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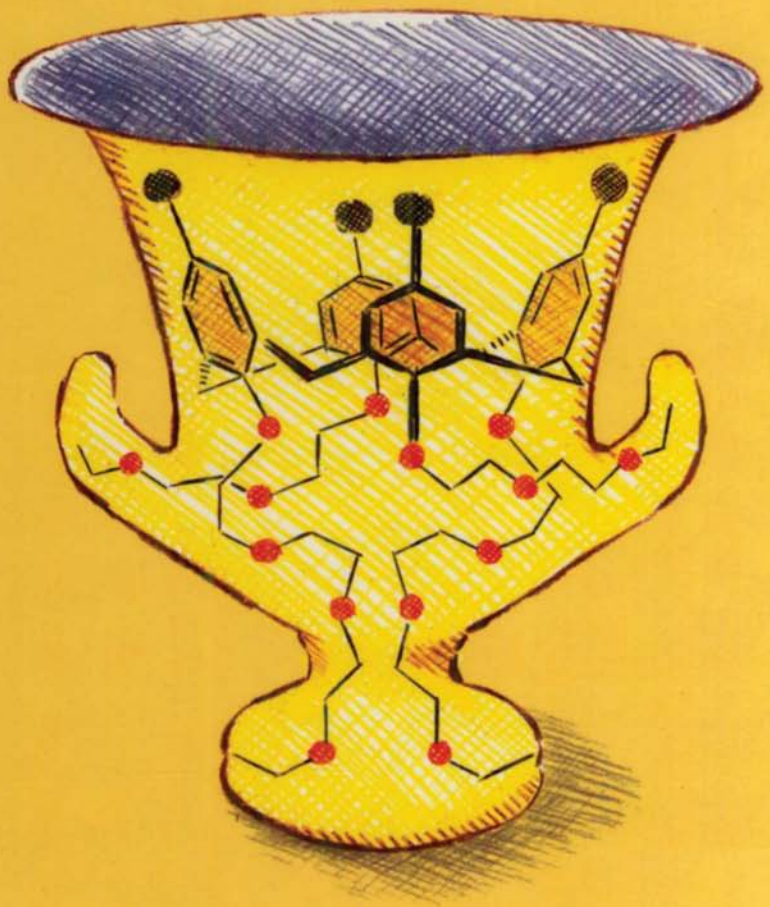
Calixarenes Revisited

by C. David Gutsche



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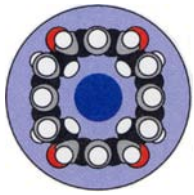

Calixarenes Revisited

C. David Gutsche
Texas Christian University, Fort Worth, USA

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Preface

Calixarenes, the predecessor to this book, was published in 1989, at which time slightly more than 200 papers relating to the topic had appeared in the chemical literature. These publications were sufficient to establish the calixarenes as a small but viable subfield of chemistry yet few enough in number to allow easy assimilation into a slim book of 222 pages. The aim of the first volume was to present a comprehensive view of the calixarenes in a relaxed and accessible fashion in the hope of providing a useful summary for those already in the field and an enticement to others to enter the field. In the years that have followed, some of the researchers already committed in 1989 have greatly expanded their efforts while many other researchers not committed in 1989 have entered the field. The result has been an explosive growth of this chemical family which remains still viable but no longer small, well over 1700 papers now populating the literature of calixarenes. Covering the progress of the last seven years with the same leisurely approach used in the previous volume is, unhappily, no longer feasible if *Calixarenes Revisited* is to remain a slim book; a more matter-of-fact account devoid of biographical vignettes has been the result. Nevertheless, *Calixarenes Revisited* builds directly on the framework of the first volume and is intended to stand on its own merits for readers already familiar with the field but to be used in tandem with *Calixarenes* by those with a less detailed background. It covers the literature through the end of 1996, concentrating on the papers published 1989–1996 but also including an occasional paper published before 1989 or after 1996.

In the preface to *Calixarenes* I alluded to my pleasure at seeing the seeds planted in the 1970s sprout and grow in the 1980s. Now, in the 1990s they approach full maturity. This pleasure comes as a mixed blessing, however. Whereas in the early days the likelihood of duplication of effort was rather small, today it is a significant concern as the number of workers has expanded and the level of competition has heightened. As the literature has proliferated, the frequency of the failure of authors to make appropriate attribution to prior work has multiplied. I hope that *Calixarenes Revisited* will help to alleviate this small, but often annoying, problem to which a number of us have unwittingly contributed.

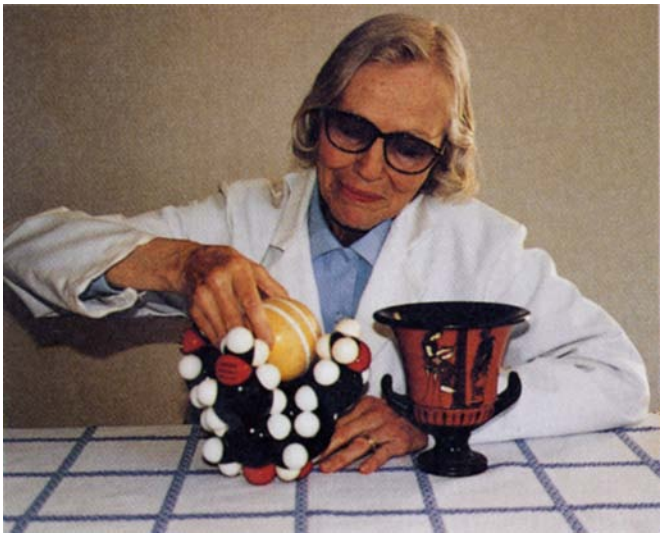
Calixarenes Revisited contains almost 1000 reference citations, which represent about half of those in the literature. Thus, it is not a truly comprehensive survey of the field but, instead, a significant sampling of the literature of the various topics of calixarene chemistry. I hope that it provides a reasonably complete detailing of all of the important topics as well as a useful starting point

for authors wanting to compile a complete bibliography of their particular niche of the field. Of course, arbitrary decisions had to be made whether or not to include particular publications, the general rule being not to include those containing material already well represented by citations in the book. Inevitably, some papers that should have been included were not, either by mistaken judgment on my part or from simple oversight, and for these omissions I express my sincere apologies.

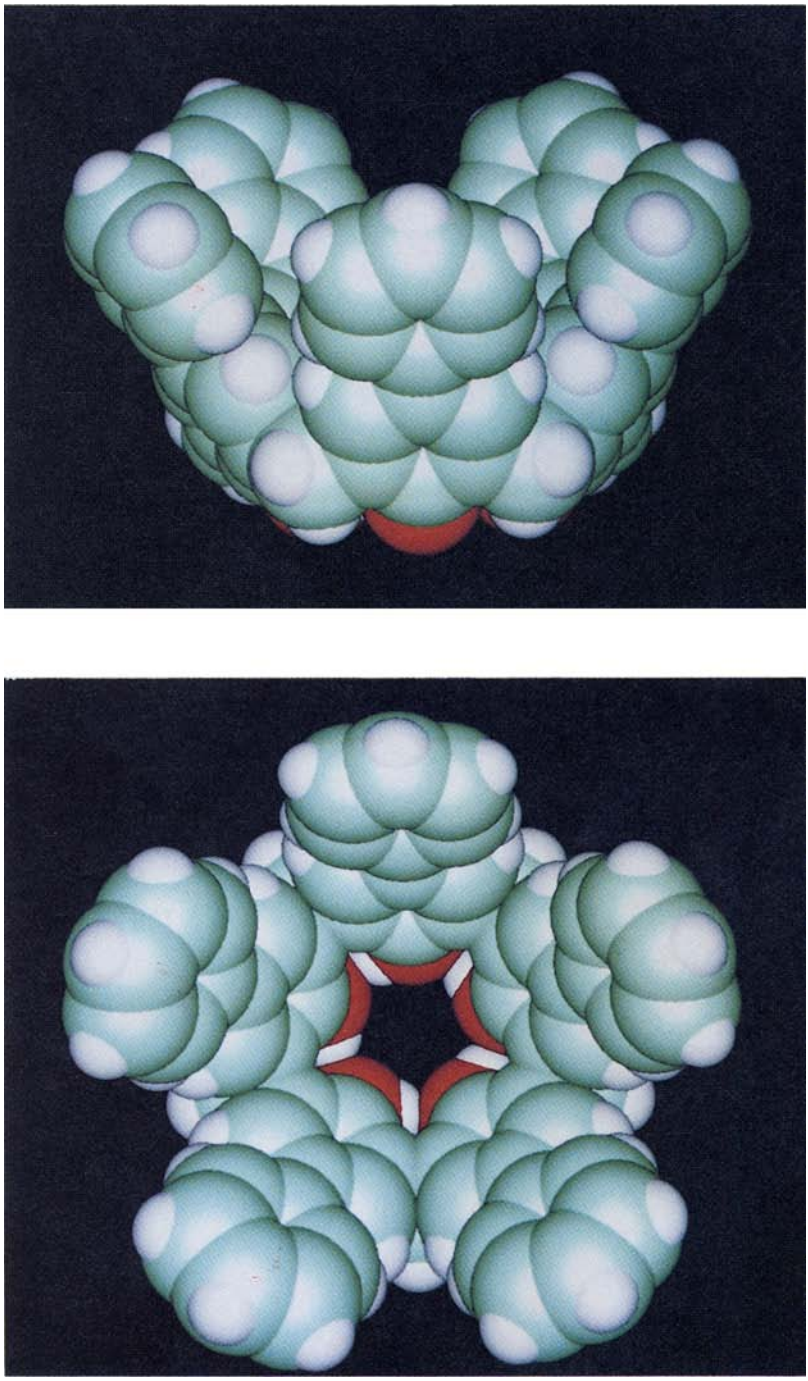
The progress that has been made in modern calixarene chemistry, starting about 25 years ago, can be attributed to the conscientious and often inspired work of many scientists. In Tolstoy's *War and Peace* an incident is described in which the generals have given up the battle and the regiment is facing defeat when a young soldier seizes the fallen flag and rushes toward the enemy, inspiring the others of his regiment to follow suit and turn defeat into victory. In like fashion, members of my own research group have often seized the calixarene flag and carried it forward as, certainly, have the members of the many other research groups around the world. It is to this army of coworkers that the chemical community owes a great debt of gratitude, for without them we generals would have nothing to show for our clever ideas and glorious schemes. The particular members of this army to whom I express special gratitude for their very careful reading of the manuscript in its final phases are Drs. Charles Gibbs, Shiv Kumar Sharma, Donald Stewart, Jian-she Wang, and Dejian Xie. Sharing in this encomium to my coworkers is my wife Alice, whose tireless efforts in collecting literature citations, ceaseless attention to editorial detail, and unerring abilities as homemaker and spouse have contributed inestimably to this second volume of the calixarene series. Finally, appreciation is expressed to the National Science Foundation and the Robert A. Welch Foundation for the research support they have provided during the preparation of this book.

