-[2,3-(OH)$_2$-4-C(O)N(C$_{14}$H$_{29}$]$_2$C$_6$H$_2$]

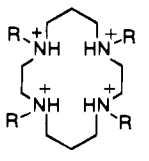


252 I(1,4-B)$_3$N$_6$30C6-1, XXXVI)



253 (Carbon)3.3.3]-1, XLIX)

Some of these macrocycles are of potential interest in medical applications such as removal of Fe^{3+} in treatment of Cooley's anemia and other diseases with iron overload. A paramagnetic complex of Fe^{3+} with **254** (log K (H_2O) = 30.6) is used as a contrast agent for liver MRI.[303]



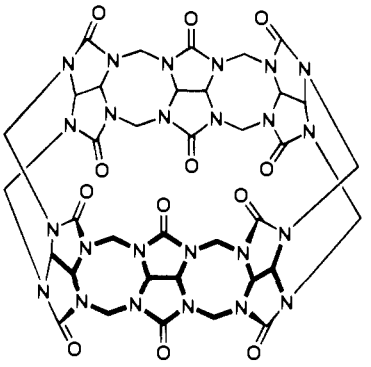
254 ($N_4$14C4-10, V)
R = $CH_2PO_3H^-$

8. Miscellaneous

a. The name Cucurbituril was suggested by Freeman and Mock for the nonadecacyclic cage structure of hexagonal symmetry which was a product of urea, glyoxal and formaldehyde acidic condensation.[304,305] The synthesis of cucurbituril was first reported in 1905.[306] The structure is rather rigid with an internal cavity of approximately 5.5 Å diameter, to which access is provided by two 4 Å diameter portals situated among the carbonyl groups.[304] Cucurbituril **255** encapsulates and tightly binds substituted ammonium ions having dimensions smaller than a *para*-substituted benzene ring.[305] The specifity of binding appears to be quite remarkable. For example, (cyclopentylmethyl)amine is held quite tightly, log K (H_2O/HCOOH, 1:1 v/v) = 5.52, while (cyclohexylmethyl)-amine is excluded from the internal cavity by its size.[304] For the n-alkylamines, $H(CH_2)_nNH_3^+$, the order of complex stability, in H_2O/HCOOH (1:1 v/v), follows the trend $n = 1 < 2 < 3 < 4 > 5 > 6 > 7$ (log K = 1.92, 2.00, 4.09, 5.00, 4.38, 3.36, and 2.00, respectively) with the n-butylammonium ion bound most tightly.[305,307] A similar trend is observed for α,ω-alkanediammonium ions, for which a hydrocarbon chain length of 5 and 6 is optimal, log K (H_2O/HCOOH, 1:1 v/v) = 6.39 and 6.44, respectively.[307] Cucurbituril complexation with other amines like arylamines, amines containing heteroatoms (oxygen and sulfur), and branched alkylamines was also studied.[307,308] Cucurbituril exhibits in aqueous solution extremely high affinity toward biological bases, spermine and spermidine (log K = 7.12 and 6.13, respectively) and has potential biochemical applications.[307] The driving forces for formation of these complexes are hydrophobic interactions (freeing of solvent molecules upon complexation) and a charge–dipole attraction with hydrogen bonding between the ammonium cations and the electronegative oxygens of the urea cabronyls that surround the portals of cucurbituril.[305,307]

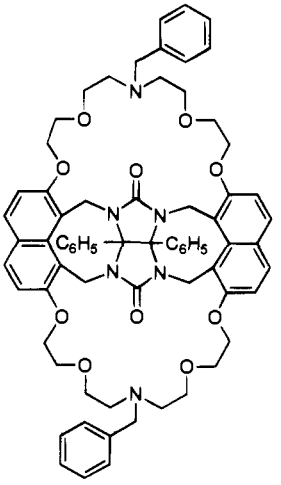
Buschmann and co-workers published the first thermodynamic data for cucurbituril interaction with alkali and alkaline-earth cations.[306] Cations are not encapsulated into the cavity of cucurbituril but are located at the portals because they interact with portal carbonyl donor atoms. All donor atoms interacting with one cation are situated in a plane so cucurbituril behaves like a macromonocyclic ligand. Cucurbituril possesses two portals and can form 2:1 (cation/ligand) complexes. Cucurbituril as a monocyclic ligand forms more stable complexes with cations than those formed by other monocyclic ligands. Stability constants of the cucurbituril complexes are several orders of magnitude higher than those with 18-crown-6, e.g., log K (H_2O) = 3.69, 4.82, 4.57, and 3.97 for the interaction of cucurbituril with Na^+, Cs^+, Ca^{2+}, and NH_4^+, respectively, and log K (H_2O) = 0.8, 0.99, 0.48, and 1.23 for the interaction of **5** with the same cations, respectively.[306] Both ligands have the same number of donor atoms and the 18-crown-6 cavity radius is quite similar to the ionic radii of the cations studied, r = 1.4 and 2.0 Å for **5** and **255**, respectively, and r = 1.00, 1.02, 1.70, and 1.70 Å for Ca^{2+}, Na^+, Cs^+, and NH_4^+, respectively.[306] The stronger binding by cucurbituril is attributed to its rigid structure and higher electric charges of its donor atoms compared with 18-crown-6. Due to the rigid structure of cucurbituril no conformational changes

upon complexation are possible. All donor atoms are preorganized and located inside the cavity.[306]



255 (Cucurbituril-1,L LXII)

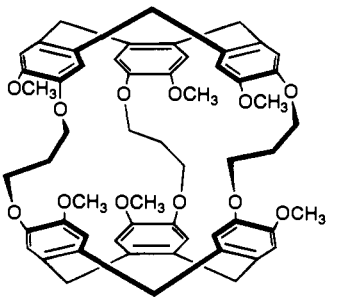
b. Several new basket-shaped macrocycles were synthesized by Nolte and co-workers in their search for receptors mimicking enzymes.[309,310] New basket-shaped macrocycles consist of three potential binding sites, a rigid concave cleft and two semiflexible crown ether handles with various aromatic moieties incorporated into the handles.[310] Alkali-metal ions and protonated aliphatic and aromatic diamines are bound to these baskets in a 1:1 ratio as determined in solvent extraction studies from water to chloroform. Metal ion complexes are proposed to have a clamshell-like or a sandwich-like structure. In aliphatic diammmonium complexes, each ammonium group is complexed at one binding site of the macrocycle and the aliphatic chain lies in the macrocycle cavity wedged in between the *o*-xylene units. One of the baskets, **256**, exhibits allosteric effects upon complexation.[309] The binding of one K^+, in $CDCl_3$/Me_2SO (3:1 v/v), induces the conversion of the macrocycle to the *aa* conformation. This conformational change in the macrocycle facilitates the binding of the second K^+. The formation constant for binding the second K^+ is 128 times larger than that of the first. In addition, the complex containing two K^+ ions binds 1,3-dinitrobenzene at the third site by $\pi-\pi$ interactions more strongly by a factor of 2−6 than does the free macrocycle.[309]



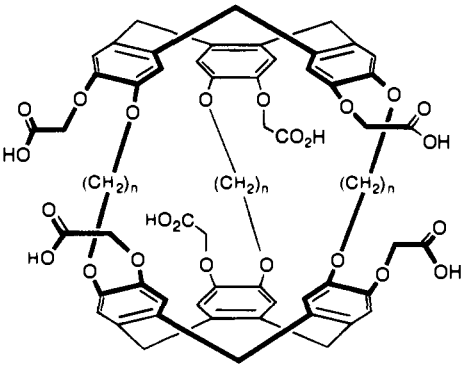
256 (Basket-5, LVII)

c. Cryptophanes and Speleands. Cryptophanes were designed by Collet and colleagues as receptors for tetrahedral substrates over a decade ago.[311] They consist of two *anti*- or *syn*-cyclotriveratrylene units assembled by three bridges. The 1992 review contains thermodynamic data for the complexation of cryptophanes with neutral molecules.[4] The interaction of **257**−**259** with quaternary ammonium cations was also studied.[311-313] The studies showed that on going from $CDCl_2CDCl_2$ to water, there was a decrease of log K values for the smallest cations (up to choline) and an increase for the larger ones, Me_3N^+−Pr, Me_3N^+−Bu, and acetylcholine, e.g., log K ($CDCl_2$-$CDCl_2$) = ~3.2, ~2.9, ~0.9, and ~0.5 and log K (D_2O) = ~3.2, ~2.5, ~1.8, and ~1.2 for the interaction of **257** with Me_3NH^+, choline, Me_3N^+Pr, and acetylcholine, respectively.[311] This behavior emphasizes the role of hydrophobic forces, which favor the complexation of the substrates having the longest side chains.[311] On going from **258** to the larger **259**, there is a dramatic increase in the stability constants, except for Me_3NH^+, which decreases.[313] A relatively loose association appears to be more favorable than a tight lock and key pairing to achieve a strong binding of quaternary ammonium cations by cryptophanes in water.[313]

Cryptophane applications look promising in the design of new materials, e.g., ferroelectric liquid crystals or organic three-dimensional charge transfer salts.[311]



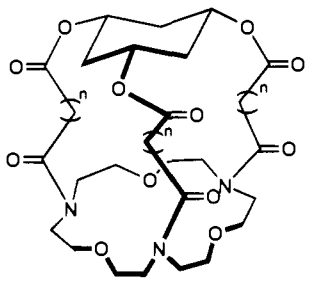
257 (Cryptophane-3, LVI)



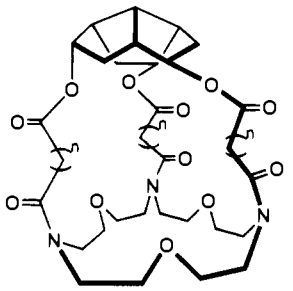
258 (Cryptophane-5, LVI)
n = 3
259 (Cryptophane-6, LVI)
n = 5

Speleands with roughly spherical intramolecular cavities resemble cryptophanes. They are formed by

hydrophobic, rigid and concave caps linked to polar substructures by several anchorage points.[314] Collet and co-workers prepared, in 1982, the first two speleands in which a cyclotriveratrylene cap was linked to an 18-[N_3O_3] crown ether by three bridges.[311] Similar speleands having hexane (**260** and **261**) or "triketone" (**262** and **263**) caps instead of a cyclotriveratrylene cap have been synthesized recently, and their complexation with methyl ammonium cation examined.[314]

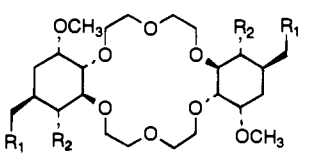


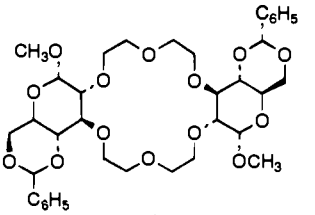
260 (Speleand-1, LVI)
n = 2
261 (Speleand-2, LVI)
n = 3



262 (Speleand-3, LVI)
n = 2
263 (Speleand-4, LVI)
n = 3

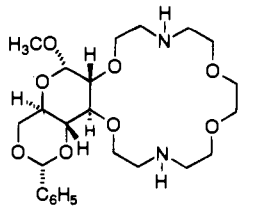
d. Several new sugar-based chiral crown ethers and cryptands, and cholic acid-based macrocycles were synthesized.[205,315–317] The complexing and extracting abilities of sugar-based macrocycles, **264**–**278**, were measured with Li^+, Na^+, K^+, and NH_4^+ cations.[315] The substituents on the sugar moiety had a significant effect on these properties, e.g., four tosyloxy groups in **273** increased the log K values for metal ion–macrocycle complex formation, changed the cation selectivity of the macrocycle, and enhanced greatly their metal ion extracting abilities.[315] For example, log K ($CHCl_3$) = 6.17, 6.23, 6.00, and 5.81 for the interaction of **273** with Li^+, Na^+, K^+, and NH_4^+, respectively, and log K ($CHCl_3$) = 4.14, 4.05, 5.04, and 4.12 for the interaction of **278** (benzylidene derivative) with the same cations, respectively. Cation extraction abilities of these two ligands in a CH_2Cl_2–H_2O system in the case of **273** are 99.5, 93.2, 98.5, and 99.6% for Li^+, Na^+, K^+, and NH_4^+, respectively, and in the case of **278** are 5.9, 14.8, 9.6, and 14.9% for the same cations, respectively.[315] Cryptands **161**–**163** are the first sugar-based cryptands to be synthesized.[205] log K values for the reactions of these cryptands with cations are remarkably higher than those of their monocyclic analogues, e.g., log K ($CHCl_3$) = 8.88, 9.37, and 9.57 for the interaction of the cryptand **161** with Na^+, K^+, and NH_4^+, respectively, and log K ($CHCl_3$) = 6.31, 5.82, and 6.65 for the interaction of the cryptand monocyclic analogue **279** with the same cations, respectively.[205] Cholic acid-based macrocycles, **280**–**282**, constitute a new and versatile type of receptor architecture but molecular mechanics suggests that the present generation of cholaphanes (cyclocholates) is too floppy for applications in molecular recognition and should be redesigned.[316]



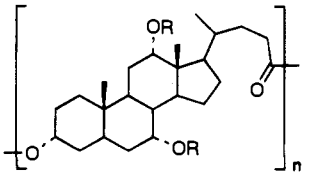


264 (18C6-10, XX)
R_1, R_2 = OH
265 (18C6-11, XX)
R_1, R_2 = $OC(O)CH_3$
266 (18C6-12, XX)
R_1 = Br; R_2 = $OCH_2C_6H_5$
267 (18C6-13, XX)
R_1 = H; R_2 = OH
268 (18C6-14, XX)
R_1 = Br; R_2 = OH
269 (18C6-15, XX)
R_1 = OH; R_2 = $OCH_2C_6H_5$
270 (18C6-16, XX)
R_1 = O-trityl; R_2 = $OC(O)CH_3$
271 (18C6-17, XX)
R_1 = OH; R_2 = $OC(O)CH_3$
272 (18C6-18, XX)
R_1 = O-tosyl; R_2 = OH
273 (18C6-19, XX)
R_1, R_2 = O-tosyl
274 (18C6-20, XX)
R_1 = O-mesyl; R_2 = OH
275 (18C6-21, XX)
R_1, R_2 = OCH_3
276 (18C6-22, XX)
R_1, R_2 = OC_4H_9
277 (18C6-23, XX)
R_1, R_2 = $OCH_2C_6H_5$

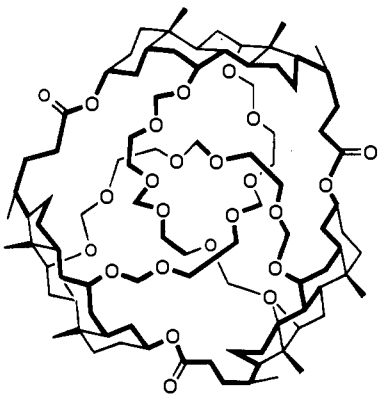
278 (18C6-24,XX)



279 ($N_2$18C6-47, XXIV)



280 (Cholaphane-2, LXI)
n = 3
R = $COCH_2(OCH_2CH_2)_2OCH_3$
281 (Cholaphane-3, LXI)
n = 4
R = $COCH_2(OCH_2CH_2)_2OCH_3$



282 (Cholaphane-4, LXI)

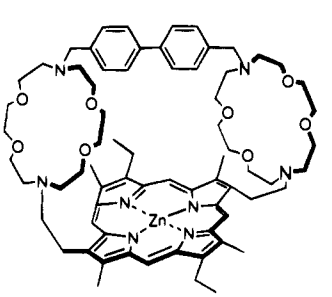
e. Porphyrins and Porphyrin Derivatives. Porphyrins are rigid aromatic macrocyclic molecules with many different reaction centers. They are abundant in nature and play important roles in reversible oxygen binding in blood, enzymatic intracellular respiration, and other biochemical redox reactions.[318] The chemistry of synthetic porphyrins is also remarkable. At present, the principal directions in the synthesis of porphyrins are new derivatives including those with sterically hindered coordination centers, capped porphyrins, "picket-fence" porphyrins, "expanded" porphyrins, and cyclophane- and crown ether-substituted porphyrins.[168,170,318–321]

One of the most important properties of the porphyrins is their ability to complex metal ions. Kinetics and mechanisms of porphyrin formation reactions with metal ions have been investigated much more exhaustively than the thermodynamic equilibria.[322] The measurement of stability constants for metal–porphyrin interactions is difficult because of their high values, limited solubilities of most porphyrins in water, and the interference of other equilibria.[323]

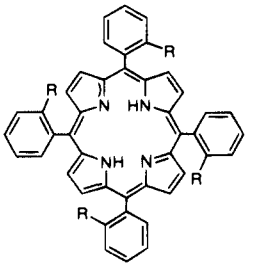
Among recently synthesized porphyrins are those which are capable of assembling several substrates within the same structural unit.[168,320] Porphyrin **283**, with two [18]-N_2O_4 crown ethers covalently bound to the porphyrin ring (which contains Zn^{2+}) and connected together by a biphenyl strip, complexes two Ag^+ *cooperatively* at each of the crown ether sites with a dissociation constant of 1.65×10^{-12} M and an average of 2.6 active sites per molecule.[168] Since only two Ag^+ can be incorporated into the lateral macrocyclic units, some complexation may also occur at the biphenyl strap. The dissociation constant would correspond to strong binding to the two macrocyclic units and weak binding to the biphenyl group.[168] "Picket-fence" **284**, containing a coordinated Zn^{2+} and bearing four hydrothiophene donor chains, binds two Ag^+ *cooperatively* with a dissociation constant of 4.8×10^{-8} dm^3 mol^{-1}.[320] Complexation studies of crown ether-substituted phthalocyanines (**285**–**287**) showed that it is possible to control the organization of phthalocyanines by using different metal salts.[170] Aggregation of these super structures with monovalent ions (K^+, Rb^+, and Cs^+) results in cofacially ordered stacks while aggregation with Ba^{2+} ion leads to the formation of networks.[170] New cationic-periphery porphyrins, **288**–**292**, have interesting features because they are protonated in a pH range suitable for studies of binding with nucleic acids.[324–326]

The number of applications of porphyrins in our lives is impressive. Some of the most challenging economic and scientific problems can be solved using porphyrins. Among these are new biotechnologies based on the principles of photosynthesis and enzymatic catalysis, the extraction of oxygen from air and water, blood replacement, solar energy converters, photosensitizers for holography, photodynamic methods for cancer treatment, protection against radiation sickness, highly stable and ecologically clean dyes, and effective and stable catalysts for varied chemical and electrochemical reactions.[318]

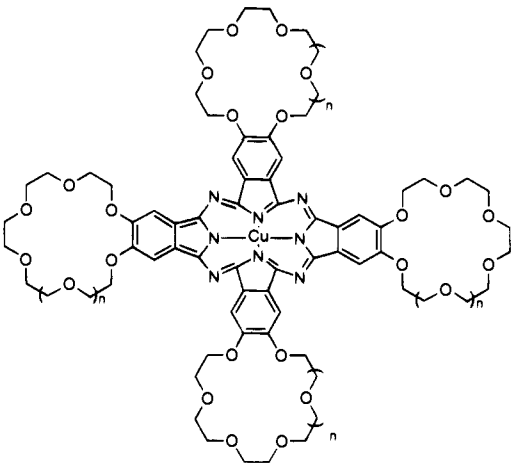
Table I (supporting information) contains thermodynamic data for the complexation of the above described porphyrins and other porphyrins with protons and various metal ions in organic and aqueous solution.