C. David Gutsche

Fort Worth, Texas
August 1997



Alice Gutsche with molecular model and calix crater



Computer-generated structure of *p*-phenylcalix[5]arene showing side and top views

Contents

Chapter 1 From Resinous Tar to Molecular Baskets 1
1.1 Introduction 1
1.2 Phenol-derived and Resorcinol-derived Calixarenes 2
1.3 Historical Perspective 2
1.4 Nomenclature and Representation 7

Chapter 2 Making the Baskets: Synthesis of Calixarenes 10
2.1 One-step Synthesis of Calixarenes 10
2.1.1 Base-induced Reactions 10
2.1.2 Acid-catalyzed Reactions 14
2.2 Fragment Condensation Synthesis of Calixarenes 17
2.3 Synthesis of Bridged Calixarenes 19
2.4 Synthesis of Dissymmetric and Asymmetric Calixarenes: Chiral Calixarenes 20
2.5 Synthesis of Calixarene-related Compounds 23
2.5.1 Homocalixarenes 23
2.5.2 Oxacalixarenes 24
2.5.3 Azacalixarenes 25
2.5.4 Calixarene-like Cyclooligomers 26
2.6 Mechanism of Calixarene Formation 28

Chapter 3 Proving the Baskets: The Characterization and Properties of Calixarenes 32
3.1 Separation and Purification of Calixarenes 32
3.2 Melting Points of Calixarenes 33
3.3 X-Ray Crystallography: The Ultimate Proof of Structure 33
3.4 pK_a Values of Calixarenes 34
3.5 Dipole Moments of Calixarenes 36
3.6 Spectral Characteristics of Calixarenes 37
3.6.1 Infrared Spectra 37
3.6.2 Ultraviolet Spectra 37
3.6.3 NMR Spectra 37
3.6.4 Mass Spectra 39

Chapter 4 Shaping the Baskets: Conformations of Calixarenes 41
4.1 Conformational Representation and Nomenclature 41
4.2 Computational Studies of Calixarene Conformations 46
4.3 Conformations of Calixarenes in the Solid State 50
4.3.1 Calix[4]arenes 50
4.3.2 Calix[5]arenes 58
4.3.3 Calix[6]arenes 60
4.3.4 Calix[7]arenes 61
4.3.5 Calix[8]arenes 62
4.4 Conformations of Flexible Calixarenes in Solution 63
4.4.1 Conformational Mobility of Calix[*n*]arenes 63
4.4.2 Conformational Mobility of Calixarene Methyl Ethers, Ethyl Ethers, Deoxycalixarenes, Calixquinones, and Calixarenethiols 66
4.4.3 Conformational Mobility of Calixarene-related Compounds 68
4.4.4 Pathways for Cone–Cone Interconversion 68
4.5 Conformationally Immobile Calixarenes 68
4.5.1 Minimum Structural Requirements for Conformational Immobility of Unbridged Calixarene Ethers and Esters 68
4.5.1.1 Fully Etherified and Esterified Calixarenes 68
4.5.1.2 Partially Etherified and Esterified Calixarenes 70
4.5.2 Conformational Immobilization *via* Bridging 72
4.6 Factors Governing Conformational Outcome of Derivatization 73
4.6.1 *O*-Tetrasubstitution of Calix[4]arenes 73
4.6.2 Mono-, Di-, and Tri-*O*-substitution of Calix[4]arenes 76
4.6.3 *O*-Substitution of Calix[5]arenes and Calix[6]arenes 78

Chapter 5 Embroidering the Baskets: Modifying the Upper and Lower Rims of Calixarenes 79
5.1 Modifying the Lower Rim of Calixarenes 79
5.1.1 Esterification 79
5.1.2 Etherification 82
5.1.2.1 With Simple Alkyl Halides 82
5.1.2.2 With Functionalized Alkylating Agents 87
5.1.3 Lower Rim-bridged Calixarenes 89
5.1.3.1 Intramolecular Bridges 89

5.1.3.2 Intermolecular Bridges 98
5.1.4 Replacement of OH with H, N, and S 100
5.2 Modifying the Upper Rim of Calixarenes 104
5.2.1 General Overview 104
5.2.2 Halogenation Routes 106
5.2.3 Nitration Routes 107
5.2.4 Sulfonation Routes 110
5.2.5 Diazo Coupling Route 112
5.2.6 Alkylation (including Chloromethylation) Route 112
5.2.7 Acylation and Aroylation Routes 114
5.2.8 Arylation Reactions 116
5.2.9 Aminomethylation: The *p*-Quinonemethide Route 117
5.2.10 *p*-Claisen Rearrangement Routes 118
5.2.11 Upper Rim-bridged Calixarenes 119
5.2.11.1 Intramolecular Bridges 119
5.2.11.2 Intermolecular Bridges 124
5.3 Oxidation of Calixarenes 129
5.3.1 Methylene Group Oxidation 129
5.3.2 Aromatic Ring Oxidation to Quinones 130
5.3.3 Aromatic Ring Oxidation to Spirodienones 132
5.4 Reduction of Calixarenes 135
5.5 Chiral Calixarenes 135
5.5.1 Chirality *via* External Attachment 135
5.5.2 Chirality *via* Upper and Lower Rim Substitution Patterns 136
5.5.3 Chirality *via meta* Substitution 141
5.5.4 Chirality in Calixarene-related Systems 143
5.6 Selective Functionalization 143
5.7 Calixarene Polymers 144

Chapter 6 Filling the Baskets: Complex Formation with Calixarenes 146
6.1 Metal Ion Complexes with Calixarenes Carrying *endo* OH, SH, or C=O Groups 147
6.2 Metal Cation Complexes with Calixarenes Carrying Substituents on the Lower Rim 150
6.2.1 Separate Pendant Arms on Lower Rim 150
6.2.1.1 Lower Rim Ethers 150
6.2.1.2 Lower Rim Esters 150
6.2.1.3 Lower Rim Ketones 152
6.2.1.4 Lower Rim Amides 152
6.2.1.5 Lower Rim Carboxylic Acids 154
6.2.1.6 Lower Rim Phosphorus- and Sulfur-containing Groups 158

6.2.1.7 Nitrogen-containing Chelating Groups on Lower Rim 158
6.2.2 Bridges on Lower Rim 159
6.2.2.1 Calixcrowns 159
6.2.2.2 Calixspherands 162
6.3 Metal Cation Complexes with Calixarenes Carrying Substituents on the Upper Rim 164
6.4 Anion Complexes with Calixarenes 165
6.5 Salt Complexes with Calixarenes 167
6.6 Molecular Complexes with Calixarenes 169
6.6.1 Solid State Complexes 169
6.6.2 Solution State Complexes with Molecular Cations 171
6.6.3 Solution State Complexes with Neutral Molecules 174
6.6.4 Gas Phase Complexes 177
6.7 Supramolecular Assemblies of Calixarenes 177
6.7.1 Dimeric Assemblies of Calixarenes 178
6.7.2 Oligomeric and Polymeric Assemblies of Calixarenes 180
6.7.3 Calixarenes in Monolayers, Interfaces, and Colloids 183