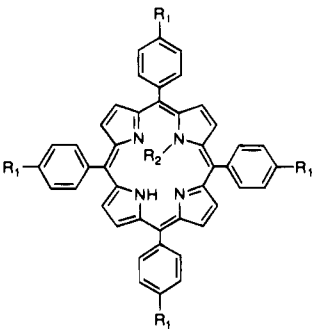
283 (Porphyrin-69, LXIX)



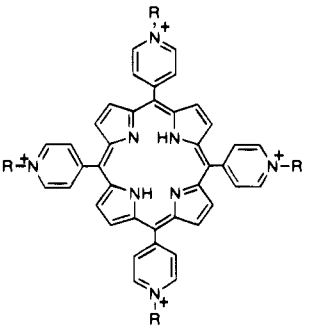
284 (Porphyrin-10, LXIII)
R = NHC(O)



285 (Porphyrin(B15C5)$_4$-2, LXXI) n = 0
286 (Porphyrin(B18C6)$_4$-1, LXXI) n = 1
287 (Porphyrin(B21C7)$_4$-1, LXXI) n = 2



288 (Porphyrin-4, LXIII) $R_1 = CH_2NH_2$; $R_2 = H$
289 (Porphyrin-5, LXIII) $R_1 = CH_2NH_2$; $R_2 = CH_3$
290 (Porphyrin-6, LXIII) $R_1 = N(CH_3)_3^+$; $R_2 = H$



291 (Porphyrin-12, LXIII) R = CH_3
292 (Porphyrin-13, LXIII) R = C_8H_{17}

B. Selectivities

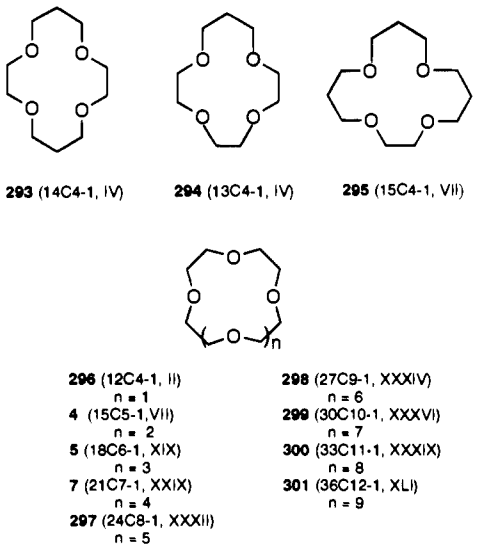
A major target of the current synthetic effort in macrocyclic chemistry is to prepare hosts which are selective for specific guests. Early studies on prediction of macrocycle selectivities suggested that cations were most strongly complexed in the case of closest match between the size of the cation and the cavity of the macrocycle, i.e., "size-match" selectivity.[1,2] Further studies have shown that the prediction of selectivity is much more complicated and that many other factors involving the host, guest, and solvent must be considered.[114] Some of these additional factors with respect to the macrocycle include shape and topology; conformational flexibility or rigidity; number, type, and arrangement of donor atoms in the ring; substituents incorporated into the ring; type and arrangement of side arms; and chelate ring size. The design of selectivity into a ligand must also take into account the cation. In addition to their different ionic radii, cations differ in their affinities for different donor atoms, have different geometrical requirements for complexation, and different charge densities. Switchable macrocycles, described in section II.A.6, represent a sophisticated example of how the selectivity of a macrocycle toward a given cation can be changed by an "on/off" switch mechanism. Other macrocycles which are extremely selective toward

Fe^{3+} ion are described in section II.A.7. More examples of macrocycle selectivities are discussed throughout the text. The following discussion focuses on the macrocycle factors presented above.

1. The Match between the Cation and Macrocycle Cavity Dimensions

The match between the cation and macrocycle cavity dimensions is especially evident in small preorganized macrocycles such as cryptands, calixarenes, spherands, cavitands, porphyrins, etc. These macrocycles have small and rigid cavities and their possible conformational changes upon complexation are very limited. Recently synthesized small aza cages illustrate this point. Characteristics common to all of these aza cages are their high molecular preorganization which confers unusual basicity behavior, and the presence of small cavities which allows selective encapsulation of metal ions of appropriate size.[189,190,192] Most of them selectively and strongly bind the small Li^+ ion.[188,190,191] The best Li^+ binder of the series, the aza cryptand **135**, shows a high log K (H_2O) value of 5.5 and regular coordination geometry, coupled with short Li–N bonds (2.06 Å)[7] all of which indicate an extremely good match between the cation and cavity radii.[190] Encapsulation of Li^+ by **135** was not influenced by the presence of Na^+ ion, even in high concentration showing a high level of discrimination between Li^+ and Na^+ ions.[7]

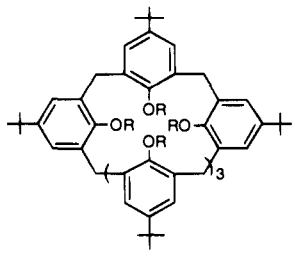
Another highly selective binder of Li^+, **293**, was synthesized by Inoue and co-workers.[63] They examined complexation of Li^+ and Na^+ ions with a series of 12- to 16-crown-4 in methanol and found that **293** has the highest selectivity for Li^+ over Na^+, e.g., log K (CH_3OH) = 2.34 and 1.63 for the interaction of **293** with Li^+ and Na^+, respectively, while log K (CH_3OH) = 2.01 and 2.06 for the interaction of **294** and log K (CH_3OH) = 1.85 and 1.80 for the interaction of **295** with the same cations, respectively.[63] The high selectivity of **293** for Li^+ over Na^+ originated from cooperative entropic and enthalpic contribution (ΔH = −1.46 and −4.81 kJ mol^{-1} and ΔS = 39.9 and 15.0 J K^{-1} mol^{-1} for Li^+ and Na^+, respectively) due to the best match between the cavity diameter of **293** and the diameter of Li^+, as shown by the examination of CPK molecular models. Therefore, complexation of Li^+ causes the least conformational change of the ligand and the most extensive desolvation of the cation and the ligand.[63] This group extended their study to a macrocycle series from the rigid **296** to the flexible **301**.[63,327] They observed that the size–fit concept still appears to play a subsidiary role even in the complexation of alkali metal ions by larger crown ethers. They concluded that complexation of alkali metal ions by these macrocycles in methanol was enthalpy driven but ion selectivity, determined by the size-fit relationship, was mostly entropy governed, e.g., log K = 2.03 and 3.47, ΔH = −27.07 and −43.51 kJ mol^{-1}, and ΔS = −51.9 and −79.6 J K^{-1} mol^{-1} for the interaction of **298** with Na^+ and K^+, respectively and log K = 2.14 and 3.98, ΔH = −25.56 and −48.70 kJ mol^{-1}, and ΔS = −44.8 and −87.2 J K^{-1} mol^{-1} for the interaction of **299** with the same cations, respectively.[327]



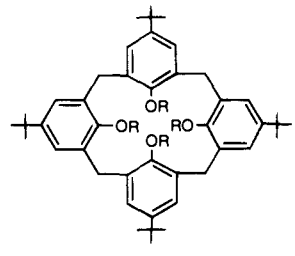
In a series of 12 new unsymmetrical cryptands which are larger than small aza cages, cryptands **145**–**147** showed high selectivity for K^+ over Na^+ by factors ranging from 40 to 200, while smaller cryptand **148** showed high selectivity for Na^+ over K^+ by a factor of over 1000.[198] It was suggested that selectivities of these cryptands are based on a "size-match" fit. None of the asymmetric cryptands studied showed strong interaction with Li^+ ion because as a free ion, Li^+ is probably too small to form complexes with these cryptands, and as a solvated ion, Li^+ is too large to fit in their cavities.[198]

The "size-match" rule seems to be valid in the case of two recently synthesized benzene-bridged macropolycyclic polyethers, **149** and **150**, which with rigid but larger cavities appeared to have good selectivities for Cs^+ over the smaller Na^+ and Pb^{2+} in methanol/water (8:2 v/v) solution, log K = 2.20 and 3.50 for the interaction with Cs^+, respectively, and little or no reaction for both of these ligands with Na^+ and Pb^{2+}.[199] Also, the suitcase-shaped macrotricycle, **152**, with a larger cavity exhibited a stronger interaction with Cs^+ than did smaller **151** and **154**, log K (H_2O) = 1.40, no interaction, and 0.50, respectively.[200]

Among calixarenes, in general, derivatives of tetramers show selectivities (sometimes high) for Na^+ over the other alkali metal ions and for Ca^{2+}, which has an ionic radius similar to that of Na^+, among the alkaline earth metal ions, e.g., for the interaction of **183** with these cations, log K (CH_3OH) = 7.89 (Li^+), 9.94 (Na^+), 9.05 (K^+), 7,72 (Rb^+), 11.02 (Mg^{2+}), 22.44 (Ca^{2+}), and 20.92 (Sr^{2+}).[233,234] Among the *p-tert*-butyl derivatives of tetramers, the selectivities toward Na^+ and Ca^{2+} can be further diversified by variation of substituents, e.g., ester derivative **303** has pronounced Na^+/K^+ selectivity (3.4 log K units)[232] and **183** (carboxyl derivative) has remarkable Ca^{2+}/Mg^{2+} selectivity (11.4 log K units).[233] Derivatives of hexamers prefer larger cations such as K^+, Rb^+, or Cs^+, but their selectivity is less pronounced, and derivatives of octamers are usually less efficient ionophores, e.g., for the interaction of **302** with alkali metal cations, log K (CH_3CN) = 3.7 (Li^+), 3.5 (Na^+), 5.1 (K^+), 4.8 (Rb^+), and 4.3 (Cs^+).[231,234]

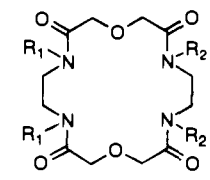


302 (Calix6-24C-11, XXXI)
X = t-C_4H_9
R = $CH_2CO_2C_2H_5$

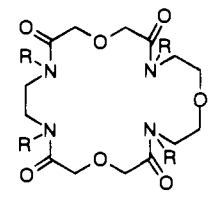


303 (Calix4-16C-26, XI)
R = $CH_2CO_2CH_2COC_6H_5$

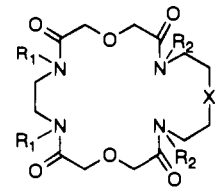
Among a series of macrocyclic tetralactams, **304**–**311**, the binding abilities varied according to macrocyclic ring size and the nature of the substituents on the nitrogen atoms.[328] A high selectivity for Ca^{2+}, Sr^{2+}, and Ba^{2+} over Na^+, K^+, Mg^{2+}, and Zn^{2+} was found in a $CHCl_3/H_2O$ system by a liquid–liquid extraction technique.[328] The stability constant determinations in tetrahydrofuran showed that 18-membered ligands have a good selectivity for Sr^{2+} vs Mg^{2+}, Ca^{2+}, and Ba^{2+} (complexes are 10, ~8, and 30–40 times more stable, respectively); 21-membered ligands show the lack of selectivity between alkaline earth cations except for Ca^{2+}, Sr^{2+}, and Ba^{2+} vs Mg^{2+} (~20 times more stable complexes); and 24-membered ligands show high selectivity for Ba^{2+} vs Ca^{2+}, e.g., the complex of Ba^{2+} with **311** is 91 times more stable than that of Ca^{2+} and exhibits the highest stability constant (log K = 6.6) observed for tetralactams.[328,329]



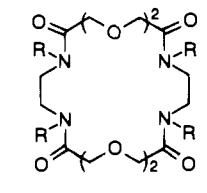
304 (K_4N_418C6-1, XXV)
R_1, R_2 = $CH_2C_6H_5$
305 (K_4N_418C6-2, XXV)
R_1 = H; R_2 = $CH_2C_6H_5$
306 (K_4N_418C6-3, XXV)
R_1 = H; R_2 = $C_{12}H_{25}$



307 (K_4N_421C7-1, XXIX)
R = $CH_2C_6H_5$



308 (K_5N_521C7-1, XXX)
R_1, R_2 = $CH_2C_6H_5$
X = NC_6H_5
309 (K_5N_521C7-2, XXX)
R_1, R_2 = $CH_2C_6H_5$
X = N-(4-FC_6H_4)
310 (K_5N_521C7-3, XXX)
R_1 = H; R_2 = $CH_2C_6H_5$
X = NC_6H_5



311 (K_4N_424C8-1, XXXII)
R = $CH_2C_6H_5$

The small azacrown, **106** also displays high selectivity which is related to the ionic radius of the cation.[143] Thus, a large difference is noted in the stability constants for cations which have similar properties but differ in ionic radius such as Mg^{2+}, Ca^{2+}, Zn^{2+}, and Cd^{2+}. Fe^{3+}, Co^{3+}, and Ga^{3+} have similar ionic radii (r = 0.64, 0.63, and 0.62 Å, respectively) and large, similar log K (H_2O) values (29.6, 29.5, and 30.2, respectively).[143] An X-ray analysis of the **106** complex with Fe^{3+} showed that the Fe^{3+} is located in a basket-like cavity, the bottom of which is formed by nitrogens in the ring and the walls are formed by methylphosphonic acid side arms. All the donor atoms of the macrocycle are coordinated to the Fe^{3+} ion.[143]

2. Conformational Rigidity or Flexibility

Conformational rigidity or flexibility of macrocycles has a significant influence on their selective behavior. Macrocycles of "rigid" type, as those described above, discriminate between cations that are either smaller or larger than the one with optimum size (peak selectivity).[330] Macrocycles of "flexible" type discriminate principally among smaller cations (plateau selectivity).[330]

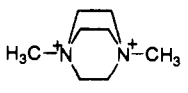
The comparison of complexing behavior of **83** and **85** where both ligands have the same sets of donor atoms in the rings shows that the complexes formed with the **83** are generally more stable. However, the larger and more flexible **85** has a much greater selective behavior toward the same series of metal ions. For example, the difference in log K (H_2O) values between Cu^{2+} and Pb^{2+} complexes with **83** and **85** is 2 and 10 log K units, respectively.[112,115]

The same effect is observed among the carboxyl derivatives **74** (DOTA), **248** (TRITA), and **249** (TETA).[125] DOTA acts like a rigid "cage" which forms very stable but unselective complexes with transition metal ions and Pb^{2+}, e.g., log K (H_2O) = 20.20 (Mn^{2+}), 22.25 (Cu^{2+}), 21.10 (Zn^{2+}), 21.31 (Cd^{2+}), and 22.69 (Pb^{2+}).[125] The increased flexibility in TRITA and particularly in TETA, produces greater selectivity on the basis of metal ion radius, e.g., log K (H_2O) = 16.74 (Mn^{2+}), 21.13 (Cu^{2+}), 19.13 (Zn^{2+}), 19.60 (Cd^{2+}), and 19.11 (Pb^{2+}) for TRITA–M^{2+} interaction and log K (H_2O) = 11.27 (Mn^{2+}), 20.49 (Cu^{2+}), 16.40 (Zn^{2+}), 18.02 (Cd^{2+}), and 14.32 (Pb^{2+}) for TETA–M^{2+} interaction.[125] In the case of TETA, the selectivity ratio of its Cd^{2+} to Pb^{2+} complexes is so large (4 log K units) that it may allow useful analytical or other applications.[125]

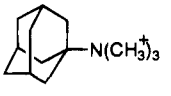
3. The Shape of Macrocycles and Topologies of Their Binding Sites

The shape of macrocycles and topologies of their binding sites can help to modify their binding properties. A new ditopic macrocycle, **160**, synthesized by Bartsch and co-workers is suitable for complexation of alkylammonium ions.[204] The binding abilities of **160** were determined by extraction of alkylammonium picrates from water into chloroform ($CDCl_3$). Extraction percents for methyl-, ethyl-, propyl-, butyl-, and *tert*-butylammonium ions were 11.5, 81.3, 91.3, 35.5, and 10.5%, respectively.[204] Examination of CKP space-filling models revealed that when the lipophilic alkyl "tail" and polar ammonium ion "head" of the alkyammonium ion are directed toward the hydrophobic and the diazacrown ether units of **160**, respectively, both ethylammonium and *n*-propylammonium ions are well accommodated within the cavity, log K ($CDCl_3/CD_3OD$, 9:1 v/v) = 2.95 for the formation of the *n*-propylammonium complex. Butyl- and *tert*-butylammonium ions are too large to fit entirely within the cavity, while the small methylammonium ion fits loosely within the cavity.[204]

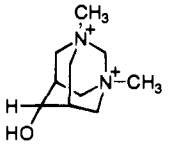
Macrotricycle **209**[267] and macrobicycle, **170**[211] are additional examples of macrocycles in which shape and arrangement of binding sites make them suitable for interaction with a specific guest. The macrotricycle has molecular recognition abilities toward linear bisalkylammonium ions, $^{+}H_3N(CH_2)_nNH_3^{+}$, due to the presence of two face-to-face N_2O_2 macrocyclic units and, in addition, fluorescence properties due to the presence of two anthracene rings. The selectivity and fluorescence effects are dependent on the chain length of the diammonium substrate, e.g., log K ($CHCl_3/CH_3OH$, 1:9 v/v) = 6.8, 7.2, 6.0, and 4.6 for the cations with n = 6, 7, 8, and 12, respectively.[267] Cyclophane **170**, in its fully extended form (C_3 symmetry), delineates a large spheroidal cavity that was confirmed by X-ray data, and exhibits a high affinity for more or less globular cations, such as **312**–**314** with log K (D_2O) of 4.1, 4.2, and 4.2, respectively.[211] The exceptionally high difference between log K values for the interaction of this ligand with methylviologen and N-methylpyridinium ions, log K (D_2O) = 6.6 and 3.5, respectively, may be attributed to combined electrostatic, hydrophobic, and π-stacking effects.[211]



312 (cation-11, LXXIII)



313 (cation-13, LXXIV)



314 (cation-47, LXXV)

Additional examples of the effect of size, shape, and topology on the complementarity of macrocycle–cation interactions include speleands and methylammonium cations,[314] cryptophanes and polymethylammonium cations,[311–313] polyphenolic hosts and quaternary ammonium cations,[212] and basket-shaped hosts and diammonium cations.[310]

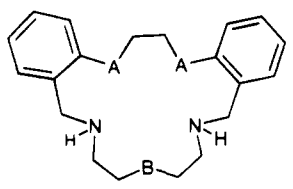
4. The Number, Kind, and Arrangement of Donor Atoms

The number, kind, and arrangement of donor atoms in the macrocyclic rings also play an important role in macrocycle selectivities. Oxygen donor atoms in crown ethers have the largest affinities for alkali, alkaline-earth, and lanthanide ions; nitrogen donor atoms favor transition metal ions; and sulfur donor atoms interact preferentially with Ag^+, Pb^{2+}, and Hg^{2+}.[90,330] Tertiary amine nitrogen donor atoms form more stable complexes with Ag^+ than do secondary amine nitrogen donor atoms.[76]

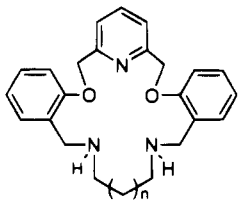
The replacement of one nitrogen by an oxygen atom in the macrocyclic ring has pronounced effects both on the kinetics of the complexation reactions (faster reaction rates) and on the stability constants of the complexes (decreased stability) with transition metal ions.[112,113] When one nitrogen atom is replaced by an oxygen atom in **39**, there is a decrease of 4–5 log K units in the stability constants for the formation of complexes with transition metal ions, except for Cu^{2+} where the decrease is 9 log K units.[113]

The Bradshaw and Izatt group has prepared a new series of 10 suitcase-shaped macrotricyclic polyethers. Suitcases **151**–**155** exhibited a variety of interactions with the metal cations studied. Both **151** and **154** favor Ba^{2+} over Sr^{2+} with log K (H_2O) = 2.50 and 4.50, respectively, for the interaction of **151** with Sr^{2+} and Ba^{2+} and log K (H_2O) = 2.40 and 3.40, respectively, for the interaction of **154** with the same cations.[200] These ligands also have appreciable interactions with Nd^{3+}, Eu^{3+}, and Er^{3+} through enhanced charge–dipole attractions, e.g., for **151**, log K (H_2O) = 3.30, 3.60, and 3.70, respectively. Suitcase **151** forms also very strong complexes with Pb^{2+}, Cd^{2+}, and Cu^{2+}, log K (H_2O) = 12.90, 6.57, and 6.32, respectively, while **154** complexes strongly with Hg^{2+}, log K (H_2O) = 10.10.[200] These complexation properties are mainly due to the high affinities of these cations for nitrogen donor atoms.[200]

Lindoy and co-workers have continued investigations on cation discrimination by structural "dislocations".[75,331–333] Dislocation is associated with a sudden change in the K value for cation–macrocycle interaction for a particular metal ion with a series of closely related ligands.[331,334] They have examined the interaction in methanol/water (95:5) of Ni^{2+}, Co^{2+}, and Cu^{2+} with an extended series of 16- to 19-membered macrocycles incorporating nitrogen, oxygen, and sulfur donor atoms.[331,332] The results confirmed that the systematic changes in the macrocyclic ligand structures (variation of the donor-atom set, the macrocyclic ring dimensions, and/or the chelate ring sizes) are clearly reflected in the stabilities of the metal complexes formed. For example, the dislocation behavior (significant increase in stability constants) for Ni^{2+}, and to a lesser extent, Co^{2+} complexes going from **315** (log K = <3.5 and <3.5, respectively) to **316** (log K = 7.7 and 10.0, respectively) appears to be associated with the greater affinity of these metal ions for nitrogen donor atoms than for oxygen donor atoms.[331] In the case of Cu^{2+}, extremely large stability constant differentials (up to 10^{10}) were achieved solely through donor atom variation within the ligand framework employed, e.g., log K = ~16.3, 6.5, and 6.9 for **317**, **315**, and **318**, respectively.[332] Interesting complexation behavior was observed for the pyridyl-derived N_3O_2 macrocycles, **319** and **320**.[57,61,333,335] The sequence of their stability constants for complex formation with transition metal ions, in general, followed the Irving–Williams stability order. The formation constant for the Cu^{2+} complex with **319** was much larger than that of the corresponding Ni^{2+} complex, log K (CH_3OH/H_2O, 95:5) = 13.92 and 6.66, respectively.[57] Compound **319** was also found to have pronounced affinity for Cd^{2+} over Zn^{2+}, log K (CH_3OH/H_2O, 95:5) = 8.73 and 5.91, respectively, while **320** showed a stability order of Cd^{2+} < Zn^{2+}, log K (CH_3OH/H_2O, 95:5) = 4.19 and 5.75, respectively.[333] For Cu^{2+} and Cd^{2+}, the substantial drop in formation constants observed on increasing the macrocyclic ring from 17-membered (log K = 13.92 and 8.73) to 18-membered (log K = 8.72 and 4.19) was ascribed to a change in coordination geometry and/or coordination number between complexes.[57,333]



315 ($B_2N_2$17C5-1, XVII) A, B = O
316 ($B_2N_3$17C5-1, XVII) A = O; B = NH
317 ($B_2N_5$17C5-1, XVII) A, B = NH
318 ($B_2S_3N_2$17C5-1, XVII) A, B = S

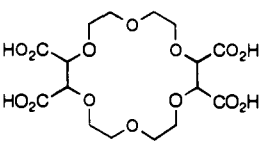


319 ($PyB_2N_2$17C5-1, XVII) n = 0
320 ($PyB_2N_2$18C5-1, XIX) n = 1

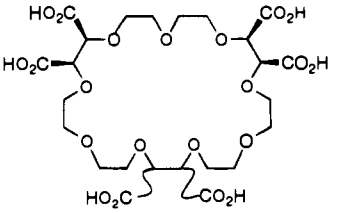
5. Substituents Incorporated into Macrocyclic Flexible Rings

Substituents incorporated into macrocyclic flexible rings lead to their stiffening and may alter both macrocycle binding strength and selectivity. Examples are macrocycles containing sugar moieties, i.e., **279**, and cryptands **162** and **163**.[205] Compound **279** compared to the unsubstituted **134** has diminished tendency to form cation complexes and decreased selectivity, especially in the case of NH_4^+, e.g., log K ($CHCl_3$) = 6.31, 5.82, and 6.65 for the interaction of **279** with Na^+, K^+, and NH_4^+, respectively, and log K ($CHCl_3$) = 6.45, 6.59, and 8.81 for the interaction of **134** with the same cations, respectively.[205] This phenomenon may be attributed to the fact that the **134** ring is flexible, while in the case of **279** the glucopyranoside unit makes the crown ring rigid and thus hinders complex formation. The steric hindrance may also contribute to the decrease of stability which is most pronounced with the large ammonium cations. The isomeric cryptand **162** and **163** with two sugar moieties form weaker complexes with each cation than does **161** with one sugar moiety, e.g., for **162** and **163**, log K ($CHCl_3$) = 5.57 (Li^+), 6.34 (Na^+), 6.26 (K^+), and 6.35 (NH_4^+) and for **161**, log K ($CHCl_3$) = 6.26 (Li^+), 8.88 (Na^+), 9.37 (K^+), and 9.97 (NH_4^+).[205] Probably, the two sugar moieties reduce the flexibility of these cryptands, and at the same time the effect of their steric hindrance increases. The same reasoning applies to the decrease in selectivity which occurs in the same order.[205]

Chiral groups incorporated into the correct location of a macrocyclic framework may allow separation of optically active enantiomeric cations.[18,27,37,39,40,83,84] The difference in log K values for the interaction of chiral (*S,S*)-**33** (diphenyl-substituted, Δlog K ($CD_3OD/CDCl_3$, 1:9 v/v) = >0.85) and chiral (*S,S*)-**32** (di-*tert*-butyl-substituted, Δlog K ($CD_3OD/CDCl_3$, 7:3 v/v) = 0.71) for the (*R*) and (*S*) forms of naphthylethylammonium ions are the highest yet observed for these types of interactions.[39] Other macrocycles having chiral recognition properties have been described earlier in this review. Incorporation of certain chiral units can also alter selectivities of macrocycles. Fronczek, Gandour, and Fyles with co-workers prepared crown ether carboxylates derived from *meso*-tartaric acid, **322** and **323**.[336] They found that *meso* tetra- and hexacarboxylic macrocycles are remarkably nonselective and inefficient cation complexing agents, compared to related crown ethers derived from (*R,R*)-(+)-tartaric acid, due to the unfavorable conformational control exerted by the tartaric units. The differences, in aqueous solution, range from a factor of about 20 for Na^+ and K^+ to factors of 20−100000 for the Ca^{2+} and Cd^{2+} complexes of *meso* 18-membered tetraacid (**322**) compared to those of *R,R,R,R*-18-membered tetraacid **321**.[336] In contrast, the Li^+ and Cs^+ complexes of *meso*-**322** are more stable than the corresponding complexes of the (*R,R,R,R*)-isomer, **321** (50-fold more in the case of Li^+; no value was given in the case of Cs^+ because no complex of Cs^+ with **321** was detected).[336]



321 (16C6-4, XIX) (*R, R, R, R*)
322 (18C6-5, XIX) (*R, S, S, R*)



323 (27C9-2, XXXIV) (meso, mixture of isomers)

6. Variations and Arrangements of Side Arms

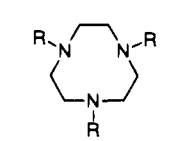
Variations and arrangements of side arms which cooperate with the macrocycle ring in the complexation process can modify the selectivities of macrocycles. Hancock, for example, observed that addition of side arms containing neutral oxygen donor atoms to a ligand leads to an increase in selectivity of the ligand for large metal ions over small metal ions and allows the design of ligands with desired selectivities.[337]

Small azacrowns, **107** with methylene(methylphosphonic acid) side arms and **108** with methylene(ethoxyphosphonic acid) side arms, exhibit a remarkable and pronounced selectivity for Mg^{2+} over Ca^{2+} in aqueous solution, (5.6 and 1.1 log K units for **107**[144] and **108**,[141] respectively).[141,144,146] The selectivity of **107** may be related to the preference of Mg^{2+} for six-coordination and to the favorable binding interaction associated with the excellent donicity of the phosphorus-bound oxygen.[144] Properties of **108**[141,146] and its possible application as an indicator of intracellular Mg^{2+} and Zn^{2+} were presented earlier (see section II.A.1.d).

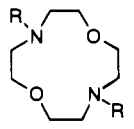
In the case of **324** which contains methylcarboxyl side arms, steric hindrance between the methyl groups of the side arms and ethylenediamine protons in the macrocyclic ring is responsible for greater selectivity of Mg^{2+} over Ca^{2+} in comparison with **86** which contains carboxyl side arms, log K_{Mg} − log K_{Ca} = 2.4 and 0.1, respectively, for **324** and **86**.[121] It was noted that the inductive effect of the side-arm alkyl group increases the electron density on the donor atoms of the macrocycle causing an increase of complex stability but the steric hindrance effect produced by the alkyl group decreases complex stability.[104,105] These two effects are delicately balanced, and it is difficult to predict what the overall influence on complex stability will be.[104,105,338]

Among the series of amide and amide ester *N*-functionalized macrocycles based on 12-, 15-, and

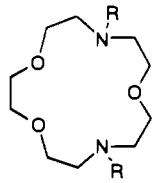
18-membered polyazaoxa rings, **325**–**331**, a strong complexation of Ca^{2+} in aqueous solution was observed with high selectivities (*ca.* 10^2 to $10^{3.5}$) over Na^+ and K^+.[54,55] Even higher selectivities of Ca^{2+} over Na^+ due to the polarity of the amide carbonyl groups was found in **55** and **56** ($>10^4$ and $>10^5$, respectively).[101] These systems illustrate how selectivities of macrocycles for cations can be enhanced by varying the side arms.



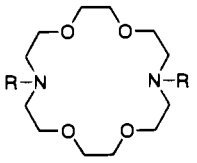
324 ($N_3$9C3-7, I)
R = $CH(CH_3)CO_2H$



325 ($N_2$12C4-3, III)
R = $CH_2CONHCH_3$
326 ($N_2$12C4-4, III)
R = $CH_2CON(CH_3)_2$
327 ($N_2$12C4-5, III)
R = $CH_2CONHCH_2CO_2C_2H_5$

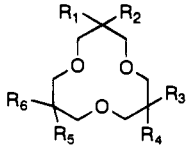


328 ($N_2$15C5-8, X)
R = $CH_2C(O)NHCH_3$
329 ($N_2$15C5-10, X)
R = $CH_2C(O)NHCH_2CO_2C_2H_5$



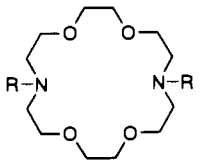
330 ($N_2$18C6-17, XXIV)
R = $CH_2C(O)NHCH_3$
331 ($N_2$18C6-18, XXIV)
R = $CH_2C(O)NHCH_2CO_2C_2H_5$

A very interesting selectivity pattern is displayed by a series of alkyl and alkyloxy side-armed macrocycles, **333**–**338**, having ether oxygen separated by propylene units.[339] These macrocycles showed a selectivity for the small Li^+ ion, not only against the larger Na^+ (2–3 log K units) and Ca^{2+} ions, but also against the small Mg^{2+} ion, e.g., log K (CD_3CN/CD_3OD, 95:5) = 1.6 for the interaction of **336** with Li^+, negligible with Na^+ and Mg^{2+}, and no significant shift displacement with Ca^{2+}.[339] The unsubstituted macrocycle **332** does not have these properties; it forms a 2:1 sandwich complex with Na^+ (log K = 3.2) whose stability approaches that of its 1:1 complex with Li^+ (log K = 3.5).[339]



332 (12C3-1, II)
R_1, R_2, R_3, R_4, R_5, R_6 = H
333 (12C3-2, II)
R_1, R_2 = CH_3
R_3, R_4, R_5, R_6 = H
334 (12C3-3, II)
R_1 = CH_3; R_2 = CH_2OCH_3
R_3, R_4, R_5, R_6 = H
335 (12C3-4, II)
R_1, R_2, R_3 R_4, R_5, R_6 = CH_3
336 (12C3-5, II)
R_1 = CH_2OCH_3
R_2, R_3, R_4, R_5, R_6 = CH_3
337 (12C3-8, II) (cis)
R_1, R_2 = H
R_3, R_6 = CH_2OCH_3
R_4, R_5 = CH_3
336 (12C3-7, II) (trans)
R_1, R_4, R_5 = CH_3
R_2, R_3, R_6 = CH_2OCH_3

The larger macrocycle, **80** with malonate side arms, displayed unusually high Sr^{2+}/Ca^{2+} and Pb^{2+}/Zn^{2+} selectivities of 2.25 and 6.75 log K (H_2O) units, respectively.[108] This high selectivity for the larger size metal ions cannot be explained exclusively by a better "size-match" fit in these systems. Larger metal ions can coordinate more carboxyl oxygens on average owing to their higher coordination number. The interaction with more donor atoms may result in larger stability constants and lead to higher selectivities for large metal ions over smaller ones.[108] The analogous macrocycle **339** with acetate side arms, exhibited Ca^{2+}/Sr^{2+} and Pb^{2+}/Zn^{2+} selectivities of 0.1 and 5.13 log K (H_2O) units, respectively.[108]



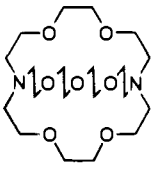
339 ($N_2$18C6-8, XXIV)
R = CH_2CO_2H

Arrangement of side arms and donor atoms may alter selectivity patterns. Two structural isomers, the EDTA derivative (**93**) and the DTPA derivative (**94**), display different selectivities toward Gd^{3+} and Zn^{2+}. The complexes of the EDTA derivative with Gd^{3+} and Zn^{2+} have log K values of 15.14 and 9.03, respectively. The Gd^{3+} and Zn^{2+} complexes with the DTPA derivative have log K values of 11.15 and 12.08, respectively. **93** exerts by far the highest selectivity for Gd^{3+} over Zn^{2+} (6.11 log K units) among known polyamino polycarboxylates; **94**, on the other hand, is selective for Zn^{2+} over Gd^{3+} (0.94 log K units).[123] The large difference in selectivity of **93** compared to **94** is due first to the mutual repulsion of the crowded negative carboxylate groups which are bound to Gd^{3+} in **94**. This results in a log K value which is lower in the case of the Gd^{3+}–**94** complex than in the **93** complex. Second, in **93**, the isolated amine nitrogen located between the two amide groups does not bind to Zn^{2+}, thus lowering the log K value for the formation of the Zn^{2+} complex compared to that for formation of the Zn^{2+}–**94** complex.[123] These systems are good examples of ligand structural discrimination in metal complex formation.[123]

7. Chelate Ring Size

Chelate ring size rather than size-match selectivity may, in some cases, control both stabilities of complex formation and selectivities of ligands for metal ions. Hancock and Luckay examined complexation of Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+} with the ligands [12]aneN_4 through [15]aneN_4 and found that the overall stability patterns of these macrocycles do not accord with the idea of a size-match phenomenon but, in general, the selectivity is controlled by the size of the chelate ring. For example, log K (H_2O) = 14.0, 17.90, and 20.0 for the interaction of the small low-spin Ni^{2+} with **39**, **48**, and **49**, respectively, even though evaluation of crystallographic data shows that this cation would fit best from the bond length view into **48** rather than **49**.[91] On the other hand, log K (H_2O) values of 13.48, 10.83, 10.12, and 9.29 are for the interaction of the large Pb^{2+} with **48**, **49**, **50**, and **51**, respectively.[91] The series of these tetraazamacrocycles form three 5-membered chelate rings plus one chelate ring which varies monotonically in size from 5- (**39**) to 8- (**50**) membered. The results obtained by several different scientific groups indicate that 6-membered chelate rings prefer small metal ions, whereas large metal ions are preferred by 5-membered chelate rings.[22,91,109,118,127]

Propylene-containing cryptands **143** and **144** with much reduced rigidities in comparison with **8** and **340** should have decreased size selectivity for cations. It is interesting that both **8** and **340** exhibit selectivity for Ba^{2+} over Sr^{2+}, log K (H_2O) = 9.7 and 8.26 for the interaction of **8** with Ba^{2+} and Sr^{2+}, respectively, and log K (H_2O) = 6.0 and 3.4 for the interaction of **340** with the same cations, respectively,[2] while ligand **144** shows the reverse selectivity for Sr^{2+} over Ba^{2+}, log K (H_2O) = 3.62 and 3.13, respectively.[197] The introduction of two additional methylene units into **8** and **340** to form **143** and **144**, respectively, makes two of the N−M^+−O chelating rings 6-membered which favors smaller cations. In the case of the **144** complexes, both Ba^{2+} and Sr^{2+} are expected to be much smaller than the cavity; hence, the effect of chelating ring size becomes more important.[197] In the case of complexes with **143**, log K (H_2O) = 4.40 and 2.0 for Ba^{2+} and Sr^{2+}, respectively. The size of Ba^{2+} may not be much smaller than that of the ligand cavity; hence, size selectivity may still be an important effect.[197]



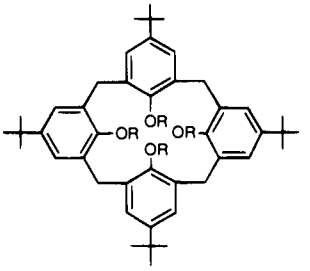
340 ([3.2.2]-1, XLVIII)

8. Properties of the Solvent Used

Properties of the solvent used, as reconfirmed by recent studies, can significantly influence macrocycle selectivity and complex stability.[35,44,67,173–176,181,186,340–347] There is an inverse relationship between the stabilities of complexes and the Gutmann donicity of the solvents,[44,340] e.g., the stabilities of all 1:1 complexes of alkali metal ions with **189** decrease in the order 1,2-dichloroethane > nitromethane > acetonitrile > acetone > dimethylformamide (log K = 5.96, 5.37, 4.63, 4.39, and 3.13 for the interaction of **189** with K^+, respectively).[340] In solvents with lower donicity, cation desolvation is less pronounced and the enhancement of stability, in general, is primarily an enthalpic effect, while the reaction entropies oppose the stability enhancement. Thus, the maximum stability for a given metal ion complex results from a balance between the binding and solvation energies.[340]

In methanol (where cation desolvation is less pronounced), the stability constants for metal ion complex formation with the novel diamide crown ethers, **325** and **326**, were 10^2 to 10^3 ($10^{6.5}$ for Ca^{2+} in the **325** complex) times higher than those in water with modest selectivity for Li^+ over Na^+ and good selectivity of Ca^{2+} over Na^+ and K^+, e.g., for the interaction of **326** with these cations log K = 5.38 (Li^+), 4.72 (Na^+), 3.85 (K^+), and 7.68 (Ca^{2+}).[55] In water, both complex stability and selectivity, especially for the more charge dense ions, were reduced; there was no discrimination for Na^+ over K^+, but good selectivity of Ca^{2+} over Na^+ and K^+ was maintained (e.g., log K = 2.55, 2.60, and 5.11 for the interaction of **326** with Na^+, K^+, and Ca^{2+}, respectively).[55] Calorimetric studies confirmed that the enthalpic effect is dominant in formation of the above complexes in methanol.[55]

The stabilities of calixarene complexes with alkali metal ions range between 2 and 5 log K units in methanol and between 2 and 6.5 log K units in acetonitrile, e.g., for the **341** log K (CH_3OH) = 2.6 (Li^+), 5.0 (Na^+), 2.4 (K^+), 3.1 (Rb^+), and 2.7 (Cs^+) and log K (CH_3CN) = 6.4 (Li^+), 5.8 (Na^+), 4.5 (K^+), 1.9 (Rb^+), and 2.8 (Cs^+).[231] The increased stabilities, from methanol to acetonitrile, are larger for Li^+ than for the other alkali metal ions. This larger stability for Li^+ complexes may be due to another specific solvent effect rather than an intrinsic property of the receptors.[231] Calorimetric studies suggest that acetonitrile enters the hydrophobic cavity of calixarenes producing a synergistic effect which preorganizes this cavity allowing it to interact more effectively with metal ions.[348]



341 (Calix4-16C-18, XI)
R = $CH_2CO_2C_2H_5$

Lada and co-workers examined complexation of **5** with Tl^+ in a variety of solvents.[44–46] The results show that in aprotic organic solvents Tl^+ ion solvation plays the predominant role in complex formation, while the influence of ligand−solvent interaction upon complexation of Tl^+ is negligible.[44] In mixtures of aprotic organic solvents with water the magnitude of the stability constants of the Tl^+−**5** complexes depend on the nature of the pure organic solvents which form the mixtures.[46] In alcohol−water mixtures, the stability constants decrease with increasing water content in all of the systems independent of the donor properties of the pure alcohols, e.g. log K = 5.2, 5.2, 4.8, 3.8, 3,3, and 2.8 for CH_3OH/H_2O mixtures where X(H_2O) = 0, 0.1, 0.2, 0.4, 0.6, and 0.7, respectively.[45] It appears that the alcohol effect is leveled in mixtures with water.[45]

C. Heat Capacities, ΔC_p

Since the 1991 review only four papers were found which reported heat capacity data. Morel and coworkers have studied cryptand−metal ion interactions and have reported ΔV and ΔC_p values.[349,350] Heat capacity changes are particularly sensitive to structural changes of cryptands in solution. Values of ΔC_p help in better understanding the nature of the solute−solvent interactions and the nature of the balance between the external effects and the internal modifications of the cryptand upon complexation. Recently, Morel and co-workers concluded from ΔS and ΔC_p values (−55 and 7 J K^{-1} mol^{-1}, respectively)

for the NH_4^+−**8** interaction in water that the hydrophobic character of the NH_4^+−**8** complex is more pronounced than that of the alkali-metal cryptates.[350] Values of ΔC_p have also been reported for complexes of **5** with K^+ ion[351] and for cyclophane-type macrocycles with a series of organic cations.[216] In the case of cyclophanes, the authors concluded that the magnitude of ΔC_p reflects a dependence on the solvent as well as on the electronic and structural properties of guests; ΔC_p tends to be greater in water than in chloroform and to be larger for methylated guests in water.[216]

III. Thermodynamics of Anion–Macrocycle Interaction

Anions play an important role in both chemical and biochemical processes and exploration of their abilities to form complexes with macrocyclic ligands can help to understand many phenomena, such as the role of anions in membrane transport and phase-transfer catalysis, the mechanism of ATP hydrolysis,[352] supramolecular catalysis,[353] the genetically engineered exchange of amino acids in a protein,[354] the interaction mechanisms of DNA with biologically important polyamines and histones,[355] and other reactions mediated by enzymes among which at least two-thirds are anions.[356] Molecular recognition of nucleobases and their derivatives has recently received much attention in the framework of biomimetic host–guest chemistry.[355] The design of organic receptor molecules capable of the selective molecular recognition of anion substrates is a subject of great theoretical and practical interest.[98] Thermodynamic data for the interaction of inorganic and organic anions with protonated macrocycles are presented in Table III of the supporting information.

A. Design of Compounds

Design criteria for ligands capable of anion binding should recognize that anion molecules are large, that they have various stoichiometries, and that they have pH chemistry. Common inorganic anions are spherical (F^-, Cl^-, Br^-, I^-), linear (N_3^-, SCN^-), trigonal planar (NO_3^-, CO_3^-, $^-RCO_2^-$), planar ($PdCl_4^{2-}$, $Pt(CN)_4^{2-}$), tetrahedral (PO_4^{3-}, SO_4^{2-}, ClO_4^-, MnO_4^-), and octahedral ($[Fe(CN)_6]^{4-}$, $[Co(CN)_6]^{3-}$, $PtCl_6^{2-}$).[357,358] Most anions exist in a limited pH range, e.g., above pH 5–6 for carboxylate,[358] above 7 for HCO_3^-,[358] pH between 2–10 for $H_2PO_4^-$ and HPO_4^{2-}.[359]

As was the case in the 1991 review, the majority of macrocyclic anion receptors consists of cyclic polyamines. In addition, there are monocyclic and polycyclic cyclophane-type macrocycles, calixarenes, and porphyrins. All of the macrocycles presented in the present review have ammonium binding sites. Ammonium cations are popular because their properties such as high water solubility, ability to form highly charged species at neutral pH, and the possibility of forming a hydrogen-bond network makes them suitable for anion coordination.[154] The macrocycles with protonated ammonium binding sites form stable and selective complexes with inorganic and organic anions mainly by attractive charge–charge interactions and hydrogen bonding,[17] although other effects such as macrocycle configuration and solvent influence may contribute to anion complexion.