Chapter 7 Using the Baskets: Calixarenes in Action 185
7.1 Calixarenes as Catalysts 185
7.2 Ion Separations 189
7.3 Molecular Separations 190
7.3.1 Separations *via* Chromatographic Columns and Crystallization 190
7.3.2 Separations *via* Interfaces 191
7.4 Calixarenes as Sensors 192
7.4.1 Ion- and Molecule-selective Electrodes 192
7.4.2 Field Effect Transistors 194
7.4.3 Chromogenic and Fluorescent Sensors 195
7.4.4 Nonlinear Optical Compounds 198
7.4.5 Other Sensors 201
7.5 Miscellaneous Applications 201
7.6 Patent Literature 207
7.7 Concluding Remarks 208

Author Index 209

Subject Index 223

CHAPTER 1

From Resinous Tar to Molecular Baskets

'The world of books is the most remarkable creation of man . . . Even the books that do not last long, penetrate their own times at least, sailing farther than Ulysses even dreamed of, like ships on the seas. It is the author's part to call into being their cargoes and passengers—living thoughts and rich bales of study and jeweled ideas. And as for the publishers, it is they who build the fleet, plan the voyage, and sail on, facing wreck, till they find every possible harbor that will value their burden'

Clarence S. Day, *The Story of the Yale University Press Told by a Friend*

1.1 Introduction

The world of organic chemistry is populated by several million compounds distributed among hundreds of families. Some of these families have commanded the attention of chemists for many decades and have reached a venerable patrician status. Many others are more recently arrived and have yet to establish their place in the hierarchy of chemical importance. Among the latter is the family of compounds called the calixarenes which, although more than 50 years old, has gained widespread attention from the chemical community only during the last decade.

Calixarenes are [1_n]metacyclophanes (**1**) that acquired their name because of the resemblance of the shape of one of the conformers of the smallest member of their family to a type of Greek vase called a calix crater (Figure 1.1). The name was initially chosen to apply specifically to the phenol-derived cyclic oligomers, but it has subsequently taken on a more generic aspect and is now applied to a wide variety of structurally related types of compounds. The calixarenes were first discussed in comprehensive fashion in 1989 in the first volume of *Monographs in Supramolecular Chemistry*,[1] where the literature on the subject that had been published up to that time was covered in reasonably complete detail in 222 pages. Since 1989, however, there has been such a rapid expansion of the field that a somewhat less comprehensive coverage of topics is now necessary if this

[1] Gutsche, C. D. *Calixarenes* in 'Monographs in Supramolecular Chemistry'; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge; **1989**.

second volume is to be anywhere near as slim as the first. It is our endeavor in this second volume to include a significant portion of the pertinent literature citations in the field through 1996, but to do so in a somewhat selective fashion. The chapter headings used in the first volume are repeated in the present volume and include synthesis, characterization and physical properties, conformations, functionalization, complexation, and practical applications. For readers already familiar with calixarene chemistry this second volume should stand as an independent work. For readers new to the field, however, reference to the first volume should be made to provide the background on which the present volume builds.

1.2 Phenol-derived and Resorcinol-derived Calixarenes

The calixarene family can be subdivided into two major branches, the phenol-derived cyclooligomers (**2**) and the resorcinol-derived cyclooligomers (**3**), as shown in Figure 1.2. Both are discussed in the previous volume.[1] The present monograph, however, will deal almost exclusively with the phenol-derived compounds, the resorcinol-derived compounds having been the subject of a 1994 publication in *Monographs in Supramolecular Chemistry*[2] and a long review article.[3]

1.3 Historical Perspective

The story of the 'resinous tar[4] to molecular baskets' now called calixarenes is described in detail on pages 1–25 of the first volume,[1] where particular emphasis is given to the work by Zinke and coworkers. Zinke's investigations,[5] starting in the early 1940s and extending into the 1950s, dealt with what were thought to be cyclotetramers obtained from the base-induced reactions of *p*-alkylphenols with formaldehyde.[6] Experiments carried out by Cornforth and coworkers[7] in the 1950s indicated that the Zinke products were actually mixtures, and the investigations by Gutsche and coworkers starting in the mid-1970s established the identity of three of the components of the mixtures as cyclic tetramer, cyclic hexamer, and cyclic octamer.[8] It was in these early papers of Gutsche that the

[2] Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests* in 'Monographs in Supramolecular Chemistry'; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge; **1994**.

[3] Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, 52, 2663–2704.

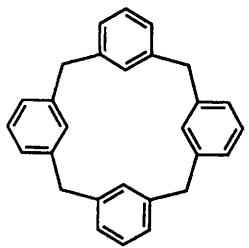
[4] Baeyer, A. *Ber.* **1872**, 5, 25, 280, 1094.

[5] Further insight into life in the Zinke laboratory at that time is provided in a delightful essay by Kappe, T. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 3–15.

[6] Zinke, A.; Ziegler, E. *Ber.* **1941**, *B*74, 1729; *idem. ibid.* **1944**, 77, 264; Zinke, A.; Zigeuner, G.; Hössinger, K.; Hoffmann, G. *Monatsh.* **1948**, 79, 438; Zinke, A.; Kretz, R.; Leggewie, E.; Hössinger, K. *ibid.* **1952**, 83, 1213.

[7] Cornforth, J. W.; D'Arcy Hart, P.; Nicholls, G. A.; Rees, R. J. W.; Stock, J. A. *Br. J. Pharmacol.* **1955**, 10, 73. Also see Cornforth, J. W.; Morgan, E. D.; Potts, K.T.; Rees, R. J. W. *Tetrahedron* **1973**, 29, 1659.

[8] (a) Gutsche, C. D.; Kung, T. C.; Hsu, M.-L. Abstracts of 11th Midwest Regional Mtg. of Am. Chem. Soc., Carbondale, IL, **1975**, no. 517; (b) Muthukrishnan, R.; Gutsche, C. D. *J. Org. Chem.* **1979**, 44, 3962; (c) Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. *J. Am. Chem. Soc.* **1981**, 103, 3782.



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$[1_4]$metacyclophane **Calix crater** **CPK model carrying a guest**

Figure 1.1 $[1_4]$*Metacyclophane, calix crater, and CPK model*

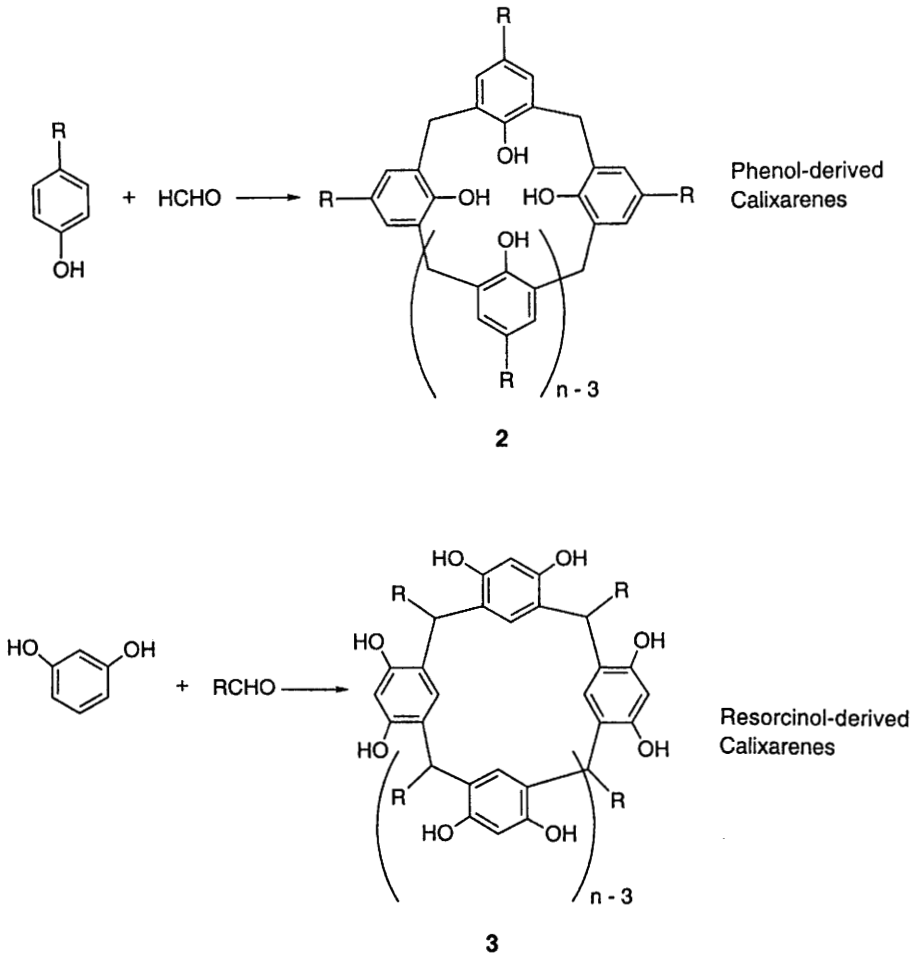

Figure 1.2 *Phenol-derived and resorcinol-derived calixarenes*

Zinke compounds acquired the name 'calixarene'.[9] During the 1980s this group devised simple and easily reproduced procedures for synthesizing *p-tert*-butylcalix[4]arene (**4**; R = *t*-Bu), *p-tert*-butylcalix[6]arene (**6**; R = *t*-Bu), and *p-tert*-butylcalix[8]arene (**8**; R = *t*-Bu) (see Figure 1.3) in good to excellent yield on any scale, from a gram or less to many kilograms.[10] The ready availability of these three calixarenes from cheap starting materials has been an important factor in the rapid escalation of research in this field during the last decade, the magnitude of which can be judged from the two books,[1,11] and the many reviews

[9] Gutsche, C. D.; Muthukrishnan, R. *J. Org. Chem.* **1978**, 43, 4905.