1. Large Polyazacycloalkanes

Bianchi and García-España and co-workers have continued studies on the complexation of large polyazacycloalkanes with inorganic anions[88,357,360–362] and negatively charged functional groups (carboxylate and phosphate) on organic and biological substrates.[352,362,363] The results confirmed their previous observations[3] that complex anions such as $Fe(CN)_6^{4-}$ and $Co(CN)_6^{3-}$ form very stable second-sphere "supercomplexes" with larger than 18-membered polyazacycloalkanes, e.g., log K (H_2O) = 3.4 and 2.7, for the interaction of these respective anions with triprotonated **42**.[357,360] They have recently examined $Pt(CN)_4^{2-}$ and $PdCl_4^{2-}$ and found them to behave in a similar manner, e.g., log K (H_2O) = 3.83 for the interaction of $Pt(CN)_4^{2-}$ with nonaprotonated **45**, and ΔH (H_2O) = −16.32 kJ mol^{-1} for the interaction of $PdCl_4^{2-}$ with decaprotonated **45**.[88,357,361] These investigators and Kimura have also measured log K values for supercomplex formation of $Fe(CN)_6^{4-}$ (refs 164 and 352), $Fe(CN)_6^{3-}$ (ref 164), and $PdCl_4^{2-}$ (ref 88) with 18-membered **41**, e.g., log K (H_2O) = 3.72 and 2.92 for the interaction of $Fe(CN)_6^{4-}$ and $Fe(CN)_6^{3-}$, respectively, with triprotonated **41**, and ΔH (H_2O) = −6.28 kJ mol^{-1} for the interaction of $PdCl_4^{2-}$ with hexaprotonated **41**. Cation–anion electrostatic interaction appears to be the main driving force which regulates the stability order of supercomplexes with di-, tri-, and tetracharged anions, $Pt(CN)_4^{2-} < Co(CN)_6^{3-} < Fe(CN)_6^{4-}$, e.g., log K (H_2O) = 2.56, 2.7, and 3.4, respectively, for the interaction with triprotonated **42**, as well as differently charged protonated receptors, e.g. log K (H_2O) = 3.07, 3.5, and 5.1, for the interaction of these anions, respectively, with tetraprotonated **42**.[357,360] In addition, the electrostatic interaction seems to regulate the stoichiometry of the complexes because 1:2 (ligand/anion) have been observed for low-charged anions ($PdCl_4^{2-}$, $PtCl_6^{2-}$), and 1:1 for highly charged ones.[357] Extensive hydrogen bonding between anion and receptor and enthalpic contribution (in the case of $PdCl_4^{2-}$) enhanced the stabilities of the supercomplexes.[88,357,361] Moreover, it was found that optimal electrostatic and hydrogen-bonding interactions between the receptor and the anion and even the mutual dimensions of the receptor's cavity and the anions are not decisive in the formation of inclusion complexes. To achieve an inclusion coordination, both dimensions and conformation of the receptor as well as the geometry of the anion and an adequate mutual disposition appear to be required.[357] This goal was apparently achieved in the case of the inclusion complex of **45** with $PdCl_4^{2-}$.[88] Crystal structure of the complex showed that the planar $PdCl_4^{2-}$ anion (with diameter of 4.3 Å)[357] was included perpendicularly to the direction of main elongation of the macrocyclic cavity; the macrocyclic cavity, with approximate dimensions of 9 × 11 Å, was formed by an S-shaped macrocycle conformation.[88]

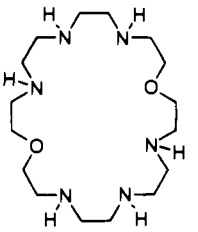
Another interesting behavior of $PdCl_4^{2-}$ was that the anion was able, as a function of pH, to interact with large polyazacycloalkanes providing either covalent or noncovalent interactions. In acidic solu-

tions, supercomplexes were formed because macrocyclic nitrogens did not compete with the chloride anions, while in basic solutions the macrocyclic nitrogens removed, at least partially, the chloride anions from the first coordination sphere and interacted directly with the Pd^{2+} ions.[88]

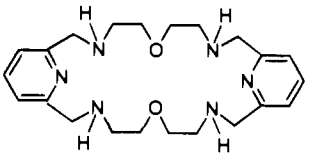
Large polyazacycloalkanes, like all cyclic polyamines, can be highly or even fully protonated in the neutral pH range becoming the best ligands for biologically important carboxylate and phosphate anions because the formation of these anions occurs in this pH region. Recently, a series of these macrocycles, ranging in size from 18- to 36-membered, were examined as potential ATPase mimics.[352,362] All of these macrocycles catalyzed the hydrolysis of ATP, with **42** being the best catalyst. The catalytic behavior correlated well with macrocycle ring size. Stability constants for the complexes formed between the phosphate species and polycycloalkanes increase with increasing degree of macrocycle protonation and decreasing macrocycle ring size and are higher than for noncyclic analogues, e.g., $\log K(H_2O) = 7.28, 6.93, 6.09, 4.83, 4.02$, and 3.53 for the interaction of ATP^{4-} with the pentaprotonated **42**, **43**, **44**, **45**, **46**, and **47**, respectively, and $\log K(H_2O) = 10.52, 9.79, 9.03, 7.82, 6.39$, and 4.16 for the interaction of ATP^{4-} with the hexaprotonated forms of the above ligands, respectively.[362] The sequence of stability constants was $PO_4^{3-} > P_2O_7^{4-} > ATP^{4-} > ADP^{3-} > AMP^{2-}$ for a given degree of protonation, e.g., $\log K(H_2O) = 10.81, 9.29, 7.28, 5.31$, and 4.99, respectively, for pentaprotonated **42**.[362] In the case of tricarboxylate anions, in addition to electrostatic factors, remarkable influences of size and shape complementarity between these anions and **42** on selectivity and complex stability were observed. For example, $\log K(H_2O) = 3.4$ and 2.5 for the interaction of *cis,cis*- and *cis,trans*-forms of the cyclohexane-1,3,5-trimethyl-1,3,5-tricarboxylate, respectively, with triprotonated **42**.[363]

2. Oxygen–Nitrogen Mixed-Donor Atom Macrocycles

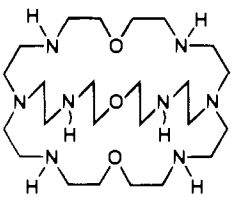
The oxygen–nitrogen mixed-donor atom macrocycle **342**, apart from its ability to form dinuclear metal complexes, has been one of the most studied macrocycles in the coordination of polyphosphates and more complex nucleotides and has been found to exhibit both ATPase and kinase activity.[362] Recent work has showed that **342** binds SO_4^{2-},[184] aspartate and serine ions,[364] malonate ion, acetohydroxamate ion, and simple phosphate ions,[359] e.g., $\log K(H_2O) = 3.68, 2.49, 3.14, 3.70, 7.60$, and 2.6 ($HPO_4^{2-}$), respectively, with pentaprotonated **342**. Other oxygen–nitrogen mixed-donor atom macrocycles such as **343** and **344** were examined for Fe^{2+} and SO_4^{2-} binding.[184] The triprotonated species of these two ligands complex SO_4^{2-} with $\log K(H_2O) = 1.2$ and 2.25, respectively.[184] SO_4^{2-} and SeO_4^{2-} ions are bound by **345** in which high charge density was achieved by organizing ammonium sites with propylene and pyridine spacers, $\log K(H_2O) = 1.5$ and 1.4, respectively, for the triprotonated ligand.[98] Rigidity was introduced by the pyridine groups and the elevated pK values resulting from use of the propylene spacers insure full protonation of the ligand in the low pH range 1–3.[98] Main driving forces in the formation of the above complexes, as in the case of other macrocyclic polyamines, are electrostatic and hydrogen-bonding interactions between receptors and anions.[98,359,364]



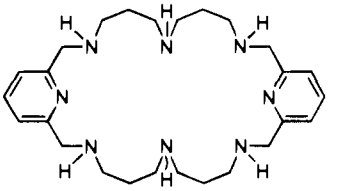
342 ($N_6$24C8-1, XXXII)



343 ($Py_2N_4$24C8-1, XXXII)



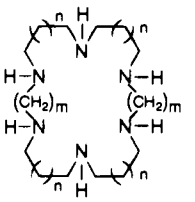
344 (N_8[3.3.3]-1, XLIX)



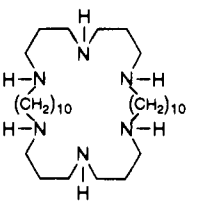
345 ($Py_2N_6$28C8-1, XXXV)

3. Ditopic Macrocyclic Polyamines

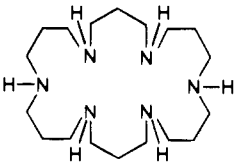
Ditopic macrocyclic polyamines containing two triamine units, such as **346**–**348**, which were designed as receptors for dianions, formed supercomplexes with $Fe(CN)_6^{4-}$, $Fe(CN)_6^{3-}$, and $Co(CN)_6^{3-}$ in aqueous solutions as well.[17,365] Since the $\log K$ values for the reaction of $Co(CN)_6^{3-}$ with equally protonated, **346**–**349**, are 3.9, 5.4, ~5.3, and 3.5, respectively, the authors concluded that the size of the macrocyclic ring as well as electrostatic and hydrogen-bonding factors influence the stability of those complexes.[365]



346 ($N_6$32C6-1, XXXVIII) m = 9; n = 0
347 ($N_6$32C8-2, XXXVIII) m = 7; n = 1



348 ($N_6$38C6-1, XLI)

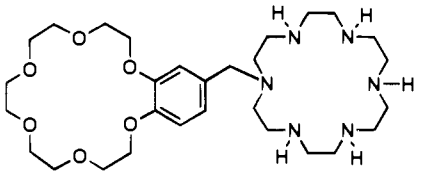


349 ($N_6$24C6-1, XXXI)

4. Biscrowns

$\log K$ values for complex formation of biscrowns, such as **125**, **126**, and **350**, with metal cations as well as with HPO_4^{2-} and ATP^{4-} are included in Table I and Table III (supporting information), respectively.[164] For example, $\log K(H_2O) = 2.48$ and 4.19 for the interaction of triprotonated **126** (B15C5)(N_6-18C6)-2 with HPO_4^{2-} and ATP^{4-}, respectively.[164] These biscrowns contain both cationic (benzocrown

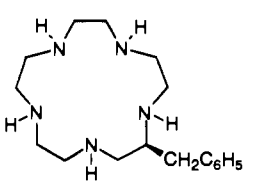
unit) and anionic (protonated azacrown unit) recognition sites and were synthesized as receptors for zwitterions (catecholamine, amino acids, etc). They bind zwitterionic molecules, e.g., log K (H_2O, pH 7) = 1.85 for the interaction of **125** with $^+H_3N(CH_2)_3COO^-$, although neither $N_6$18C6 azacrown alone nor benzocrown alone interacts with amino acids in solutions of neutral pH.[164] The most reasonable explanation of the observed phenomenon is that a cooperative action of both units makes these biscrowns ditopic receptors for zwitterions.[164]



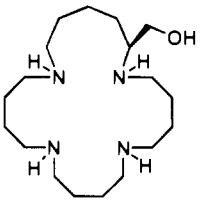
350 [(B18C6)($N_6$18C6)-1, XLIV]

5. Small Azamacrocycles

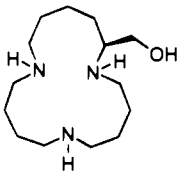
Smaller protonated azamacrocycles interact with simple as well as more complex inorganic and organic anions. Complexation properties of tri- and tetraprotonated **50** with SO_4^{2-}, Cl^-, NO_3^-, and IO_3^- were explained as "based principally on the solvation state of the polyamine and hydrogen bonding capabilities of the anions. The polyamine solvation structure depends, in turn, on the extent of protonation, the number of protonated and unprotonated sites, and the extent of internal stabilization of protonated nitrogen sites".[366] The results obtained in water for the complexation of the small highly branched hexaprotonated **116** with ATP^{4-}, $Fe(CN)_6^{4-}$, $Co(CN)_6^{3-}$, and $P_2O_7^{4-}$ (log K = 5.71, 4.73, 2.78, and 6.41, respectively)[154] were compared with those for the interaction of the related hexaprotonated polyazacycloalkane **43** (log K = 9.79, 7.1, 3.9, and 11.56, respectively)[154,360] and discussed in terms of the different ligand topologies.[154] The results for the complexation in water of the triprotonated **40** with Cl^-, NO_3^-, IO_3^-, SO_4^{2-}, oxalate ion, and squarate ion (log K = 0.05, −0.05, 1.12, 1.51, 1.53, and 1.26, respectively) were discussed in terms of internal hydrogen bonding and solvation effects.[367] The first reported optically active 15-membered macrocyclic polyamine **351** which was synthesized from L-phenylalanine, appeared not to have chiral recognition ability toward L- and D-tartrate anions at neutral pH, which is probably due to lack of sufficient steric bulkiness.[164] Between two newly synthesized macrocycles, tetraaza **352** binds ATP^{4-} 35 times stronger than triaza **353**.[368] Both of these macrocycles have a CH_2OH arm attached to the methylene carbon. The weaker binding by triaza **353** is probably due to partial protonation of the ligand at the reaction pH and its not-so-well-defined stoichiometry with multiple species formation.[368] On the other hand, the tetraprotonated **352** forms a definite 1:1 complex and a sum of charge−charge interactions between this ligand and tetraanion ATP^{4-} can be also a factor of stronger binding.[368]



351 ($N_5$15C5-3, X)



352 ($N_4$21C4-1, XXIX)

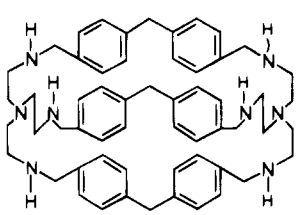


353 ($N_3$16C3-1, XIV)

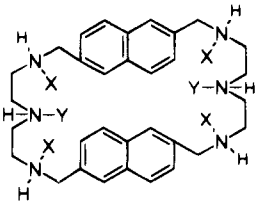
6. Monocyclic and Bicyclic Cyclophane-type Macrocycles

Monocyclic and bicyclic cyclophane-type macrocycles, synthesized by Lehn and co-workers, in their protonated form complex dicarboxylate ions in water.[369−371] In these complexes, the matching of the shape and size of the macrocycle cavity to the shape of the anion is important for optimum complex stability. Macrobicyclic **354**, which has an ellipsoidal shape, binds dicarboxylate ions with linear recognition, e.g., for the interaction with $^-OOC(CH_2)_nCOO^-$ ions, log K (D_2O, pH 6) = 3.15, 3.36, 3.41, 3.32, 3.28, and 3.15 for n = 2, 3, 4, 5, 6, and 7, respectively.[371] This ligand was found to form a very stable complex with terephthalate dianion, log K (D_2O, pH 6) = 4.78.[371] Monocyclic **355** and bicyclic **356**−**359** are bisintercaland type receptors and bind strongly and selectively planar (flat) anionic substrates such as aromatic dicarboxylates and nucleotides, e.g. log K (H_2O) = 4.3 (pH 6) and 4.08 (pH 7.8) for the interaction of AMP^{2-} with **355** and **356**, respectively.[369,370] Incorporation of two intercalator units into these macrocycle rings resulted in multifunctional receptors which exhibit molecular recognition toward anionic substrates based on both stacking (hydrophobic) and electrostatic effects.[369,370] The same binding properties toward nucleotides and aromatic monocarboxylates are exhibited by cyclophane **360** which binds, for example, AMP^{2-} with log K (H_2O) = 3.28.[353−355] A new cyclophane-type macrocycle **174** complexes both metal cations and in the protonated form anions such as $P_2O_7^{4-}$ and ATP^{4-}, e.g., triprotonated form of the ligand binds the above anions with log K (H_2O) of 3.32 and 2.58, respectively.[218] An interesting set of cyclophane-type macrocycles are photoresponsive isomers **361** and **362** which change their cavity shapes in response to photoinduced *cis*−*trans* isomerization of the two azobenzene moieties.[265] This macrocycle binds strongly $^-OOC(CH_2)_nCOO^-$-type dicarboxylate ions (see also following paragraph III.B).[265]

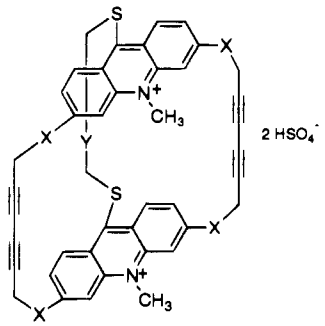
Table III (supporting information) contains thermodynamic data for the formation of complexes of other cyclophane-type macrocycles mostly with anionic fluorescent dyes but also with aromatic guests bearing sulfonate or carboxylate residues.[354,372−374] Among them are Murakami's cage-type cyclophanes, **363**−**366**, that exhibit size-sensitive and regioselective molecular recognition due to three-dimensionally extended hydrophobic cavities constructed with rigid



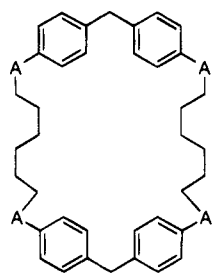
354 {(1,4-B)$_6$N$_6$[2.2.2)-1, XLVII}



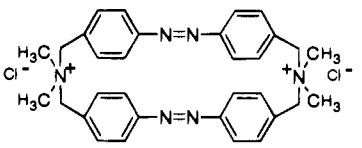
355 (Nap$_2$N$_6$30C6-2, XXXVI)
X = H; Y = lone pair
(tetraprotonated)



356 (Cyclophane-13, LIII)
X = O; Y = $(CH_2)_4$
357 (Cyclophane-14, LIII)
X = O; Y = CH_2OCH_2
358 (Cyclophane-15, LIII)
X = O; Y = $CH_2O(CH_2)_2OCH_2$
359 (Cyclophane-16, LIII)
X = NH; Y = CH_2OCH_2



360 ((1,4-B)$_4$N$_4$34C4-2, XXXIX)
A = $N(CH_3)_2^+Cl^-$

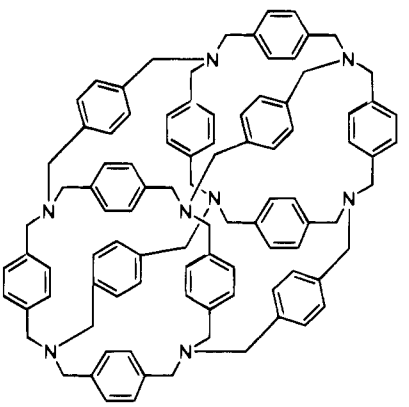


361 ((1,4-B)$_4$N$_6$26C6-1, XXXIII)
(cis)
362 ((1,4-B)$_4$N$_6$26C6-2, XXXIII)
(trans)

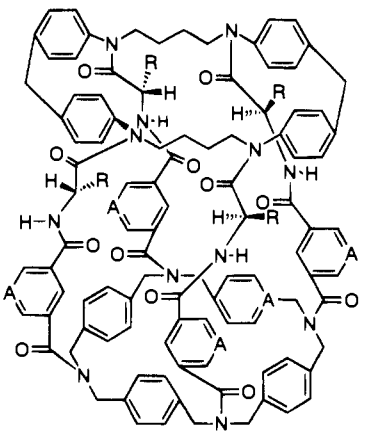
skeleton and chiral binding sites (except **363** which does not have chiral binding sites).[375–380] These cages are expected to be used as carriers in selective transport, artificial enzymes, and multifunctional receptor models capable of performing effective molecular discrimination in aqueous media and bilayer membranes.[376,378,381]

7. New "Expanded Porphyrins"

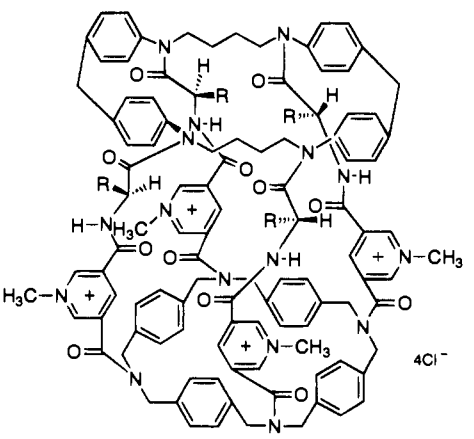
New "expanded porphyrins", e.g., sapphyrins and anthraphyrins, synthesized by Sessler and co-workers, have larger size and show some unexpected properties in comparison with well known porphyrins.[382] Protonated sapphyrins with core diameters about 5.5 Å and anthraphyrins with larger-than-sapphyrin core diameters unexpectedly bound anions.[383] On the other hand, protonated porphyrins with their approximately 4 Å diameter are too small for anion binding,[382] except for cationic, meso-substituted porphyrins which bind nucleotides.[384] The halide anion binding ability of the diprotonated sapphyrin **367** showed that sapphyrin acts as a selective receptor for fluoride over chloride and bromide ions both in methanol and dichloromethane, log K (CH_3OH) = 4.98, ~2, and <2, and log K (CH_2Cl_2) = >8, 7.26, and 6.18, respectively.[385] Anthraphyrin **368** binds chloride ion more effectively than fluoride ion, log K (CH_2Cl_2) = 5.30 and 4.15, respectively.[386] These results are consistent with a solution-state model in which a single fluoride ion is complexed within the plane of the sapphyrin core, whereas chloride and bromide ions are bound in an out-of-plane ion-pair-like fashion.[385] Crystallographic studies support an extension of this model to the solid