[10] (a) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1990**, 68, 234; (b) Gutsche, C. D.; Dhawan, B.; Leonis, M.; Stewart, D. *ibid.* **1990**, 68, 238; (c) Munch, J. H.; Gutsche, C.D. *ibid.* **1990**, 68, 243.

[11] 'Calixarenes, A Versatile Class of Macrocyclic Compounds', Vicens, J.; Böhmer, V. Eds.; Kluwer: Dordrecht; **1991**.

(short,[12] medium length,[13] and long[14]) that have been written on the calixarenes.

It is interesting to plot the growth of interest in the calixarenes, as depicted in Figure 1.4. Beginning with the 19th century experiments of Adolf von Baeyer, continuing through the early part of the 20th century with the introduction of Bakelite by Leo Baekeland, and extending to the early 1940s with the experi-

[12] Short reviews: (a) Vocanson, F.; Lamartine, R. 'The Chemistry of *p-tert*-Butyldihomooxacalix[4]arene', *Acros Org. Acta* **1996**, 2, 1, 6–7; (b) Asfari, Z.; Vicens, J. 'Calix[4]-bis-crowns', *Acros Org. Acta* **1996**, 2, 8–9; (c) Gutsche, C. D. 'Calixarenes', *Aldrichim. Acta* **1995**, 28, 3–9; (d) O'Conner, K. M.; Arrigan, D. W. M.; Svehla, G. 'Calixarenes in Electroanalysis', *Electroanalysis* **1995**, 7, 205–215; (e) Takeshita, M.; Shinkai, S. 'Recent Topics on Functionalization and Recognition Ability of Calixarenes', *Bull. Chem. Soc. Jpn.* **1995**, 68, 1088–1097; (f) Asfari, Z.; Wenger, S.; Vicens, J. 'Calixcrowns and Related Molecules', *Pure Appl. Chem.* **1995**, 67, 1037–1043; (g) Asfari, Z.; Vicens, J. 'The Chemistry of the Calix[5]arenes', *Acros Org. Acta* **1995**, 1, 18–21; (h) Danil de Namor, A. F.; Blackett, P. M.; Garrido Pardo, M. T.; Pacheco Tanaka, D. A.; Sueros Velarde, F. J.; Cabaleiro, M. C. 'From Molecules to Electrolytes. Electrochemical and Thermodynamic Aspects of the Interaction of Phenol and Resorcinol Based Calixarenes with Amines', *Pure Appl. Chem.* **1993**, 65, 415–422; (i) Roundhill, D. M.; Georgiev, E.; Yordanov, A. 'Calixarenes with Nitrogen or Phosphorus Substituents on the Lower Rim', *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 101–109; (j) Linnane, P.; Shinkai, S. 'Calixarenes: Adaptable Hosts Par Excellence', *Chem. Ind. (London)* **1994**, 811–814; (k) Asfari, Z.; Wenger, S.; Vicens, J. 'New Complexing Macrocycles: The Calixcrowns', *Supramol. Sci.* **1994**, 1, 103–110; (l) Swager, T. M.; Xu, B. 'Liquid Crystalline Calixarenes', *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 389–398; (m) Asfari, Z.; Weiss, J.; Vicens, J. 'Double-Calixarene Design, Synthesis, and Properties', *Synlett* **1993**, 719–725; (n) van Dienst, E.; Iwema Bakker, W. I.; Engbersen, J. F. J.; Verboom, W.; Reinhoudt, D. N. 'Calixarenes, Chemical Chameleons', *Pure Appl. Chem.* **1993**, 65, 387–392; (o) Schwing-Weill, M.-J.; Arnaud-Neu, F.; McKervey, M. A. 'Modulation of the Cation Complexing Properties in the Lower Rim of Chemically Modified Calixarene Series', *J. Phys. Org. Chem.* **1992**, 5, 496–501; (p) Asfari, Z.; Vicens, J. 'Calixarenes' *Janssen Chim. Acta* **1992**, 10, 3–10; (q) McKervey, M. A.; Böhmer, V. 'Calixarenes – Supramolecular Pursuits', *Chem. Br.* **1992**, 28, 724–727; (r) Gutsche, C. D.; Rogers, J. S.; Stewart, D.; See, K. A. 'Calixarenes: Paradoxes and Paradigms in Molecular Baskets', *Pure Appl. Chem.* **1990**, 62, 485–491; (s) Böhmer, V. 'Special Calixarenes, Synthesis and Properties', New Separation Chemistry Techniques for Radioactive Waste and Other Specific Applications; Elsevier Applied Science: London; **1991**, pp. 133–141.

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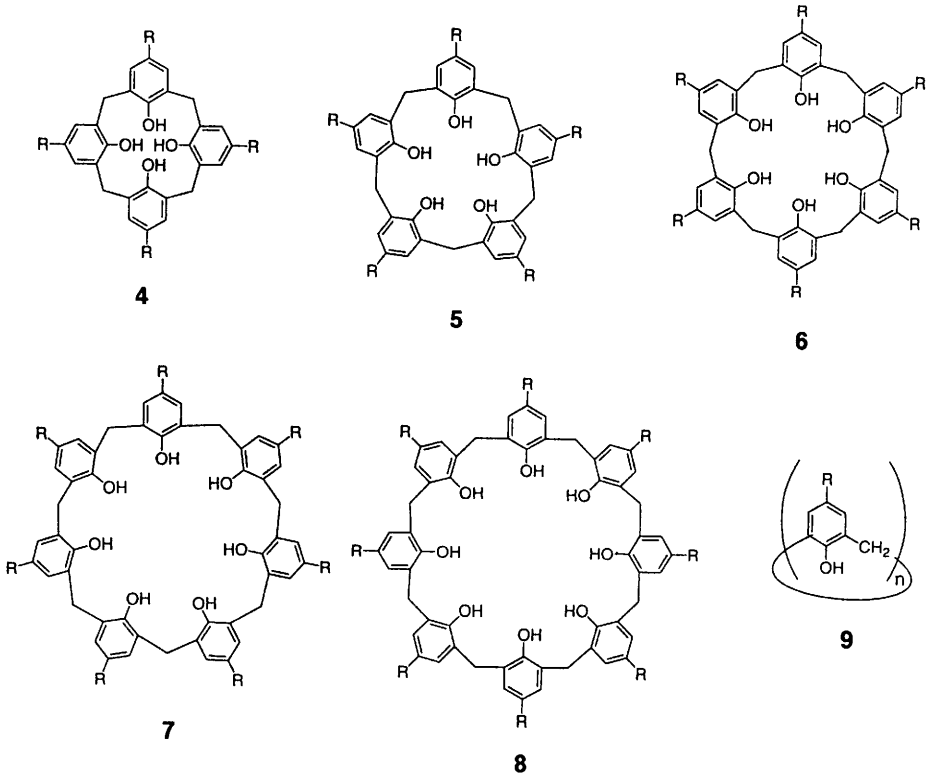

Figure 1.3 *Family of* p-tert-*butylcalix*[n]*arenes*

ments of Zinke and Niederl,[15] the growth curve is almost flat. A minor flurry of activity occurred in the 1950s in the laboratories of Cornforth and Hayes and Hunter, adding a slight positive lift. However, not until the 1970s with the entry of the Mainz group of Kämmerer (and then Böhmer), the Parma group of Andreetti, Pochini, and Ungaro, and the St Louis group of Gutsche (along with