363 (Cyclophane-25, LIV)
(Kyuphane)



364 (Cyclophane-26, LV)
A = N; R = $CH(CH_3)_2$
(+)
365 (Cyclophane-27, LV)
A = NCH_3^+, Cl^-; R = $CH(CH_3)_2$
(+)

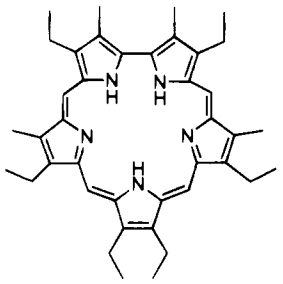


366 (Cyclophane-28, LV)
R = $CH(CH_3)_2$ (-)

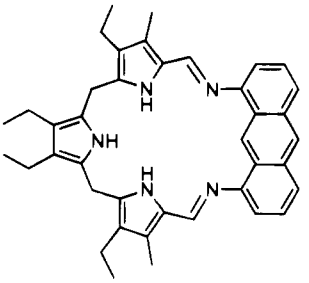
state of the above complexes; fluoride ion is bound in the plane of sapphyrin[382,385] and chloride ion is held 0.795 Å above the planar portion of anthraphyrin which corresponds with near-in-plane encapsulation.[383,386] The main driving force in these complexes is the formation of hydrogen bonds between anions and proton-bearing pyrrolic nitrogen atoms. Recent studies showed that sapphyrins also have complexing affinities for phosphate-type anions.[383]

8. Calixarenes

A few studies on anion binding by calixarenes have been made. It is known that calixarenes can be

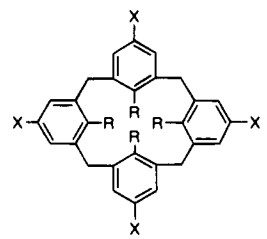


367 (Porphyrin-52, LXVI)
(Sapphyrin)

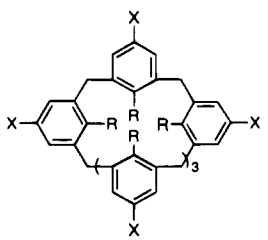


368 (Porphyrin-53, LXVII)
(Amthraphyrin)

selectively functionalized both at the phenolic groups (lower rim) and at the para positions of the phenol rings (upper rim).[387] Complexation of functionalized sulfonylated calix[4]arenes of both types, **370–372**, with several inorganic anions were examined in chloroform.[387] Surprisingly, in all cases a selectivity for HSO_4^- was observed with **372** showing the highest log K values for all anions (log K = 2.99, 2.56, 2.38, and <0 for the interaction of **370** with HSO_4^-, Cl^-, NO_3^-, and ClO_4^-, respectively; log K = 2.13, 1.86, 1.63, and <0 for the interaction of **371** with the above anions, respectively; and log K = 5.01, 3.10, 2.71, and <0 for the interaction of **372** with the same anions, respectively.[387] These high log K values for **372** may be due to the presence of four amide groups in addition to four sulfonamide moieties.[387] Calixarenes **369**, **373**, and **374** modified with amino acids at the upper rim become most hydrophobic at pH 5–6 and their selectivity in guest inclusion is significantly affected by medium pH.[388] The anionic dye, 1-anilino-8-naphthalenesulfonate, is bound at pH 2.5 with the aid of hydrophobic and electrostatic interactions, log K (H_2O, pH 2.5) = 3.39, 4.26, and 3.08 for **369**, **373**, and **374**, respectively, whereas it is only slightly bound at pH 10 because of electrostatic repulsion.[388] The opposite complexing phenomena were observed in the case of the cationic dye, [2-[5-(dimethylamino)-1-naphthalenesulfonamido]ethyl]trimethylammonium perchorate.[388]



369 (Calix4-16C-52, XII)
R = OCH_3;
X = CH_2S-$SCH_2CH(NH_2 \cdot HCl)CO_2H$
370 (Calix4-16C-57, XII)
R = $OCH_2CH_2OCH_3$; X = $SO_2NHC_3H_7$
371 (Calix4-16C-58, XII)
R = $OCH_2CH_2OCH_3$; X = $SO_2NH(t\text{-}C_4H_9)$
372 (Calix4-16C-59, XII)
R = $OCH_2CH_2OCH_3$
X = $SO_2NHCH_2CH_2NHC(O)CH_3$

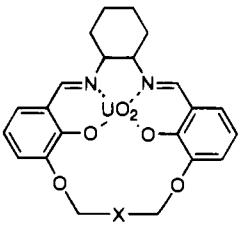


373 (Calix6-24C-9, XXXI)
R = OCH_3; X = $CH_2N(CH_3)_3^+ Cl^-$
374 (Calix6-24C-10, XXXI)
R = OCH_3; X = CH_2S-$SCH_2CH(NH_2 \cdot HCl)CO_2H$

B. Selectivities

As in the case of cations, selectivity of macrocycles toward anions is governed by many factors and usually several factors simultaneously are responsible for this property.

The main driving forces in anion–macrocycle interaction, as was mentioned earlier, are electrostatic and hydrogen-bonding effects. Accordingly, equally protonated large polyazacycloalkanes are more selective for the higher charged $Fe(CN)_6^{4-}$ than for the lower charged $Fe(CN)_6^{3-}$ but do not differentiate between $Fe(CN)_6^{3-}$ and $Co(CN)_6^{3-}$ which bear the same charge,[360] e.g., log K (H_2O) = 3.9, 4.2, and 6.4 for the interaction of hexaprotonated **349** with $Co(CN)_6^{3-}$, $Fe(CN)_6^{3-}$, and $Fe(CN)_6^{4-}$, respectively.[365,389] ATP^{4-} fails to interact with the tetrapositively charged macrocycle 1,1,4,4,7,7,10,10-octamethyltetraazacyclododecane, in which hydrogen bonding has been prevented by quaternization of the amine groups.[362] Hydrogen bond-induced selectivity is also observed in the case of **375** which, in dimethyl sulfoxide, shows selectivities of $>10^{2.5}$, $>10^{3.5}$, and $>10^5$ for $H_2PO_4^-$ over Cl^-, NO_2^-, and HSO_4^-, respectively.[390] The ^1H NMR spectrum indicates the $C(O)NH\cdots H_2PO_4$ hydrogen-bond interaction contributes to the overall anion complexation.[390]



375 (Metallohost-5, LXII)
X = $C(O)NHCH_2(CH_2OCH_2)_2CH_2NHC(O)$

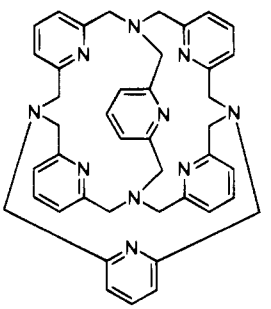
Structural factors such as shape and size can also enhance selectivity and sometimes override electrostatic interactions. Large polyazacycloalkane **42** interacts much more strongly with benzenetricarboxylate ions than with the more flexible citrate ion.[363] All of the stepwise stability constants for 1,2,3-benzenetricarboxylate ion are about 10^3 greater than those for the citrate ion although both of them have the same basicity, i.e., log K (H_2O) = 8.2 and 4.6, respectively, for the interaction of these anions, respectively, with the pentaprotonated form of the ligand.[363] This value represents one of the highest selectivities (>1000) reported up to now for the interaction of polycarboxylate ions with polyammonium ion receptors in water.[363] In the case of 1,2,3- and 1,3,5-benzenetricarboxylate ions, if electrostatic factors were the only ones controlling the interactions, the stability constant with triprotonated **42** would always be much higher for the 1,2,3-tricarboxylate ion. In fact, the difference in log K values is very small, log K (H_2O) = 3.2 and 3.1, respectively.[363] Molecular modeling studies showed that, in the case of 1,2,3-benzenetricarboxylate ion, an interaction would require a partial unfavorable folding of the receptor, while a very good structural complementarity was suggested for 1,3,5-benzenetricarboxylate ion and a triprotonated receptor.[363] These results provide examples of how the better structural fit of the 1,3,5-benzenetricarboxylate ion compensates for the higher charge density of the 1,2,3-benzenetricarboxylate ion.[363]

The significant influence of structural and/or electrostatic factors was observed in the interaction of anions with bis-intercaland-type **355** and **356–359** (see also section III.A).[369,370] The ligands were designed for flat organic anionic substrates such as

aromatic carboxylates and nucleotides. The macrocycle **355**, for example, favors terephthalate among the three benzenedicarboxylate isomers, *ortho*-, *meta*-, and terephthalate, log K (D_2O, pH 6) = 3.6, 5, and 5.2, respectively, which is due to significant complementarity resulting from both electrostatic and structural (stacking) effects.[370] The same selectivity factors control molecular recognition of **355** for nucleotides. The stabilities of these complexes increases with the number of negative charges (AMP^{2-} < ADP^{3-} < ATP^{4-}) as well as with the size (CMP^{2-} < UMP^{2-} < AMP^{2-} < GMP^{2-}) of the substrates.[370] However, in the cases of fumarate and maleate, **355** favors the first one over the second one indicating that structural effects dominate over electrostatic factors which would favor maleate, log K (D_2O, pH 6) = 4.4 and 3.5, respectively.[370] Structural factors also override electrostatic effects in the complexation of **356**–**359** with planar anionic substrates. The log K values are insensitive to the charge on the substrates but increase by factors of 10–100 in going from one to two or three rings, e.g., terephthalate ion < 2,6-naphthalenedicarboxylate ion < 2,6-anthraquinone disulfonate ion; log K (H_2O, pH 7.8) = 3.54, 4.25, and 5.60, respectively, for the interaction of these ions with **356**.[369] The increase of log K values corresponds to an increase in contact area between the substrates and intercalator (acridine) units.[369] The observed **357** selectivities for the 2,6-naphthalenedicarboxylate over the 1,8-naphthalenedicarboxylate isomer may be due to a better receptor–substrate fit, log K (H_2O, pH 7.8) = 4.25 and 3.80, respectively.[369]

Size-based selectivity plays a major role when macrocycles have limited conformational possibilities upon complexation. A good example among recently synthesized macrocycles is the highly symmetrical cage, **376**.[391] This cage with a cavity diameter of 3.8 Å forms an inclusion complex with Cl^- (ionic diameter of 3.34 Å), log K (CF_3COOD/D_2O, 1:1 v/v) = 0.92, but not with the larger Br^- or I^-, (ionic diameters of 3.8 (3.64)[392] and 4.4 Å, respectively).[391] Another cage, **363**, shows size-sensitive and also regioselective (operating through electrostatic interaction) molecular discrimination originating from the semirigid geometry of the hydrophobic cavity and specific protonation geometry.[378] "Expanded" porphyrins with their rigid structures represent one more example of size-based selectivity. One of them, **367** (5.5 Å cavity diameter) binds fluoride ion over chloride and bromide ions with an unusual selectivity of more than 1000-fold.[385] This high selectivity may be attributed to the fact that fluoride ion (ionic diameter of 2.38 Å) can be included within the porphyrin cavity, while the larger chloride and bromide ions (ionic diameters of 3.34 and 3.64, respectively)[392] cannot.[385] In turn, larger porphyrin **368** binds chloride ion 14 times more effectively than fluoride ion apparently because of a better size-based fit (for log K values see section III.A).[386]

The sulfonylated calix[4]arenes, **370**–**372**, show selectivity toward HSO_4^- over $H_2PO_4^-$, Cl^-, NO_3^-, and ClO_4^- in chloroform. Calixarene **372**, which forms the most stable complexes with all anions, exhibits for HSO_4^- a selectivity of about 10^2 over Cl^- and NO_3^- which is probably due to the fact that its



376 (Cyclophane-5, LI)

three-dimensional cavity has more optimal shape for accommodating the tetrahedral HSO_4^- than the spherical Cl^- or the planar NO_3^- (for log K values see section III.A).[387] Calixarenes **369**, **373**, and **374**, as described in the preceding section III.A, reveal pH-dependent selectivity toward organic anions and cations.[388]

Switchable mechanisms built into a macrocyclic ring can also be considered as a way to achieve a controlled selectivity. The cyclophane-type macrocycles **361** (*cis*-isomer) and **362** (*trans*-isomer) change their cavity shapes in response to a photoinduced *cis*–*trans* isomerization of the two azobenzene moieties. The *cis*-form of this macrocycle has an open cavity large enough to complex aliphatic anions possessing the general structure $^-OOC(CH_2)_nCOO^-$, while the *trans*-form with two azobenzene units close to each other is incapable of anion inclusion.[265] The driving forces for dicarboxylate binding are the electrostatic interactions between the two N^+ cations of the host and the two carboxylate groups of the guest and the hydrophobic effects between the *cis*-azobenzene units of the host and the $-(CH_2)_n-$ chain of the guest. In addition, the *cis*-form of the macrocycle can differentiate among dicarboxylate anions on the basis of size. The *cis*-form does not complex the anion with $n = 0$ and the stability sequence for the rest of the examined dicarboxylate ions is as follows: $n = 4 > n = 8 > n = 1$ (log K = 4.94, 4.01, and 3.90, respectively). According to CPK models of dicarboxylate ions with linearly extended $-(CH_2)_n-$ chains, the distance between the two COO^- charges is 3.6, 7.2, and 12.4 Å for anions with n = 1, 4, and 8, respectively, while the distance between two N^+ charges in the *cis*-macrocycle is 9.6 Å. Hence, the anion with $n = 4$ fits best the cavity of the receptor allowing the most effective electrostatic and hydrophobic interactions.[265]

C. Heat Capacities, ΔC_p

No heat capacity change data were found for macrocycle–anion interactions.

IV. Thermodynamics of Neutral Molecule–Macrocycle Interaction

Since the 1992 review,[4] about 100 new papers on neutral molecule–macrocycle interactions have been published. The motivation to study these interactions is understandable because of the function of neutral molecules in many chemical and biological processes.

A. Design of Compounds

Thermodynamic and kinetic studies provide a quantitative base for understanding the effect of

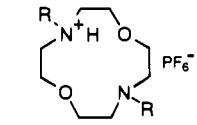
macrocycle and guest parameters on stabilities of the resulting complexes. In turn, this understanding can lead to the rational design of new macrocycles and to predictions of their effectiveness in forming complexes of desired stabilities with guest species. Table IV (supporting information) contains data for the interaction of crown ethers, cyclophane-type macrocycles, calixarenes, porphyrin derivatives, and others with various neutral molecules.

1. Crown Ethers

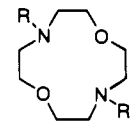
Crown ethers are known to form intramolecular charge-transfer complexes with neutral molecules. Recent thermodynamic studies have involved charge-transfer complexes formed by crown ethers and crown thioethers with π-electron acceptors such as tetracyanoethylene, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, chloranil, etc., and σ-electron acceptors such as iodine.[393-396] The presence of benzene groups in macrocyclic rings enhances the stability of resulting complexes which suggests that the aromatic groups play an important part as electron donors.[395] Introduction of a proton-accepting and phosphorus-containing group on the benzene ring contributes to crown ether multifunctionality in their complexation with neutral molecules.[397] Preliminary studies showed also that the presence of cyclohexane groups in macrocyclic rings can increase the donor ability of macrocyclic oxygens by increasing their basicity.[395] The stabilities of charge-transfer complexes depends on the properties of the solvents used. The stabilities of complexes formed by crown thiaethers with π-electron acceptors decrease as the dielectric constant (D) of the solvent increases.[393] On the other hand, according to Rady,[398] **49** forms 10.6 times stronger complexes with 2,4,6-trinitrophenol in chloroform (D = 4.7) than in carbon tetrachloride (D = 2.2).

Hydrogen bonding and dipolar interaction can also contribute to the stabilization of crown ether complexes with neutral molecules. Spencer and co-workers have undertaken calorimetric studies of the interaction of simple crown ethers with various neutral molecules.[71,399,400] The results of their investigation are interesting. They found that, in the case of *m*-cresol and dimethyltin chloride, a hydrogen bond attaches specifically to an individual oxygen atom in the macrocyclic rings and that there was no observable collective effect due to an increased number of oxygen atoms.[399,400] In contrast, a collective action of oxygen atoms in the ethers is responsible for binding malononitrile and acetonitrile via dipole–dipole and hydrogen-bonded interactions and perhaps increased conformational flexibility which comes with larger ring sizes.[71,400]

Stoddart and co-workers recently reported the complexation of alcohols by monoprotonated, disubstituted 1,7-diaza-12-crown-4 receptors, **377** and **378**. They found that **378** forms a 40 times more stable complex with methanol, log K (CD_2Cl_2) = 1.67, than that formed by its nonprotonated analogue **379**, log K (CD_2Cl_2) = 0.04.[401] Monoprotonated macrocycles provide an example of two-point binding. They can form simultaneously two N···H–O and N^+–H···O hydrogen bonds with a neutral ROH substrate because the lone electron pair on the neutral nitrogen atom acts as a good hydrogen-bond acceptor and the protonated nitrogen atom is a strong hydrogen-bond donor.[401]

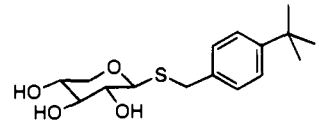


377 ($N_2$12C4-8, III) R = $CH_2C_6H_5$
378 ($N_2$12C4-9, III) R = $CH_2CH_2C_6H_5$

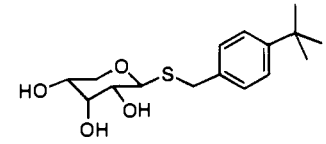


379 ($N_2$12C4-6, III) R = $CH_2CH_2C_6H_5$

New macrocycles, **28** and **30**, containing sulfoxide and phosphine oxide groups were prepared for complexation of ionic species and molecules with multiple hydrogen-bond donors.[80] Sulfoxide and phosphine oxide groups are very suitable for this purpose because they have large local dipoles and are strong hydrogen acceptors. Initial binding studies showed, however, that affinities of monosaccharide derivatives as multiple hydrogen-bond donors for **28** and **30** were relatively low, log K (CD_2Cl_2) = 1.48–1.60 for the interaction of both ligands with both, **380** and **381**.[80]



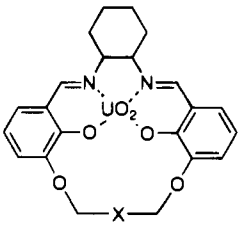
380 (guest-1, LXXVI)



381 (guest-2, LXXVI)

The search for effective hosts for neutral guests has resulted in the synthesis of hosts possessing "immobilized" electrophilic Lewis acid cation centers.[402-404] Metallohosts **375** and **382–386**, prepared by Reinhoudt and co-workers, have uranyl cation complexed in salen or salophene moieties and illustrate the concept of proton-assisted complexation of neutral polar molecules. These macrocycles can form strong and selective complexes with neutral molecules and also can serve as carriers of these molecules. In fact, **383–385** are, to the best of Reinhoudt and co-workers' knowledge, the first macrocycles to transfer urea across a membrane with efficiency of more than 95%. All possible binding sites of **383–385** are used for the interaction with urea that results in log K (CH_3CN) > 5 for all complexes formed.[403] Metallohost **385** binds selectively barbituric acid, log K ($CDCl_3$) = 2.73, and enhances its flux 3.7 times through a supported liquid membrane.[404] Boron-containing macrocycles, synthesized by Reetz and co-workers selectively complex amines by three-point binding as confirmed by crystallographic studies and NMR spectra.[402] The ^{11}B and ^{13}C NMR results indicate the existence of a dative B–N bond and formation of hydrogen bonds between the amine hydrogen atoms and the crown ethers.[402]

Allosteric effects have been displayed by the basket **256**, a novel macrocycle which possesses three potential binding sites such as a cleft and two crown



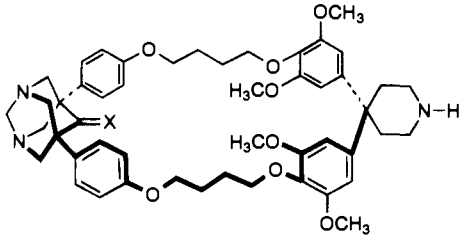
382 (Metallohost-1, LXII)
X = $(CH_2OCH_2)_3$
383 (Metallohost-2, LXII)
X = $(CH_2OCH_2)_4$
384 (Metallohost-3, LXII)
X = $(CH_2OCH_2)_5$
385 (Metallohost-4, LXII)
X = $(CH_2OCH_2)_6$
386 (Metallohost-6, LXII)
X = $(CH_2)_5C(O)NH$-(2,6-Py)-$NHC(O)(CH_2)_5$

ether rings.[309] The binding of one K^+ by this macrocycle significantly facilitated the coordination of a second K^+. Basket **256** can also bind 1,3-dinitrobenzene at the third site by $\pi-\pi$ interaction. However, it was observed that the **256** complex containing two K^+ ions binds 1,3-dinitrobenzene more strongly than does free **256** by a factor of 2–6, depending on the solvent used, log K ($CHCl_3/Me_2SO$, 9:1 v/v) = 0.86 and 0.08, respectively.[309]

2. Cyclophane-type Macrocycles

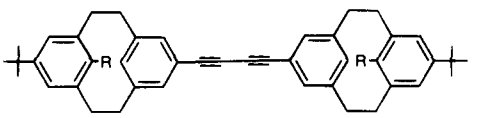
Cyclophane-type macrocycles represent another large group of ligands which form complexes not only with organic cations and anions but also with neutral molecules. They are represented by numerous macrocycles containing hydrophobic mono-, bi-, or polycyclic cavities with oxygen, nitrogen, sulfur, or mixed-donor atoms, and with a variety of functional groups.

Diederich and co-workers have synthesized the water-soluble cyclophanes, **387** and **388**, featuring carbonyl and hydroxyl residues, respectively, converging in a precise geometrical array into large apolar binding cavities.[405] Incorporation of 6-cyano-2-naphthol into such cavities causes the energetically unfavorable desolvation of these strongly solvated convergent groups, log K (CD_3OD/D_2O, 4:6 v/v) = 1.60 and <1 for **387** and **388**, respectively.[405] An analogous macrocycle **389**, which lacks a functional group, is a much better receptor for 6-cyano-2-naphthol, log K (CD_3OD/D_2O, 4:6 v/v) = 2.31.[405] On the basis of this observation, work is being pursued on receptors with convergent, precisely located intracavity catalytic residues.[405]



387 [(1,4-B)$_4$32C4-1, XXXVII]
X = O
388 ((1,4-B)$_4$32C4-2, XXXVII)
X = H, OH
389 ((1,4-B)$_4$32C4-3, XXXVII]
X = H_2

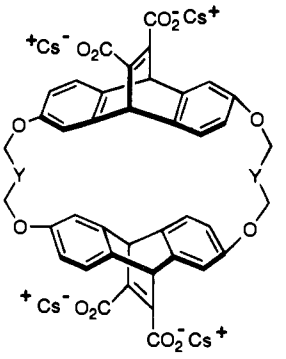
Carboxyl convergent groups have been used in cyclophanes to form molecular tweezers. These tweezers are the first to be constructed from two connected hydrocarbon cyclophanes.[406] The resulting host **390** binds strongly and selectively biologically important neutral molecules such as pyrimidine and purine bases by hydrogen bonds in a noncollapsible niche between the two convergent groups, e.g., log K (CH_2Cl_2) = 4.82, 4.61, and 4.15, for the interaction with 2,6-diaminopurine, adenine, and uracil, respectively.[406] It was suggested that the synthesis of other molecular tweezers of this type with various spacers, other functional groups, and with more than two convergent fixed functions would be worthwhile.[406]



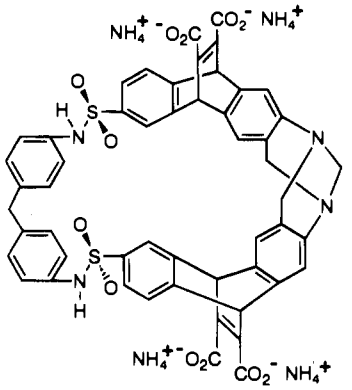
390 (Tweezer-1, XLIII)
R = CO_2H

Dougherty and co-workers designed a series of chiral macrocycles which incorporated two ethenoanthracene units connected by different functional groups.[215,216,407] Ethenoanthracene units provide a concave, rigid, hydrophobic surface for binding. The interactions of these macrocycles with numerous guests were studied to provide new insights into noncovalent binding interactions, especially cation-π interactions. The cation-π interaction is a description for the stabilizing force between a positive charge and the face of an aromatic ring.[215,407] The cation-π interaction is important in a variety of biological receptors, especially those that bind the prototypical neurotransmitter acetylcholine.[214] It is assumed that cation-π interactions play an important role in the complexation of organic cations are also possible in complexation of neutral molecules.[215] Nitro-substituted neutral guests[407] and azulenes are bound to the ethenoanthracene macrocycles due to hydrophobic effects and/or favorable donor–acceptor interactions.[215] In the case of nitro-substituted guests, a cation-π interaction with the formal positive charge on the N of the NO_2 is possible, and in the case of azulenes "it is tempting to ascribe the strong binding of these guests to a cation-π interaction, in which the 'cation' is the 7-membered ring of the azulene".[215] Azulenes are the most strongly bound neutral guests, e.g., log K (H_2O, pH 9) = 6.60 and 6.90 for the interaction of **391** with azulene and 1,2-azulenedicarboxaldehyde, respectively, and log K (CD_3CN) = 3.37 for the interaction of this ligand with 6-nitroquinoline.[215] Structurally related to the above macrocycles is chiral **392** which displays selectivity in the molecular recognition of steroids, alkanes, and alicyclic substrates in aqueous media.[408]

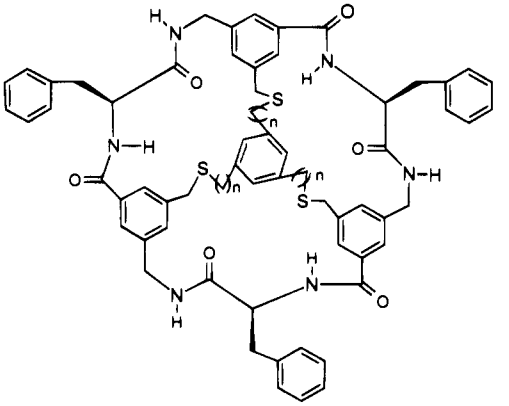
Several new polycyclic cyclophanes intended for peptide recognition were prepared by Still and coworkers.[409–411] These cyclophanes, **393–395**, bind peptides and glycosides with high selectivity for



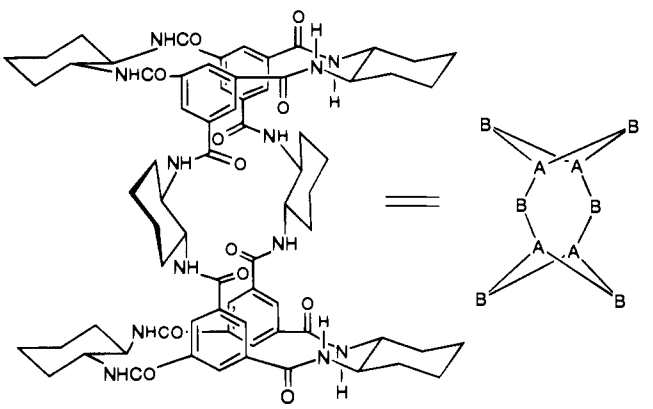
391 (Ethenoanthra-19, L)
Y = 1,4-C_6H_4 (*R, R, R, R*)



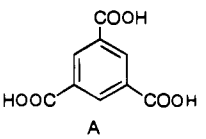
392 (Ethenoanthra-31, LI)



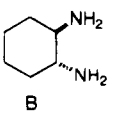
393 (Cyclophane-11, LIII)
n = 0
394 (Cyclophane-12, LIII)
n = 1



395 (Cyclophane-29, LV)



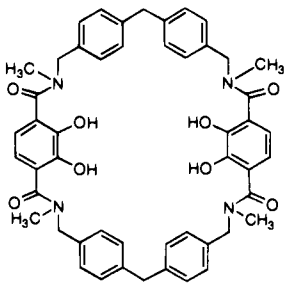
A



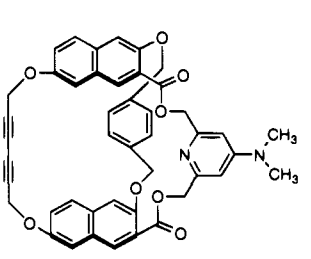
B

functionality and stereochemistry, e.g., log K ($CDCl_3$) = 2.20 and 1.10 or 2.57 and 3.23 for the interaction of **393** with Ac-L-Ala-O*t*Bu and Ac-D-Ala-O*t*Bu or 1-*O*-octyl-α-D-glucopyranoside and 1-*O*-octyl-β-D-glucopyranoside, respectively.[409,410] The key features of **393** and **394** which make them highly selective are deep binding cavities having entrances studded with appropriately positioned alternating hydrogen-bond donor and acceptor sites and lack of conformational flexibility in the case of **393**.[409] Cyclophane **395** is an example of a large synthetic receptor which has minimal structural complexity but its binding selectivities approach those of biological receptors.[411]

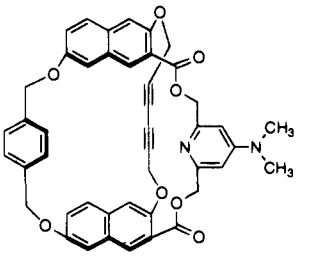
Table IV in the supporting information contains thermodynamic data for the interaction of neutral molecules with many other cyclophane-type macrocycles such as monocyclic bis(catechol)-containing cyclophane **396** tailored to be selective for piperazine and structurally related amines;[412,413] tris(catechol)-containing hexapus cyclophane **250** whose binding ability toward neutral molecules is enhanced after coordination of Fe^{3+};[373] cyclophanes having hydrophobic cavities of definite shape and size that form inclusion complexes with various charged and uncharged organic guests;[208,209] cage-type cyclophanes, **365** and **366**, providing hydrophobic cavities which exhibit chirality-based discrimination toward steroid hormones and are expected to be used as multifunctional receptor models;[414,415] cyclic dimers and tetramers which bind *p*-benzoquinone by means of hydrogen bonding and $\pi-\pi$ interactions;[416] and cyclophanes with concave functionality, **397** and **398**, which are remarkably "sticky" toward aromatic hydrogen-bond-donating guests such as phenols.[417]



396 $[K_4(1,4\text{-}B[6]N_4[38]C4\text{-}1, XLI)$

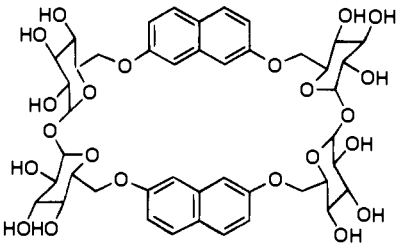


397 (Cyclophane-17, LIII)

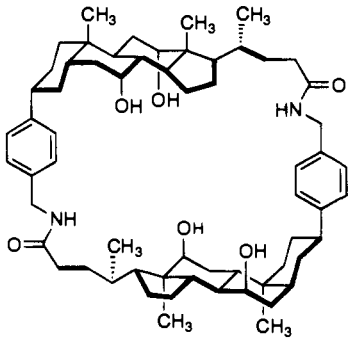


398 (Cyclophane-18, LIII)

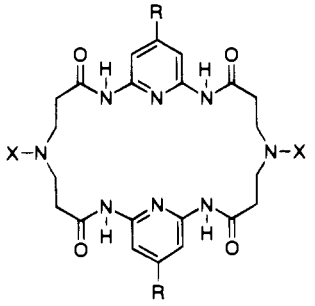
Table IV in the supporting information also has data for **399** considered as a cyclodextrin–cyclophane hybrid which displays affinity for electron-deficient aromatic guests;[418] **400** which is a diastereo- and enantioselective receptor for octyl glucoside;[419] and macrocyclic bis(diaminopyridines), **401–404**, prepared to bind a pyrimidine dimer by hydrogen bonding and to photosplit the bound dimer in a manner resembling enzyme-mediated photorepair of pyrimidine dimers in DNA.[420,421]



399 (Glycophane-1, LXI)



400 (Cholaphane-1, LXI)

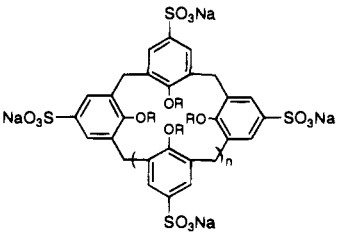


401 ($K_4Py_2N_6$24C8-1, XXXII)
R = H; X = Ts
402 ($K_4Py_2N_6$24C8-2, XXXII)
R = OC_2H_5; X = Ts
403 ($K_4Py_2N_6$24C8-3, XXXII)
R = H; X = $C(O)C_3H_7$
404 ($K_4Py_2N_6$24C8-4, XXXII)
R = H; X = $C(O)(CH_2)_3$-3-indole

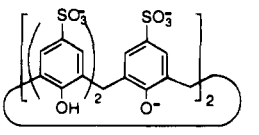
3. Calixarenes

Calixarenes, macrocyclic phenol–formaldehyde condensates, are receptors for small neutral molecules, although in the deprotonated form they become effective cation binders. CPK models and X-ray crystallographic studies reveal that calix[4]arenes have a rigid bowl-shaped structure with one side open and another side closed, while calix[6]arenes and calix[8]arenes constitute a cavity-shaped stoma and their ring is relatively flexible.[422] New studies on interactions, both in aqueous and organic media, between calixarenes and neutral molecules have been reported recently. Water-soluble calixarenes are most interesting because they are comparable with cyclodextrins as potential enzyme mimics.

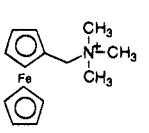
New water-soluble host calixarenes, bearing chiral substituents such as (*S*)-2-methylbutoxy groups, have been synthesized recently by Shinkai and co-workers.[422] These authors used CD spectral measurements to explore the interactions of the resulting calixarenes with aliphatic alcohols. The results lead to the conclusion that complexation does not induce conformational changes in rigid calix[4]arene, while in the case of calix[6]arene and calix[8]arene, e.g., **405** and **406**, guest inclusion rigidifies their rings through the conformational change from alternate to cone and guest inclusion occurs in an induced-fit manner.[422] Recently synthesized water-soluble calixarenes (**369**, **373**, and **374**), which are modified with amino acids at the upper rim, bind neutral guests such as pyrene at acidic and basic pH, e.g., log *K* (H_2O, pH 2.5) = 5.61 and log *K* (H_2O, pH 10) = 6.15 for **374**. In the case of charged guests, the selectivity displayed by these calixarenes is significantly affected by the medium pH (see section III.A).[388] Interaction of water-soluble **407** with cationic and uncharged ferrocene derivatives was examined by Gokel and Kaifer, log *K* (H_2O, pH ~7) = 4.04, 3.88, and 3.56 for **408–410**, respectively.[246] These authors concluded that nonelectrostatic interactions resulting from optimal steric fit, probably of the guest's ferrocene subunit into the calixarene cavity, provide most of the stabilization necessary for complex formation. Electrostatic interactions are of secondary importance.[246]



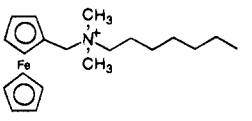
405 (Calix6-24C-16, XXXI)
n = 3; R = $CH_2CH(CH_3)C_2H_5$
406 (Calix8-32C-8, XXXVII)
n = 5; R = $CH_2CH(CH_3)C_2H_5$



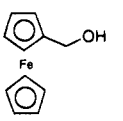
407 (Calix6-24C-20, XXX)



408 (cation-8, LXXIII)



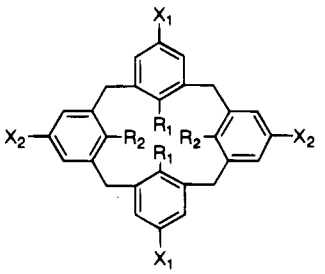
409 (cation-9, LXXII)



410 (guest-12, LXXVI)

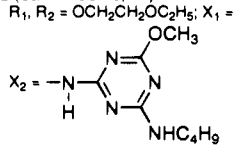
The interaction of calixarenes with neutral molecules in organic solvents involves competition between complexation and solvation of guests by solvent molecules. An important consequence of the interaction of calixarenes with amines is the generation of new species resulting from proton transfer from the calixarene molecule to the amine. Danil de Namor and co-workers have studied the complexation of larger calixarenes, **176** and **177**, with various amines in benzonitrile. These workers first reported electrochemical, thermodynamic, and structural data for the interaction of calixarenes with 1,10-diaza-18-crown-6 **134** and cryptand **8**, e.g., log *K* (C_6H_5CN) = 3.15 and 3.84, ΔH (C_6H_5CN) = −37.34 and −57.29 kJ mol^{-1}, and ΔS (C_6H_5CN) = −65.0 and −118.6 J K^{-1} mol^{-1} for the interaction with calixarene **177**, respectively.[423–425] In all of the cases, the process is enthalpy driven with a considerable loss of entropy

which may be partly due to the interaction of two components to give a single component (ion pair). The enthalpy change value for the interaction of **177** with cryptand **8** ($\Delta H = -57.29$ kJ mol^{-1}) is about twice that in the case of atropine ($\Delta H = -30.55$ kJ mol^{-1}) which suggests that cryptand **8** hosts in its cavity a proton from the calixarene.[423,424] New calixarenes, **411** and **412**, are examples of molecular receptors in which recognition of neutral molecules in chloroform takes place on the molecular platform formed by the selective functions on the upper rim rather than in the cavity.[426,427] Calixarene **412** has two diaminotriazine moieties at the upper rim which coordinate phenobarbital by six hydrogen bonds,[427] whereas calixarene **411** has two 2,6-diaminopyridine moieties for coordination of a flavin guest.[426] The molecular-recognition site of **411** is "closed" by intramolecular hydrogen bonds between two 2,6-diaminopyridine moieties. The binding of Na^+ to the metal-recognition site of this calixarene induces the rotation of the carbonyl groups, which disrupts the intramolecular hydrogen bonds and effectively opens the molecular recognition site making it accessible for coordination of the flavin guest.[426]

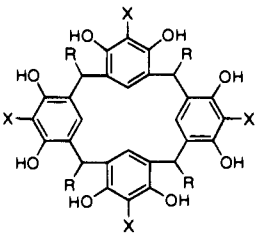


411 (Calix4-16C-46, XII)
$R_1 = OC_3H_7$
$R_2 = OCH_2C(O)NH(2,8\text{-Py})NHC(O)C_7H_{15}$
$X_1, X_2 = t\text{-}C_4H_9$

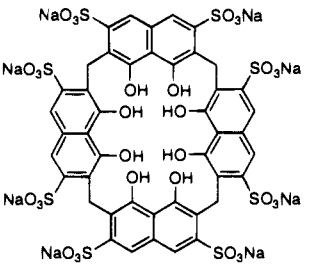
412 (Calix4-16C-60, XII)
$R_1, R_2 = OCH_2CH_2OC_2H_5$; $X_1 = H$



Resorcinol-containing cyclotetramers **413**–**418** and cyclotetrachromotropylene **419** consisting of four naphthalene units are preorganized, rigid species. Resorcinol-containing cyclotetramers have four independent binding sites composed of a pair of hydrogen-bonded OH groups on adjacent benzene rings. Aoyama and co-workers have studied complexation of these macrocycles with a variety of chiral and achiral guests such as di(poly)ols including steroids and sugars, monools and nucleotides.[428–431] They found an exceptional selectivity of achiral **414** toward some chiral guests. For example, methyl glucopyranoside, which is insoluble in chloroform and carbon tetrachloride, is solubilized in these solvents upon formation of a 2:1 (host/guest) sugar-encapsulated complex with **414**. Remarkable β/α anomer selectivity toward methyl glucopyranoside was detected by NMR and CD spectroscopy and competitve extraction but no log K values are given.[429] On the other hand, n-octyl glucopyranoside is soluble in chloroform and is bound to **414** to give a 1:4 (host/guest) complex with a low anomer selectivity, log K ($CHCl_3$) = 8.28 and 8.51 for n-octyl α-D-glucopyranoside and n-octyl β-D-glucopyranoside, respectively.[429] The selectivities were large enough to use this macrocycle as a novel, supramolecular probe for the assignment of stereochemistry of chiral guests.[428,429] They also postulated that CH-π interactions involving electron-rich benzene rings of the host as π-bases in cooperation with a network of multiple hydrogen bonds formed between host and guest are responsible for complexation in apolar organic media.[431] Their results suggest also that in water CH-π interactions are at least partially responsible for the complexation.[430] The same conclusion was reached by Poh and co-workers in the recent examination of cyclotetrachromotropylene (**419**) complexation with alcohols, sugars, and phenols in water.[432,433] The authors suggest that, in the cases of sugars and alcohols, the interaction between the aromatic π-bonds of the host and the C–H bonds of the guests is the major driving force in complex formation and the number of guest C–H bonds interacting with the host is a good measure of the hydrophobic interaction strength between the guest and the host.[433]