Comprehensive Supramolecular Chemistry; Gokel, G., Ed.; Pergamon Press: Oxford; **1996**, Vol. 1, pp. 537–603; (c) Böhmer, V. 'Calixarenes, Macrocycles with (Almost) Unlimited Possibilties', *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 713–745; (d) Roundhill, D. M. 'Metal Complexes of Calixarenes', *Progr. Inorg. Chem.* **1995**, 533–592; (e) Böhmer, V.; Kraft, D.; Tabatabai, M. 'Inherently Chiral Calixarenes', *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 17–39; Brodesser, G.; Vögtle, F. 'Homocalixarenes and Homocalixpyridines', *ibid.* **1994**, 19, 111–135; (f) Shinkai, S. 'Calixarenes – The Third Generation of Supramolecules', *Tetrahedron* **1993**, 49, 8933–8968; (g) van Loon, J.-D.; Verboom, W.; Reinhoudt, D. N. 'Selective Functionalization and Conformational Properties of Calix[4]arenes: A Review', *Org. Prep. Proced. Int.* **1992**, 24, 437–462; (h) Gutsche, C. D. 'Calixarenes: An Overview', *Inclusion Compounds*; Atwood, J. L.; Davies, J. E. D.; MacNicol, D., Eds.; Oxford University Press: Oxford; **1991**, Vol. 4, pp. 27–63; (i) Böhmer, V.; Kämmerer, H. 'Oligonuclear Phenolic Compounds to Calixarenes', in *Chemistry and Physics of Macromolecules*; Fischer, E. W., Schulz, R. C.; Sillescu, H., Eds.; VCH: Weinheim; **1991**, pp. 13–38; (j) Gutsche, C. D. 'Calixarenes and the Art of Molecular Basketmaking', in *Synthesis of Macrocyclics: The Design of Selective Complexing Agents*; Izatt, R.M.; Christensen, J. J., Eds.; Wiley: New York; **1987**, pp. 93–165; (k) Gutsche, C. D. 'The Calixarenes', *Top. Curr. Chem.* **1984**, 123, 1–47.

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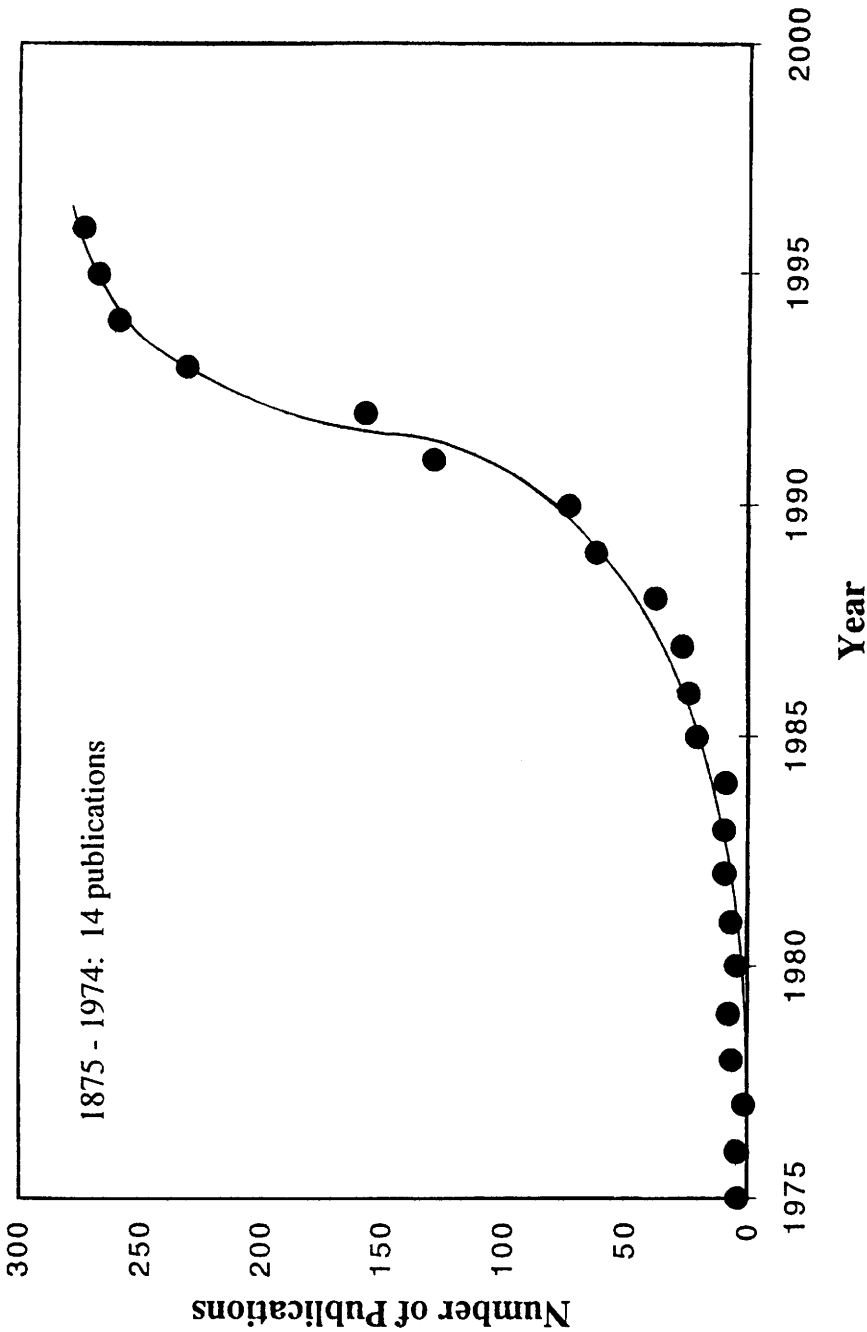
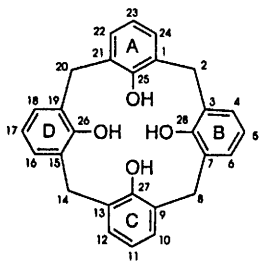


Figure 1.4 *Growth curve of interest in calixarene chemistry*

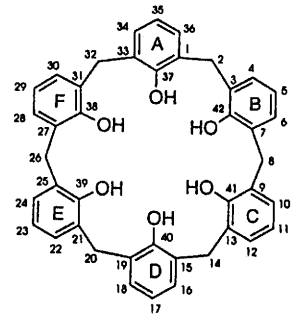
the Petrolite group of Buriks *et al.*) does the curve begin to move inexorably upward. Then, starting in the mid-1980s and continuing to the mid-1990s the curve becomes ever more steeply ascending, now reaching a plateau with the publication of five or more papers/week. The items of fascination that have led to this explosive growth are the subject of the remainder of this book.

1.4 Nomenclature and Representation

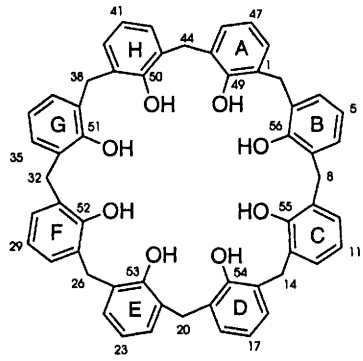
The original calixarene nomenclature implicitly included the OH groups as part of the structure being named. As the field has matured and proliferated, however, this presumption no longer seems warranted, and the term 'calixarene' is better applied only to the basic structures devoid of substituents, as illustrated in Figure 1.5 for the cyclic tetramer, dihomooxatetramer, cyclic hexamer, and cyclic octamer derived from a *p*-substituted phenol and formaldehyde. The phenol-derived and resorcinol-derived cyclooligomers can be differentiated by referring to the former as *endo*-OH calixarenes (*i.e.* the OH groups oriented toward the



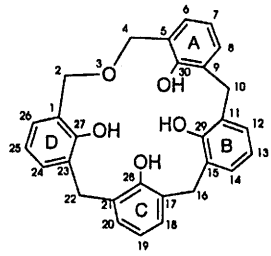
calix[4]arene-25,26,27,28-tetrol



calix[6]arene-36,37,38,39,40,41,42-hexol



calix[8]arene-49,50,51,52,53,54,55,56-octol



2,3-dihomo-3-oxacalix[4]arene-27,28,29,20-tetrol

Figure 1.5 *Nomenclature of calixarenes*

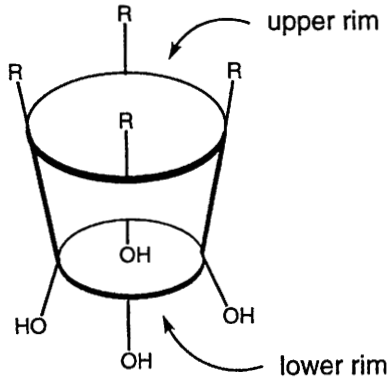


Figure 1.6 *Representation of the calixarenes and designation of the faces*

annulus) and the latter as *exo*-OH calixarenes (*i.e.* the OH groups oriented away from the annulus). As illustrated in the next chapter, calixarenes are now known that contain both *endo*- and *exo*-OH groups. Clearly, both the phenol-derived and the resorcinol-derived cyclooligomers are members of the calixarene family, as was recognized by the earlier assignment of the name 'calixresorcarene' to the latter.[1] Unhappily, it is becoming increasingly the custom to shorten this to 'resorcarene', belying its cyclic array. By analogy, the phenol-derived cyclooligomers should be called 'phenarenes', clearly a less felicitious and descriptive name than 'calixarenes'. It is hoped, therefore, that the 'calixresorcarene' name will be retained even though it flies in the face of the power of brevity.