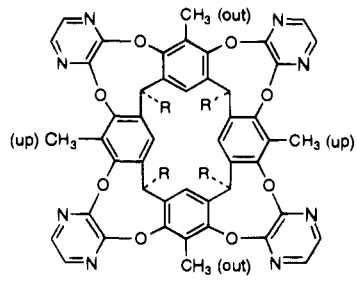
413 (Calix4-16C-64, XIII)
$R = CH_3$; $X = H$
414 (Calix4-16C-65, XIII)
$R = (CH_2)_{10}CH_3$; $X = H$
415 (Calix4-16C-66, XIII)
$R = (CH_2)_2SO_3Na$; $X = H$
416 (Calix4-16C-67, XIII)
$R = (CH_2)_2SO_3Na$; $X = CH_3$
417 (Calix4-16C-68, XIII)
$R = (CH_2)_2SO_3Na$; $X = OH$
418 (Calix4-16C-69, XIII)
$R = CH_3$; $X = N{=}N\text{-}(4\text{-}SO_3^-C_6H_4)$



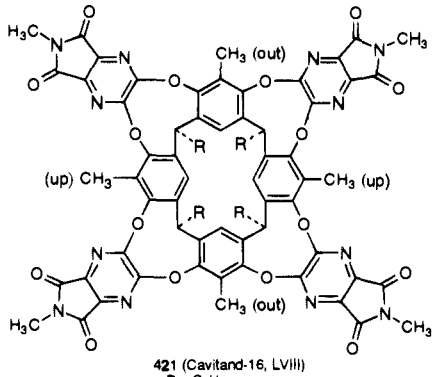
419 (Tetrachrom-1, LXI)

4. Cavitands and Carcerands

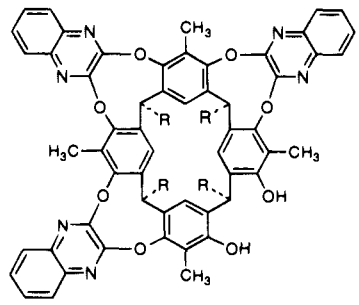
Cram, Dalcanale, and Soncini with co-workers have reported the synthesis of new members of this series.[434–437] Cavitands are organic compounds with large enforced concave surfaces of molecular dimensions.[437] Cram's "velcrands", e.g., **420**–**422**, which possess both host and guest character can form 4-fold, lock–key dimers named velcraplexes in organic solvents.[435,438] Solvophobic and entropic contributions are driving forces in this kind of coordination.[435] Cavitands **423** and **424**, prepared by Dalcanale and co-workers, selectively bind aromatic guests in organic solvents, e.g., log K (Me_2CO) = 1.82, 1.68, and 1.46 for the interaction of **424** with benzene, fluorobenzene, and chlorobenzene, respectively.[437] Shell closure of two cavitands created a large hemicarcerand which is a rigid hollow host. This molecule can be viewed as a globe, made up of bowl-shaped northern and southern hemispheres, with bridging groups as spacers spanning the equator so the interior space of the globe can be designed for a specific range of sizes and shapes of guests.[438] For example, **425** showed a sharp discontinuity based on the shape of the guest by complexation of p-xylene, but not o-xylene and m-xylene.[434]



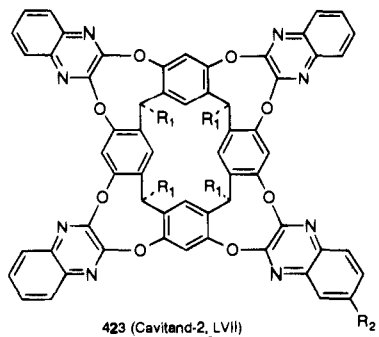
420 (Cavitand-4, LVII)
R = C_5H_{11}



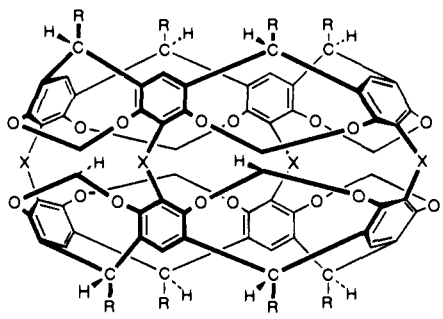
421 (Cavitand-16, LVIII)
R = C_5H_{11}



422 (Cavitand-18, LIX)
R = C_5H_{11}



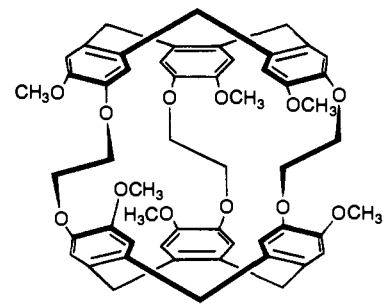
423 (Cavitand-2, LVII)
R_1 = C_6H_{13}; R_2 = H
424 (Cavitand-3, LVII)
R_1 = C_6H_{13}; R_2 = CH_2OH



425 (Carcerand-3, LX)
R = $CH_2CH_2C_6H_5$
X = -OCH_2(1,2-C_6H_4)CH_2O-

5. Cryptophanes and Speleands

Structural characteristics of cryptophanes and related speleands which act as hosts for cationic and neutral organic guests have been described in section II.A.8.c. Cryptophanes showed selectivity among neutral halomethanes and hydrocarbons according to their shape, size, and even chirality.[311] Recently, Collet and co-workers reported the first studies on methane complexation by cryptophanes.[439] Of the cryptophanes studied, only the smallest **426** is able to complex with methane molecules in $(CDCl_2)_2$ solvent, $\log K = 2.11$, $\Delta H = -6.7$ kJ mol^{-1}, and $\Delta S = 17$ J K^{-1} mol^{-1}. This selectivity can be explained partially by the better host–guest size fit of **426**. Both enthalpic and entropic contributions are favorable for methane complexation.[439] Speleands **260–263** with spheric rigid intramolecular cavities are, in principle, suitable for the inclusion of small organic molecules. However, NMR complexation studies of speleands with dichloromethane and chloroform in 1,2-dichloroethylene medium do not show significant differences in the chemical shifts of the guests. These results do not rule out the existence of inclusion complexes because in the absence of aromatic rings in the host the chemical shift displacements can be very small.[314]



426 (Cryptophane-2, LVI)

6. Porphyrins and Porphyrin Derivatives

Many types of thermodynamic data have been reported for complexation of neutral molecules by porphyrins and macrocycles with porphyrin subunit(s) built into their rings. Thermodynamic and kinetic studies are essential for better understanding of the unique role of porphyrins in many biological processes. For example, porphyrin **427** containing four convergent hydroxyl groups available for pairing shows a specific molecular recognition via multipoint hydrogen bonding toward ubiquinone analogues. This system is of interest because of the importance of quinone–porphyrin interactions in the study of electron transfer in photosynthesis and in the respiratory chain.[440] Porphyrin **428**, synthesized by Hamilton and co-workers, is an example of how hydrogen bonding groups within synthetic receptors can be used to direct the complexation of barbiturate substrates to a position above the plane of the porphyrin ring. This phenomenon has a possible similarity to the arrangement of the active site in barbiturate-induced cytochrome P-450. On the basis of this observation, Hamilton and his colleagues intend to

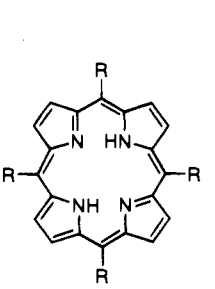
develop a synthetic model for hydroxylation reactions.[441] Also, porphyrin-bridged cyclophanes, **429** and **430**, prepared by Diederich and co-workers, can serve as synthetic models of cytochrome P-450 enzymes.[442] These ligands bind polycyclic aromatic hydrocarbons in alcoholic solvents by $\pi-\pi$ stacking interactions. However, the stability of the complexes does not parallel the size of the apolar surface of the guest but is related to the orientation of the guest in the cavity of the host. "Equatorially" bound acenaphthylene and "axially" bound phenanthrene show the best fit in the cavity of **429** and form the most stable complexes, log K ($CD_3OD/D_2O/CD_3CO_2D$, 95:4.85:0.15 v/v/v) = 3.02, 3.12, 2.52, and 2.20 for acenaphthylene, phenanthrene, naphthalene, and pyrene, respectively.[442] Sanders and co-workers have prepared a molecular bowl **431** by constructing a metalloporphyrin on one face of a tetrameric cyclocholate.[443] The porphyrin provides a floor for the bowl and an electrophilic zinc atom which binds amines, while each of the four cholates contributes a wall and a potentially binding or catalytic hydroxy group which faces into the resulting cavity.[443] The molecular bowl selectively binds morphine by combination of nitrogen–metal ligation and hydrogen bonding, e.g., log K (CH_2Cl_2) = 5.36, 4.11, and 2.38 for the interaction of **431** with morphine, codeine, and codeine methyl ether, respectively.[443] Some new "expanded" porphyrins such as **432** have been reported by Sessler and his group. These ligands show high affinity toward neutral molecules (e.g., phenol, catechol) and could provide the basis for a new approach to the recognition of biologically important substrates such as catecholamines and carbohydrates.[444]

B. Selectivities

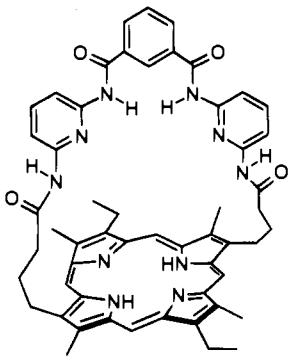
The molecular design of artificial receptors that can precisely recognize and specifically bind guest molecules has recently become a very active area of research.[426] As in the case of cations and anions, selectivities of macrocycles toward neutral molecules are governed by many factors.

Ring-size selectivity is shown for *N*-methylurea by macrocyclic metallohosts **382–385** in acetonitrile, log K (CH_3CN) = <1, 2.95, 3.32, and 4.23, respectively. The stability constants for the resulting complexes increase with macrocycle ring size.[403] Size-based selectivity is also found in complexes of the molecular bowl, porphyrin **431**, whose structure and binding abilities are described in section IV.A. This porphyrin, among other interesting binding patterns, shows size discrimination in the binding of larger alkaloids such as brucine and strychnine. For brucine, the recognition factor is +1.6 kJ mol^{-1}, corresponding to an intrinsic binding ratio of 0.5 between the molecular bowl and the reference porphyrin. This result indicates that brucine is too large to enter the bowl but forms a very stable complex by coordination to the outside face of the porphyrin subunit.[443]

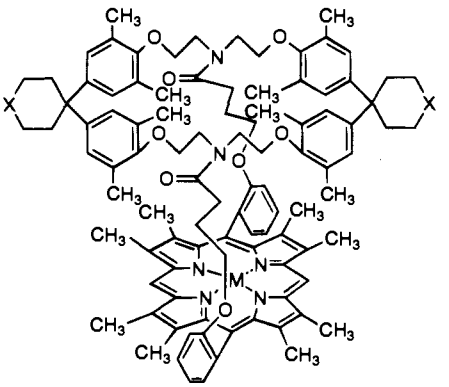
Selectivities based on size and shape recognition are displayed by some cryptophanes. The smallest, **426**, with a size preference of 55 Å, strongly binds methane[439] which is too small to be bound by larger



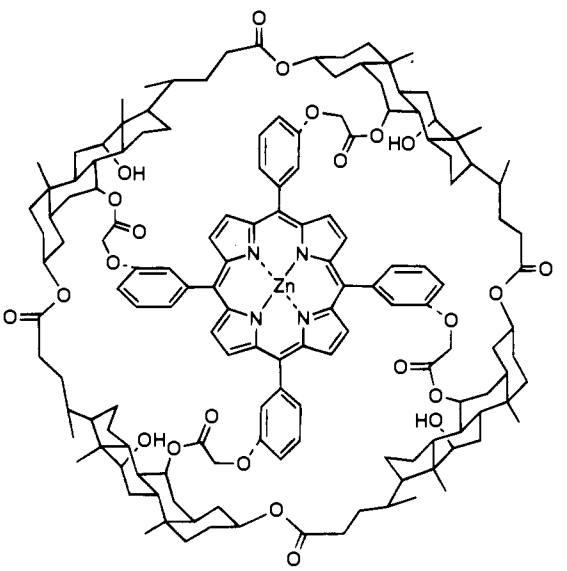
427 (Porphyrin-21, LXIV)
R = 1-(2-OHNap)



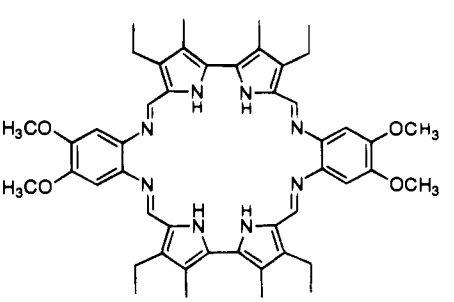
428 (Porphyrin-67, LXVIII)



429 (Porphyrin-71, LXX)
X = NC_2H_5; M = 2H
430 (Porphyrin-72, LXX)
X = $NHC_2H_5^+$ Br^-
M = Fe-Br

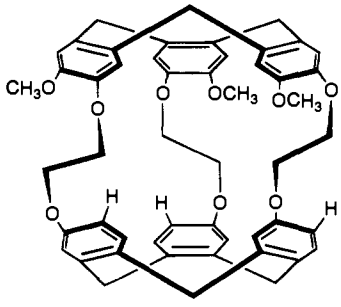


431 (Porphyrin-70, LXIX)



432 (Porphyrin-54, LXVI)

members of the series. Cryptophane **433** prefers to bind guests of size around 60 Å, whereas the larger **257** preferentially binds guests of size around 75 Å.[311] Cryptophane **433** discriminates between $CHCl_3$ and $CHBrCl_2$ by 1.26 kJ mol^{-1} although the difference in volume of these two molecules is only 5%, but does not discriminate between isobutane and $CHBr_2Cl$ which have the same van der Waals volume. On the other hand, acetone is much more weakly bound than $CHCl_3$ although they have the same size suggesting that **433** can differentiate between tetrahedral ($CHCl_3$) and flat (acetone) molecules.[311]



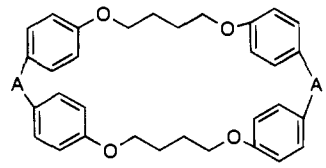
433 (Cryptophane-1, LVI)

Chiral and enantiomerically pure **392** shows shape selectivity toward acyclic substrates and some shape-selective ability toward steroids in water. This ligand is able to enclose a cyclohexanoid ring well but the presence of an axial substituent significantly inhibits binding, log K (D_2O) = 4.63 and 3.80 for *cis*-4-*tert*-butylcyclohexanol and *trans*-4-*tert*-butylcyclohexanol, respectively.[408] This macrocycle can also distinguish between enantiomers of menthol, log K (D_2O) = 3.40, 3.30, and 3.00 for (−)-menthol, (+)-menthol, and (+)-isomenthol, respectively.[408]

The study of macrocycle interaction with neutral molecules shows that complementary positioning of recognition sites, particularly hydrogen bonding, $\pi-\pi$ interactive, hydrophobic groups, chiral units, electrophilic metal centers, and other active groups, into the macrocycle are very important in molecular recognition and can lead to strong, specific, and targeted interactions.

Hamilton and co-workers, by varying the hydrogen-bonding regions and electronic characteristics of the $\pi-\pi$ stacking groups in the macrocycle structure, synthesized selective receptors for organic substrates such as nucleotide bases, flavins, barbiturates, and dicarboxylic acids.[3] Recently, they reported a new barbiturate receptor, porphyrin **428**, formed by connecting a bis(diaminopyridine) derivative to a porphyrin ring, log K ($CDCl_3$) = 6.48 for barbital.[441] Following similar techniques, Reinhoudt and co-workers made two other new barbiturate receptors, calixarene **412**, which has two diaminotriazine moieties attached at the upper rim of calix[4]arene, log K ($CDCl_3/Me_2SO$, 95:5) = 1.99 for barbital,[427] and metallohost **386** which consists of an immobilized uranyl cation and a 2,6-diamidopyridine moiety, log K ($CDCl_3$) = 2.73 for phenobarbital.[404]

A charge-mediated size selectivity in the binding of neutral hydrophobic aromatic substrates has been achieved by Schwabacher et al. in **434** and **435** with negatively and positively charged centers, respectively.[445] The authors used a model proposed by Hunter and Sanders[446] which allows one to predict that the positive charge would be attracted to the face and the negative charge to the edge of an aromatic ring.[445]



434 [(1,4-B)$_4$P$_2$30C6-1, XXXVI]
A = $P(O)O^-Na^+$
435 ((1,4-B)$_4$P$_2$30C6-2, XXXVI]
A = $P(CH_3)_2^+ I^-$

Many recent papers report selective recognition of chiral organic substrates by targeted inclusion of chiral groups into the macrocyclic structure. Cyclophanes **393** and **395** complex a variety of peptides and octyl glucosides with high selectivity.[409,411] Cyclophane **393** binds certain α-amino acid derivatives with enantioselectivities in the range of 8−13 kJ mol^{-1} (90−99% ee favoring L).[409,410] This ligand also showed selectivity between different classes of amino acids, e.g., derivatives of serine and threonine were bound ≥8 kJ mol^{-1} more tightly than those of alanine, valine, and leucine.[409] In turn, cyclophane **395**, with binding selectivities approaching those of biological receptors, binds amino acid residues in peptide chains with very high selectivities for chirality (up to 99+% ee) and side-arm identity (up to 13+ kJ mol^{-1}).[411] Cyclic tetrahydroxycholaphane (**400**) discriminates effectively between the stereoisomers of octyl glucosides, showing a diasteroselectivity of *ca.* 5.5:1 in the cases of *n*-octyl α-D-glucopyranoside and *n*-octyl β-D-glucopyranoside, log K ($CDCl_3$) = 2.75 and 3.49, respectively, and an enantioselectivity of *ca.* 3:1 in the cases of *n*-octyl β-D-glucopyranoside and *n*-octyl β-L-glucopyranoside, log K ($CDCl_3$) = 3.49 and 3.00, respectively.[419] The cyclodextrin−cyclophane hybrid (**399**) displays improved chiral discrimination for amino acid derivatives in comparison to that for the cyclodextrins.[418] Novel cage-type **365** and **366** bearing chiral binding sites provided by L- and D-valine residues exhibit discrimination toward steroid hormones in D_2O/CD_3OD, as affected by hydrophobic and $\pi-\pi$ interactions and additionally by different modes of hydrogen bonding in the cases of α- and β-estradiol.[414,415]

C. Heat Capacities, ΔC_p

No new ΔC_p values are available.

V. Kinetics of Macrocycle Interaction with Cations, Anions, and Neutral Molecules

Kinetic studies of macrocycle interactions with cations, anions, and neutral molecules not only provide essential information on the rate and mechanism of complexation reactions but lead to better understanding of phenomena which govern macrocycle selectivity toward various guests as well. Kinetic and activation parameters for macrocycle interactions with cations, anions, and neutral molecules are given in Tables V, VI, and VII, respectively, of the supporting information, together with the method, temperature, and solvent used in their determina-

tion. When necessary, relevant equations or other information are also given under the condition heading.