Since vases ordinarily stand upright on their bases and since calixarenes derive their name from a Greek vase, calixarene structures should generally be depicted with the aryl carbon between the methylene groups (*i.e.* usually carrying an oxygen function) pointing downward and the aryl *para* carbon pointing upward. Accordingly, the face bearing the *endo* hydroxyl groups is designated as the 'lower rim', and the face bearing the *para* substituents is designated as the 'upper rim' (Figure 1.6). 'Upside-down' representations of the calixarenes frequently appear in the literature, and Böhmer has suggested the designations 'narrow rim' and 'wide rim' to avoid the orientation-dependency. All such designations, however, become vague when applied to larger calixarenes in which there may be no well-defined 'upper, wide rim' or 'lower, narrow rim'. Still another designation that might be useful is based on the cyclic structure *per se*, without recourse to either its orientation or its shape. It names the lower, narrow rim as the '*endo* rim' and the upper, wide rim as the '*exo* rim'. In this book, however, the 'upper rim/lower rim' nomenclature will be retained.

As already indicated, the term 'calixarene' is variously employed in different contexts. In colloquial usage (*e.g.* as often employed in the discussion section of a paper) the name implies the presence of hydroxyl groups as, for instance, in '*p-tert*-butylcalix[4]arene' as applied to **4** (R = *t*-Bu). More precisely, in keeping with the suggestion above, the accurate specification of a compound (*e.g.* as used in the experimental section of a paper) implies only the basic skeleton to which

the substituents, including the OH groups, are attached at positions designated by appropriate numbers. Thus, **4** (R = *t*-Bu) becomes 5,11,17,23-tetra-*tert*-butylcalix[4]arene-25,26,27,28-tetrol. The abbreviated names will be frequently used when it is clear that all of the *p*-positions (*exo* positions) are occupied by the same group (*e.g.* four *tert*-butyl groups in *p-tert*-butylcalix[4]arene; eight *tert*-butyl groups in *p-tert*-butylcalix[8]arene, *etc.*). In cases where it might be ambiguous, however, the name will be made more explicit by indicating the number of *p*-substituents (*e.g.* tetra-*p-tert*-butylcalix[4]arene, mono-*p-tert*-butylcalix[6]arene, *etc.*).

The calixarenes represented by the numbers **4**–**8** appear many times throughout this book, so to designate these structures they will be represented by a number (*i.e.* **4**–**8**) which specifies the number of aryl residues in the cyclic array) and a superscript which specifies the *p*-substituent (*i.e.* *t*-Bu, H, SO_3H, *etc.*) Thus, *p-tert*-butylcalix[4]arene is represented as $\mathbf{4}^{t\text{-Bu}}$; *p*-H-calix[6]arene (more correctly named simply as calix[6]arene) is represented as $\mathbf{6}^{\mathbf{H}}$, *etc.* To avoid any confusion with the other numbers in the text the numbers **4**–**8** when used in this fashion appear in a characteristic font. In many instances when the generalized identity and position of attachment of substituents are made more specific, the following conventions are used: (a) the same group (*i.e.* R or Y) appearing on the carbon or oxygen of two or more aryl residues is specified as $R^{1,2}$, $R^{1,3,4}$, R^{1-4}, $Y^{2,4,6}$, *etc.*; (b) a group bridging two positons is specified as R^1R^2, R^1R^3, Y^1Y^4, *etc.*

Another nomenclature device that is used throughout the book as an easy way to indicate the arrangement of substituents on the upper or lower rims of a calixarene is to label the rings A, B, C, *etc.*, and to specify the rings to which the substituents are attached. Thus, a di-*p-tert*-butylcalix[4]arene can be designated as an 'A,B-' or an 'A,C-di-*p-tert*-butylcalix[4]arene'; the symmetrical trimethyl ether of a calix[6]arene can be designated as an A,C,E-trimethyl ether, *etc.* The ways for naming and representing the conformational isomers of calixarenes are discussed in Section 4.1.

CHAPTER 2

Making the Baskets: Synthesis of Calixarenes

'The whole difference between construction and creation is exactly this: that a thing constructed can only be loved after it is constructed; but a thing created is loved before it exists'

G. K. Chesterton, Preface to Dickens's *Pickwick Papers*

This author's attention to phenol–formaldehyde cyclooligomers began in the 1970s when it became clear that molecular baskets would be necessary for the construction of enzyme mimics. Already known at that time were the cyclodextrins and the crown ethers. However, the cyclodextrins were not available by *de novo* synthesis, being accessible only by isolation from natural sources, and the crown ethers in their unadorned form appeared to be more like discs than baskets. With neither of these systems meeting the author's particular requirements at the time, a search for an alternative was initiated and, as chronicled in the first volume of this series, led to useful procedures for making the cyclooligomers that now are called calixarenes. Concomitant with the author's exploration of one-step methods for synthesizing calixarenes, multi-step methods were being exploited first by Kämmerer and later by Böhmer. These two approaches provide the basis for the modern era of calixarene chemistry, complementing one another in their abilities to let the chemist fashion the basic baskets that ultimately produced the great variety of compounds discussed in this book.

2.1 One-step Synthesis of Calixarenes

2.1.1 Base-induced Reactions

Synthesis is the lifeforce, the *sine qua non*, for creating the members of chemical families. For some families of compounds the chemist must rely on Nature to achieve the task, but for many other families chemists can employ their own ingenuity in coaxing the elements into proper combinations. The ultimate utility of a family of chemical compounds is usually related to the ease with which this can be done, the calixarenes providing a good case in point. Like the cyclodex-

trins, which were discovered at the turn of the century but which did not become actively investigated until Dexter French showed how they could be separated and purified,[16] the calixarenes languished for three decades following their discovery in the 1940s. The early procedures for their one-step preparation were not routinely reproducible and led to difficultly separable mixtures. This changed in the early 1980s with the introduction of reliable procedures for preparing *p-tert*-butylcalix[4]arene (**4**$^{t\text{-Bu}}$), *p-tert*-butylcalix[6]arene (**6**$^{t\text{-Bu}}$), and *p-tert*-butylcalix[8]arene (**8**$^{t\text{-Bu}}$) (designated as the 'major calixarenes'), although gaps remained in the family unit since neither the cyclic pentamer (**5**$^{t\text{-Bu}}$) nor the cyclic heptamer (**7**$^{t\text{-Bu}}$) (designated as the 'minor calixarenes') are obtained in comparable yields from one-step reaction mixtures.[17] In response to the recent interest in the cyclic pentamer **5**$^{t\text{-Bu}}$, which retains the conformational features of the cyclic tetramer but possesses a somewhat larger cavity, moderately satisfactory syntheses have now been published[18] which provide this compound in *ca.* 15–20% yield. A recent study[19] directed to optimizing the yield of the cyclic heptamer **7**$^{t\text{-Bu}}$ provides conditions for obtaining it in *ca.* 11–17% yield.

Although *p-tert*-butylphenol is the quintessential starting material for the one-step synthesis of calixarenes, a few other *p*-substituted phenols have been reported to yield calixarenes, albeit with generally less clean results.[20,21] *p*-Benzylphenol, for example, gives a 33% yield of *p*-benzylcalix[6]arene along with *p*-benzylcalix[8]arene.[22] The product mixture from *p*-phenylphenol and formaldehyde, previously reported to contain *p*-phenylcalix[6]arene (**6**^{Ph}), *p*-phenylcalix[7]arene (**7**^{Ph}), and *p*-phenylcalix[8]arene (**8**^{Ph}),[23] has been shown also to contain *ca.* 20% of *p*-phenylcalix[4]arene (**4**^{Ph}).[24] *p*-Cresol has been reported to give *p*-methylcalix[6]arene in 74% yield,[25] *p*-adamantylphenol to give *p*-adamantylcalix[8]arene in 72% yield,[26] and *p*-benzyloxyphenol to give *p*-benzyloxycalix[8]arene in 48% yield.[27]

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[20] The resorcinol-derived calixarenes, generally made *via* acid catalysis, have recently been found to be accessible by base-induced condensation as well; Konishi, H.; Iwasaki, Y.; Morikawa, O.; Okano, T.; Kiji, J. *Chem. Express* **1990**, 5, 869; Konishi, H.; Iwasaki, Y. *Synlett* **1995**, 612.

[21] Many phenols have been tried, generally without success. A typical example is reported by Yilmaz, M.; Vural, U. S. *Synth. React. Inorg. Met.-Org. Chem.* **1991**, 21, 1231, who used 4-nitrophenol, 4-hydoxybenzoic acid, 4-hydroxyacetophenone, 1,4-dihydroxybenzene, 4-phenoxyphenol, 4-hydroxybenzyl alcohol, 4-cyanophenol, 4-hydroxymethylbenzoic acid and 4-hydroxyethylbenzoic acid and in all cases obtained amorphous, unextractable material.