A. Cation–Macrocycle Interaction

To gain insight into the underlying selectivities of *crown ethers and cryptands* toward alkali metal cations in nonaqueous media, two hypothetical mechanisms should be considered. The first, which follows the models based on the Eigen–Winkler reaction mechanism, is a *dissociative* (unimolecular) mechanism with dissociation and recombination steps as given by eqs 1a and 1b, respectively:[447,448]

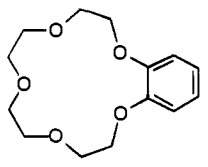
$$(M{:}L)^+ \underset{k_1}{\overset{k_{-1}}{\rightleftharpoons}} M^+ + L \qquad (1a)$$

$$M^+{*} + L \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (M^*{:}L)^+ \qquad (1b)$$

The second is an *associative* exchange (bimolecular) mechanism as given by eq 2:[447,448]

$$(M{:}L)^+ + M^+{*} \overset{k_2}{\rightleftharpoons} (M^*{:}L)^+ + M^+ \qquad (2)$$

Competition between these two mechanisms is affected by the nature of the solvent. For example, metal interchange in the **436** complex with Na^+ in a solvent of low donor number (DN), such as nitromethane (DN = 2.7), proceeds by the associative pathway, while in acetonitrile (DN = 14.1) the dissociative pathway is preferred.[447] In mixtures of these solvents, as the acetonitrile content is increased, a gradual change from the associative to the dissociative pathway is observed.[447] The global dissociation process is the result of a series of stepwise sodium–oxygen bond ruptures accompanied by sodium-solvent bond formation.[447] The exchange processes are also controlled by the temperature. At the lower temperatures, the associative process is prevalent, whereas as the temperature increases, the dissociative mechanism becomes more competitive.[447] The associative exchange is mainly controlled by conformational changes of the ligand during the concerted partial decomplexation of one cation and partial complexation of a second one, while solvation of the complexed cation plays a major role in the dissociative mechanism.[447,448] An associative exchange mechanism is consistent with a large negative entropy of activation, whereas identical enthalpies of activation for the Li^+ and Na^+ complexes with **4** or **436** suggest that the size of the cation does not play a governing role in the mechanism, e.g., $\Delta H^{\ddagger}$ (CH_3NO_2) = 21 and 21 kJ mol^{-1}, and $\Delta S^{\ddagger}$ (CH_3NO_2) = −54 and −76 J K^{-1} mol^{-1} for the interaction of **4** with Li^+ and Na^+, respectively.[448]



436 (B15C6-1, VIII)

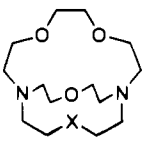
Similar mechanisms and correlations have been reported for alkaline earth metal complexes with **5** in several nonaqueous solutions.[449] The authors observed a correlation between the donor number of the solvents, and decomplexation rates and activation parameters, e.g., k_d = 2.6 × 10^3 and 1.8 × 10^3 s^{-1}, $\Delta H^{\ddagger}$ = 11.7 and 14.2 kJ mol^{-1}, and $\Delta S^{\ddagger}$ = −141 and −135 J K^{-1} mol^{-1} for the interaction of **5** with Mg^{2+} in nitromethane (DN = 2.7) and acetonitrile (DN = 14.1), respectively.[449] The activation energy for the release of **5** from its complexes increases with increasing donicity of the solvent. They also observed that, with the exception of Ba^{2+}, the k_d values in a given solvent decrease with increasing ionic size, which reflects the increase in the kinetic stability of this complex with ionic size, e.g., k_d = 2.6 × 10^3, 2.4 × 10^3, and 5.5 × 10^2 s^{-1} for the interaction of **5** with Mg^{2+}, Ca^{2+}, and Sr^{2+}, respectively, in nitromethane.[449]

A kinetic study of bivalent transition metal interaction with crown ethers in methanol and acetonitrile showed that complex formation obeyed the Eigen–Winkler reaction mechanism.[450] Because the ion desolvation rates in the case of transition metal ions are much slower than those for alkali metal ions, the rate of ligand rearrangement may become relatively fast.[450]

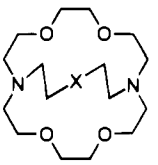
Cryptands form exceptionally stable complexes with cations. Since the 1991 review,[3] several new papers have been published on the kinetics of cryptand interaction with alkali metal ions[174,175,181–183,187] and transition metal ions.[193,451,452] Results of these studies confirmed a strong correlation between the thermodynamic stability and lability of cryptates with such factors as the structure of the cryptand, the number and type of the cryptand donor atoms, the nature of the metal ion, and the nature of the solvent.[175,181] In turn, thermodynamic stability constants correlate strongly with dissociation rate constants, e.g., in trimethyl phosphate, log K = 5.38 and k_d = 6.92 s^{-1} for the interaction of **437** with Na^+, and log K = 2.40 and k_d = 23.3 s^{-1} for the interaction of **438** with Li^+.[181] The kinetics of reactions, as indicated earlier, is also sensitive to solvent variation. It is generally found that the magnitude of k_d increases (stability constant decreases)[181] with increase of solvent DN. The magnitude of k_d is much more dependent than that of k_f on the nature of the solvent.[174,181,182]

Cryptands such as **132**,[174,187] **438**,[181] **133**,[175] and **439**,[183] recently studied by Lincoln and co-workers, have oxygen donor atoms replaced with methylene units which made their structure more open and flexible. In general, the complexes formed between these cryptands and alkali metal cations are less stable thermodynamically and more labile than those of cryptands having donor atoms in place of methylene groups and are disposed to exist in partially *exclusive* forms.[175,181] For example, the $(Li{\cdot}\mathbf{132})^+$ complex exists in *exclusive–inclusive* equilibrium in solution and is less stable than the *inclusive* $(Li{\cdot}\mathbf{437})^+$ complex having the same number and type of donor atoms but which has a more rigid structure.[174] However, the unusual clamlike structure of **132** is more able to approach optimum binding distances

with Li^+ than is **8** which possesses more donor atoms. The result is that the $(Li\cdot\mathbf{132})^+$ complex is more thermodynamically stable and, depending on the solvent, of a similar or lesser lability than the $(Li\cdot\mathbf{8})^+$ complex.[174] Cryptand **439** forms a labile Na^+ cryptate with the decomplexation rate being 3760 times faster in methanol than that of the $(Na\cdot\mathbf{8})^+$ complex. This low decomplexation rate for the $(Na\cdot\mathbf{8})^+$ complex is the major reason for the much greater stability of this cryptate.[183]



437 ([2.1.1]-1, XLVI) X = O
438 ([2.1.C_5]-1, XLVI) X = CH_2



439 ([2.2.C_6]-1, XLVI) X = $-(CH_2)_4-$

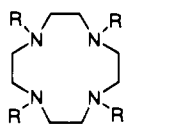
To extend the data available on the influence of the solvent on cryptate chemistry, Lincoln with his group examined interactions of cryptands with alkali metal cations in trialkyl (methyl, ethyl, and *n*-butyl) phosphate solvents having similar donor numbers and found that the dominant mechanism for metal ion exchange in these solvents involves unimolecular decomplexation of the metal ion.[181,182]

Kinetic data on transition metal cation interactions with **131**[451] and the novel methylated aza-cryptand **137**[193] have been reported. The complexation of Cu^{2+} with **131** in acetonitrile, dimethylformamide, and dimethyl sulfoxide proceeds through the Eigen–Winkler mechanism.[451] The aza-cryptand **137** does not behave as a cryptand ligand toward the metal ions Cu^{2+}, Zn^{2+}, and Cd^{2+} because, as shown by the crystal structure, the cation is not completely embedded inside the cryptand cavity and emerges by at least one coordination site.[193] This cryptand complex with Cu^{2+} presents low thermodynamic stability with high inertness toward acid dissociation, which is in accord with the general behavior of cryptates.[193]

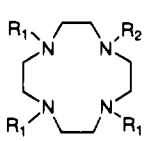
Thermodynamic as well as kinetic studies on *lariat ether* complexes with cations has been of considerable interest because of the use, especially of Gd^{3+}, Ga^{3+}, or In^{3+} complexes, in medicine as contrast agents in magnetic resonance imaging[118,124,126,137,453] and of Y^{3+} complexes as labels for monoclonal antibodies.[119,453,454] In addition, lariat ether complexes have found application as ion-selective reagents in analytical chemistry and as carriers in membrane transport.[129] Lariat ethers have sufficient binding strength to envelop cations in a three-dimensional manner resembling that of the cryptands. On the other hand, they have dynamics resembling those of the crown ethers.[99,455] Lariat ether complexes which are applied in medicine should be kinetically stable with respect to acid- or cation-catalyzed dissociation pathways in order to avoid the premature loss, for example, of highly toxic "free" $^{153}Gd^{3+}$, $^{67,68}Gd^{3+}$, $^{111}In^{3+}$, or ^{90}Y radioisotopes, which can be bound by serum proteins or may build up in radiosensitive organs such as bone, bone marrow, or gastrointestinal mucosa.[119,124,140,453]

Most recently published papers concerning lanthanide complexes with macrocyclic polyamine carboxylates are characterized by high stability of the complexes, and the inertness of the complexes toward metal release in water.[119–121,124,129,130,132–134,137,138,456] The formation rates for the reaction of trivalent lanthanide ions with the small 9-membered macrocyclic polyamine carboxylate, **86**, are independent of the size of the metal ion, but dissociation rates vary with the size of the metal ion.[119,129] In the case of 12-membered macrocyclic polyamino carboxylates, e.g., **101**, thermodynamic stability and inertness increase with increasing charge density of the metal ion, but for the relatively more rigid ligands such as **74** and **102**, the stability constants for the formation of Gd^{3+} and Lu^{3+} complexes are controlled by the cavity size and/or structural changes.[129] It was noted that kinetic inertness to lanthanide ion release in tetraazamacrocyclic ligand complexes is dependent on the size of the macrocyclic ring, e.g., **74** complexes are more stable and less prone to lanthanide dissociation than are complexes of **249**.[457] The Gd^{3+} complexes, with well-matched macrocycle cavity and metal ion size, are the most inert toward dissociation *in vitro* and *in vivo*.[138] It appears that the Gd^{3+} complex with **74** is the most inert lanthanide complex reported so far.[132] This complex shows low formation and very low dissociation rates, k_f (D_2O) = 29 M^{-1} s^{-1} and acid-catalyzed k_d (D_2O) = 8.4 × 10^{-6} s^{-1}.[132] Compound **74** forms a strong complex with $^{90}Y^{3+}$ which dissociates at pH <2; such kinetic stability augurs well for its use in tumor targeting using radiolabeled antibodies.[119] The larger 18-membered **91** has complexation rates with lanthanides 100 times faster than those of **74**.[133]

The kinetics of dissociation of Gd^{3+} and Y^{3+} complexes with a series of macrocyclic polyamines functionalized with phosphinic acid, **105**, **440**–**445**, have been measured at low pH using ^{153}Gd- and ^{90}Y-labeled complexes.[453,458] Some of the above phosphinate complexes, although slightly less stable than their carboxylate analogues, are sufficiently kinetically inert for *in vivo* therapeutic applications.[453,458]



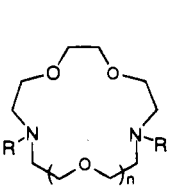
440 ($N_4$12C4-8, III) R = $CH_2P(O)(C_4H_9)OH$
441 ($N_4$12C4-9, III) R = $CH_2P(O)(C_6H_5)OH$
442 ($N_4$12C4-10, III) R = $CH_2P(O)(CH_2C_6H_5)OH$



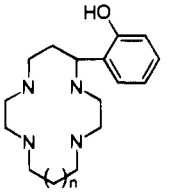
443 ($N_4$12C4-14, III) R_1 = $CH_2P(O)(CH_3)OH$, R_2 = $CH_2CON(C_4H_9)_2$
444 ($N_4$12C4-15, III) R_1 = $CH_2P(O)(CH_3)OH$, R_2 = $CH_2CON(CH_2C_6H_5)_2$
445 ($N_4$12C4-16, III) R_1 = $CH_2P(O)(C_4H_9)OH$, R_2 = $CH_2CONHCH_3$

Kinetic processes have been studied for the formation of complexes of lanthanide, alkali metal, and transition metal cations with lariat ethers having 2-hydroxyethyl side arms, **113**, **115**, **446**, and **447**;[150,152,455,457] Na^+ with a lariat ether having 2-methoxyethyl side arms, **114**;[151] Cu^{2+} with tetraazamacrocycles without side arms, **48** and **49**, and tetraazamacrocycles possessing 2-hydroxyphenyl

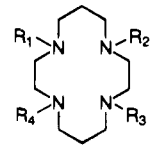
substituents, **448** and **449**;[459] transition metal cations with N-alkylated and C-alkylated cyclam derivatives, **450–458**;[460,461] transition metal cations with mono- and dioxomacrocyclic tetracycloamines, **459–461**, in which the dissociation rates demonstrate the importance of the ring size and the number of amide groups;[462] and Cu^{2+} with tetrathiaethers in which the effect of "noncomplexing" anions on kinetics was examined.[463] In the last system, it was found that nitrate is the only anion which does not interact with Cu^{2+} complexes.[463] An interesting finding of kinetic studies of macrocycles bearing double functions of thia and amide donors, **462** and **463**, is that these macrocycles are selective for the noble metal ions but do not recognize other divalent metal cations such as Cu^{2+}, Ni^{2+}, or Co^{2+} in aqueous methanol solution.[464] Kimura points out that "among amide-containing macrocycles, such highly selective recognition of Pt^{2+} and Pd^{2+} against Cu^{2+}, Ni^{2+}, and Co^{2+} cations has no precedent".[464d]



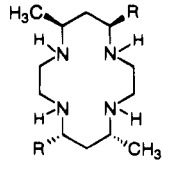
446 ($N_2$15C5-2, X)
R = CH_2CH_2OH
n = 1
447 ($N_2$18C6-11, XXIV)
R = CH_2CH_2OH
n = 2



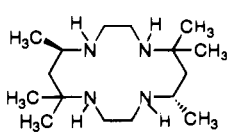
446 ($N_4$13C4-3, IV)
n = 0
449 ($N_4$14C4-11, V)
n = 1



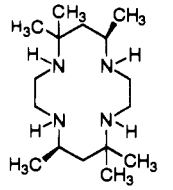
450 ($N_4$14C4-2, V)
R_1 = CH_3; R_2, R_3, R_4 = H
451 ($N_4$14C4-3,V)
R_1, R_4 = H; R_2, R_3 = CH_3
452 ($N_4$14C4-4, V)
R_1, R_2, R_3 = CH_3; R_4 = H
453 ($N_4$14C4-5, V)
R_1, R_2, R_3, R_4 = CH_3



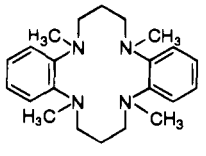
454 ($N_4$14C4-16, V)
R = H
455 ($N_4$14C4-17, V)
R = C_6H_5



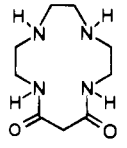
456 ($N_4$14C4-20, V)
(tet a)



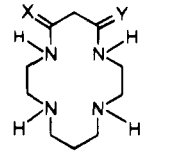
457 ($N_4$14C4-21, VI)
(tet b)



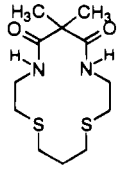
458 ($B_2N_4$14C4-2, VI)



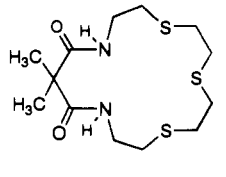
459 ($K_2N_4$13C4-2, IV)



460 ($KN_4$14C4-1, VI)
X = O; Y = H_2
461 ($K_2N_4$14C4-1, VI)
X, Y = O

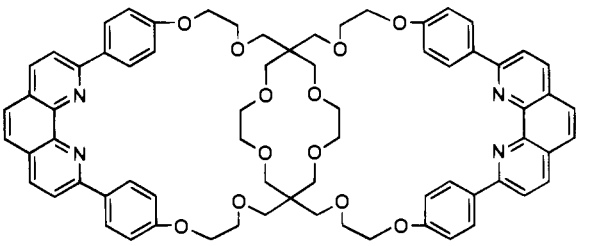


462 ($K_2S_2N_2$14C4-1, VI)

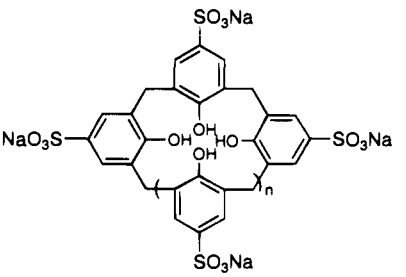


463 ($K_2S_3N_2$16C5-1, XVI)

Kinetic and activation parameters for complexes of other types of macrocycles have been measured. The formation of Li^+ and Cd^{2+} complexes with **464** involves two kinetically observable steps; the slower one consists of two processes and has a negative activation enthalpy, supporting a preequilibrium between two complexed species in the mononuclear rearrangement leading to the catenate structure.[465] The fluctuation in conformation of calixarene **341** molecules plays a very important role in the high complexation rate of Na^+.[466] The kinetic parameters for the binding of UO_2^{2+} to calixarene-based "super-uranophiles" such as **179**, **465**, and **466** have been evaluated and it has been found that **465** acts as a good uranophile for experiments involving dynamic processes (e.g., solvent extraction, membrane transport, etc.).[245] For the synthetic receptor cucurbituril (**255**), a more detailed description of which appeared earlier in the text, the rate of inclusion complex formation correlates with the molecular diameter of alkylammonium cations but not with the thermodynamic stability of the complexes formed.[307,308,467]

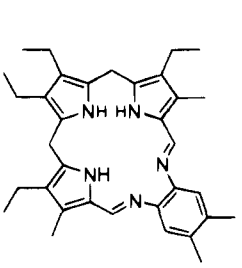


464 (Catenand-1, XLV)

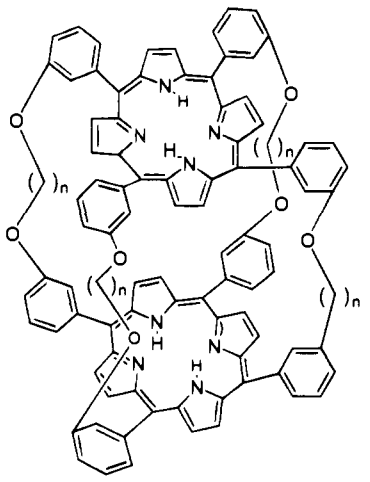


465 (Calix5-20C-1, XXVII)
n = 2
466 (Calix6-24C-3, XXX)
n = 3

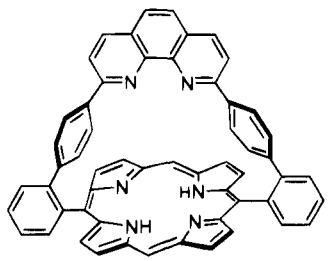
There are several publications on porphyrin interactions with metal cations. Kinetic studies of the formation of the Gd^{3+} complex with a novel structurally "expanded" **467** in methanol/water (50:50 v/v) mixture show that the half-life for decomplexation and/or decomposition of the complex is 37 days. This kinetic stability, coupled with the high observed relaxivity at pH 7.2, suggests that this complex or its congeners might be effective as paramagnetic contrast agents.[468] In porphyrin cyclophane dimers, **468** and **469**, both porphyrin fragments react at identical rates with Cu^{2+} salts in pyridine and acetic acid solution.[469] The kinetic study of the complexation of Cu^{2+} and Ag^+ ions with phenanthroline capped **470** in dimethyl formamide revealed the formation of mixed valence homodinuclear complexes together with a kinetically enhanced complexation within the porphyrin core.[470] Other papers, discussing kinetic aspects of complexation of well-known porphyrins mostly with transition metal ions have been published.[318,469,471–475]



467 (Porphyrin-51, LXVI) (Texaphyrin)



468 (Porphyrin-62, LXVII) n = 3
469 (Porphyrin-63, LXVII) n = 4



470 (Porphyrin-68, LXVIII)

B. Anion–Macrocycle Interaction

Table VI in the supporting information contains kinetic data for monomeric cationic porphyrin **291** complexation with 2′-deoxyadenosine 5′-monophosphate in aqueous solution. The measured rate constants are consistent with a simple stacking model for the interaction.[384]

C. Neutral Molecule–Macrocycle Interaction

Table VII in the supporting information presents kinetic data for several macrocyclic compounds with neutral organic guests. Collet and co-workers studied the interaction of cryptophane **426** with methane between −74 and 25 °C using NMR techniques.[439] They found that the half-life of the complex was 9×10^{-3} s at −74 °C and 6×10^{-6} s at 25 °C; the corresponding dissociation barriers ($\Delta G_d^{\ddagger}$) were 41.0 and 43.9 kJ mol^{-1}, respectively.[439]

Cram and co-workers published several papers which contain kinetic data on interaction of "velcrands" (e.g., **420**, **421**, and **422**)[435] and hemicarcerands (e.g., **425**) with neutral molecules.[434,476,477] The "velcrands" possess both host and guest character and do not encapsulate guests but instead form in organic solvents 4-fold, lock–key dimers named by the authors "velcraplexes".[435,438] In the homo- and heterodimers, the keys and locks are, respectively, methyl groups and corresponding holes that serve to position and hold monomers in place.[435,438] Activation free energy ($\Delta G^{\ddagger}$) values for the associative and dissociative processes in chloroform are remarkably high for dimers held together only by dipole–dipole, van der Waals, and solvophobic forces.[435] The authors attribute these high $\Delta G^{\ddagger}$ values to the fact that dimer formation involves exchanging attractions between up to 18 molecules of solvent and two large monomeric faces for attractions between two faces with approximately 100 close contacts.[435] Hemicarcerands (e.g., **425**) are globe-shaped compounds with enforced hollow interiors possessing holes in their shells which allow entry and departure of neutral guests.[438] The authors suggest that the complexes with neutral molecules are held together largely by steric interactions that inhibit decomplexation and proposed the term, *constrictive binding* for this phenomenon.[434,477]

VI. Future Prospects

The key to the selectivities found in this review has been the ability of investigators to design or program information into host macrocycles thus allowing these hosts to recognize individual guest species. The capability to program the correct information into host molecules has increased dramatically as host and guest parameters affecting selectivity have been identified and quantified. Many examples have been given in the text that illustrate these principles.

From the perspective of over two decades of intense interest by many investigators in macrocyclic chemistry, one notices particularly the explosion of synthetic work leading to novel molecules that often have remarkable guest selectivities. It is of particular interest to note the increasing number of highly competent scientists who find it challenging and fun to design and prepare unusually complex hosts that have highly specific guest binding abilities.

We expect these efforts to continue and intensify. Furthermore, it is likely that these unique systems will find applications in new scientific areas where molecular recognition processes are important. The prospect for the future in macrocyclic chemistry is exciting.

Concerning the ability of the organic chemist to synthesize molecules with desired properties, Rebek[478] has observed that "the question is no longer *if* something can be built, but *what* to build and *why*". We foresee a future where creative chemists will continue to prepare new molecules designed for specific separations and other molecular recognition uses. We expect that the chemical systems that result may have important applications in chemical and allied industries.

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Supporting Information Available. Thermodynamic and kinetic data for the interaction of protons, cations, anions, and neutral molecules with macrocycles (Tables I–VII and relevant Charts I–LXXVII) and a complete list of references are available as supporting information via the Internet only. Please see any current masthead page for accessing information.

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