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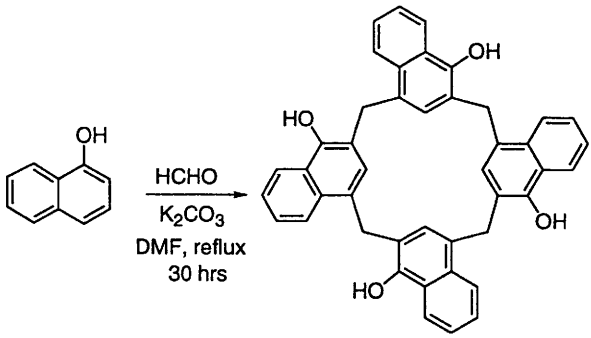

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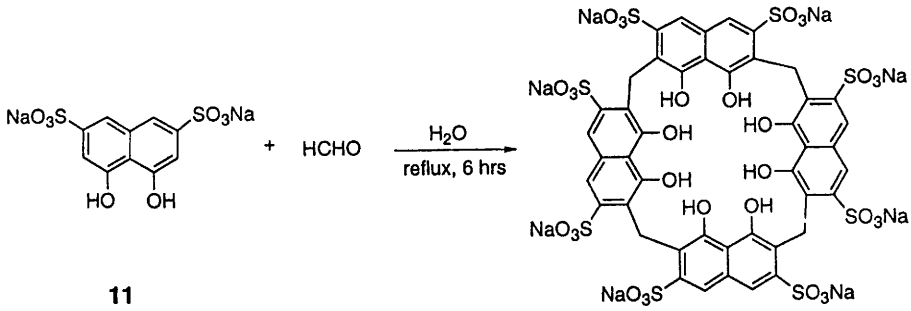
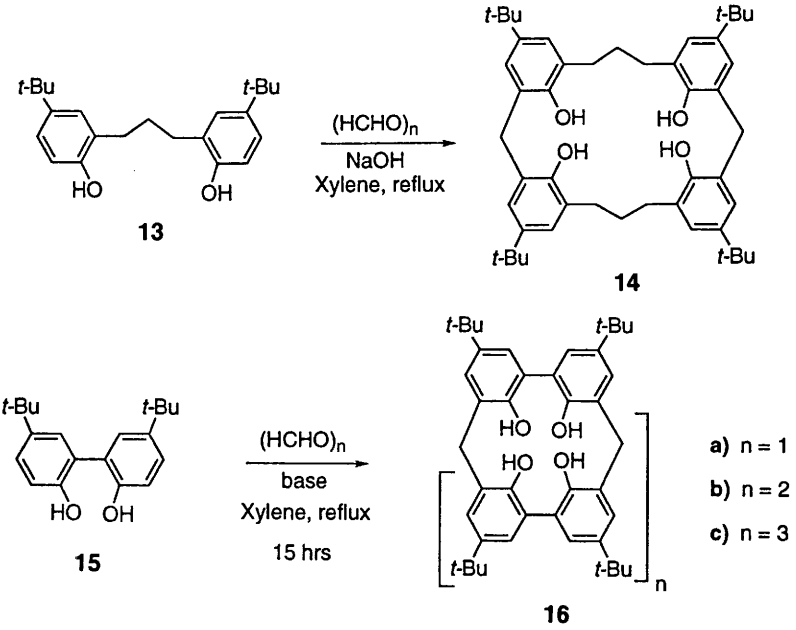


11 **12**

Interesting calixarenes[20] and calixarene-related compounds have been obtained in one-step reactions from 1-naphthol, from the naphthalenediol disulfonate **11**, and from and the bis-phenols **13**, **15**, and **17**. Although 2-naphthol reacts with formaldehyde to yield a simple bis-naphthol, 1-naphthol produces a mixture containing 9.6% of the symmetrical *exo*-OH cyclic tetramer **10** accompanied by 5% and 16% of two other cyclic tetramers in which the naphthol residues are unsymmetrically placed in the cyclic array.[28] When the disodium salt of 1,8-dihydroxy-3,6-naphthalenedisulfonic acid (chromotropic acid) (**11**) is treated with an aqueous solution of formaldehyde and the mixture is allowed either to stand at room temperature for a week or is refluxed 6 h, a high yield of the *endo*-OH cyclic tetramer **12** is formed.[29] The ease with which this condensation occurs is surprising in view of the deactivating effect of the sulfonic acid groups

[28] Georghiou, P. E.; Li, Z. *Tetrahedron Lett.* **1993**, 34, 2887; Georghiou, P. E.; Li, Z. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 55; Georghiou, P. E.; Ashram, M.; Li, Z.; Chaulk, S. G. *J. Org. Chem.* **1995**, 60, 7284; Georghiou, P. E.; Li, Z.; Ashram, M.; Miller, D. O. *J. Org. Chem.* **1996**, 61, 3865.

[29] Poh, B.-L.; Lim, C. S.; Khoo, K. S. *Tetrahedron Lett.* **1989**, 30, 1005; Poh, B.-L.; Lim, C. S. *Tetrahedron* **1990**, 46, 3651; Poh, B.-L.; Tan, C. M.; Loh, C. L. *ibid.* **1993**, 49, 3849.



adjacent to the locus of condensation with the formaldehyde.[30] Interesting cation effects have been noted in the one-step reactions of the bisphenols **13** and **15** with paraformaldehyde. With NaOH as the base, compound **13** affords a 90% yield of **14**, while with LiOH, KOH, RbOH, or CsOH as the base, **13** gives yields only in the 10–36% range.[31] With NaOH as the base, compound **15** affords a product containing 51% of **16b** and only a trace of **16c**, whereas with CsOH as the base, **16c** is produced in 66% yield accompanied by only 4% of **16b**.[32,33] With KOH as the base, approximately equal amounts of the two cyclooligomers are formed, while none of the bases yielded any of the cyclic dimer **16a**. A substituent effect is noted in the heat-induced condensation of **17** with formaldehyde to form **18** (containing exocyclic OH groups), the reaction proceeding in considerably higher yield when R = *t*-Bu than when R = Me.[34] These compounds have also been prepared in a stepwise fashion[34] starting with the bromomethylation of **20a** to give **20b**, condensation with a phenol to give **21** followed by treatment with HCHO in an autoclave at 180 °C to produce 49% of **18**.

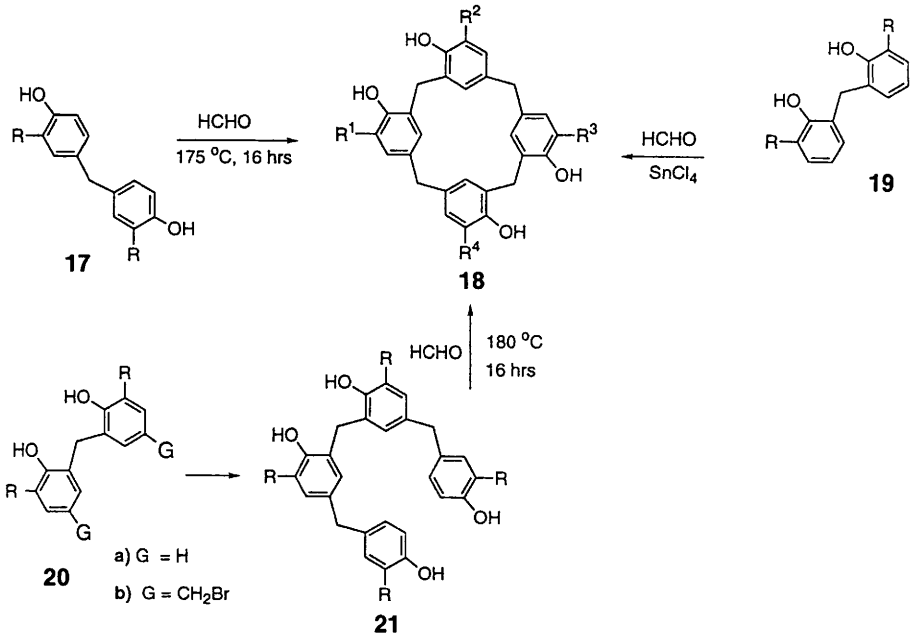
[30] It is interesting to note that 1-amino-8-hydroxy-3,6-naphthalenedisulfonic acid also condenses with HCHO to form a cyclic tetramer, but only one of the *o*-positions of each of the naphthalene units is involved; the other bridges are formed to the amino function at C-1: Poh, B-L.; Chin, L. Y.; Lee, C. W. *Tetrahedron Lett.* **1995**, 36, 3877.

[31] Yamato, T.; Saruwatari, Y.; Nagayama, S.; Meeda, K.; Tashiro, M. *J. Chem. Soc., Chem. Commun.* **1992**, 861.

[32] Yamato, T.; Hasegawa, K-i.; Saruwatari, Y.; Doamekpor, L. K. *Chem. Ber.* **1993**, 126, 1435; Yamato, T.; Yasumatsu, M.; Saruwatari, Y.; Doamekpor, L. K. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 315.

[33] O'Sullivan, P.; Böhmer, V.; Vogt, W.; Paulus, E. F.; Jakobi, R. A. *Chem. Ber.* **1994**, 127, 427.

[34] Böhmer, V.; Dörrenbächer, R.; Frings, M.; Heydenreich, M.; de Paoli, D.; Vogt, W.; Ferguson, G.; Thondorf, I. *J. Org. Chem.* **1996**, 61, 549.



2.1.2 Acid-catalyzed Reactions

In addition to the three major calixarenes $\mathbf{4}^{t\text{-Bu}}$, $\mathbf{6}^{t\text{-Bu}}$, and $\mathbf{8}^{t\text{-Bu}}$ and the two minor calixarenes $\mathbf{5}^{t\text{-Bu}}$ and $\mathbf{7}^{t\text{-Bu}}$, a number of 'large calixarenes'[35] separated from one-step reaction mixtures have been characterized. Initially,[24] these were isolated from base-induced reactions of *p-tert*-butylphenol and formaldehyde by using various sequences of selective extraction and chromatographic procedures, which afforded compounds **9** (R = *t*-Bu; n = 9–16) in yields generally well below 1%. More recently it has been discovered that considerably greater amounts of these large calixarenes are present in the acid-catalyzed reaction mixture of *p-tert*-butylphenol and formaldehyde (generated from trioxane) and that calixarenes as large as n = 20 or greater are present.[24] It had long been thought that the acid-catalyzed reactions of *p*-alkylphenols and formaldehyde produced linear oligomers almost exclusively,[36] but it is now realized that under certain conditions the acid-catalyzed reaction produces calixarenes in almost quantitative yield.[24,37]

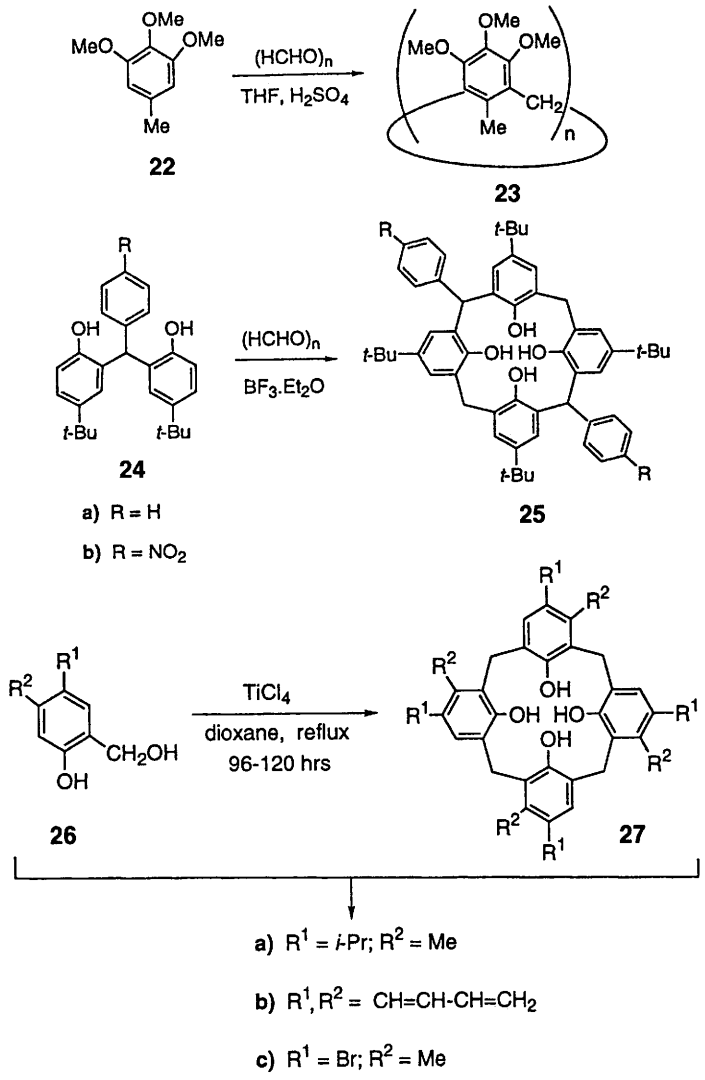
[35] Since the research on the 'large calixarenes' has been carried out in the laboratories of Gutsche and coworkers in the big state of Texas, these compounds have been colloquially designated as 'Texarenes'.

[36] Ludwig, J. F.; Bailie, A. G., Jr. *Anal. Chem.* **1986**, 58, 2069.

[37] Acid-catalyzed condensation of resorcinols and aldehydes, on the other hand, provides the method of choice for the synthesis of the calixresorcarenes. An interesting variation on this theme has been discovered by Botta and coworkers in which the starting materials are 2,4-dimethoxycinnamates: Botta, B.; DiGiovanni, M. C.; Monache, G. D.; De Rosa, M. C.; Gacs-Baitz, E.; Botta, M.; Corelli, F.; Tafi, A.; Santini, A.; Benedetti, E.; Pedone, C.; Misiti, D. *J. Org. Chem.* **1994**, 59, 1532; Botta, B.; Delle Monache, G.; De Rosa, M. C.; Carbonetti, A.; Gacs-Baitz, E.; Botta, M.; Corelli, F.; Misiti, D. *ibid.* **1995**, 60, 3657.

In a reaction similar in some respects to those described above, 3,4,5-trimethoxytoluene (**22**) reacts with paraformaldehyde under acidic conditions[38] to yield a mixture of cyclooligomers **23** with $n = 4$–13. Calix[4]arenes carrying substituents on the bridge methylene groups (**25**) have been prepared by the acid-catalyzed reaction of triphenylmethanes **24** with paraformaldehyde and obtained in 18–30% yields.[39]

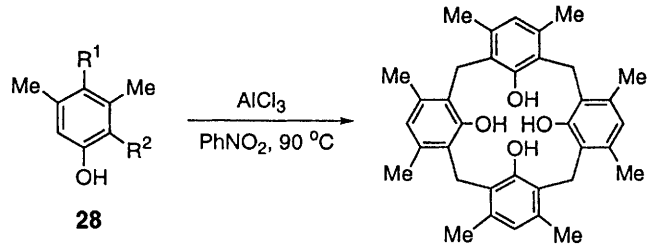
Hydroxymethylphenols yield oxacalixarenes under mild conditions of acid



[38] Schätz, R.; Weber, C.; Schilling, G.; Oeser, T.; Huber-Patz, U.; Irngartinger, H.; von der Lieth, C.-W.; Pipkorn, R. *Liebigs Ann. Chem.* **1995**, 1401.

[39] (a) Sartori, G.; Maggi, R.; Bigi, F.; Arduini, A.; Pastorio, A.; Porta, C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1657; (b) Sartori, G.; Bigi, F.; Porta, C.; Maggi, R.; Mora, R. *Tetrahedron Lett.* **1995**, 36, 2311.

catalysis (see Section 2.5.2) but can also lead to calixarenes under more strenuous conditions. For example, monohydroxymethyl phenols **26a**, **26b**, and **26c**, prepared either by hydroxymethylation with formaldehyde and base or by reduction of the corresponding carboxylic acid, yield calix[4]arenes **27a**,[40] **27b**,[40] and **27c**[41] in 29%, 5%, and 25% yield, respectively, when treated with $TiCl_4$. Both hydroxymethylphenols **28a** and **28b** produce the same octamethylcalix[4]arene **29** in *ca.* 34% yield when treated with $AlCl_3$ in nitrobenzene at 90 °C, **28a** isomerizing to **28b** prior to cyclization.[42] Although the bisphenols **19** fail to form calix[4]arenes under the heat-induced cyclization conditions that are successful with **17** (*vide supra*), cyclization of **19** (R = *t*-Bu) can be induced with $SnCl_4$ to give a 46% yield of **18** accompanied by 16% of the analogous calix[6]arene and 9% of the analogous calix[8]arene.[43] However, **19** (R = Me) yields only linear oligomers under comparable conditions.[39b] An especially interesting example using a bisphenol is the condensation of 2,4-dihydroxy-3-hydroxymethylbenzophenone (**30**), which yields a calix[5]arene (**31**) containing both *endo* and *exo* OH groups.[44]

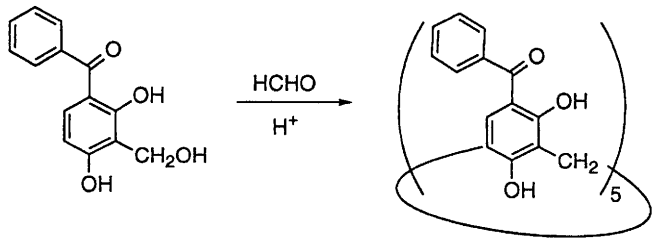


28

a) $R^1 = CH_2OH$; $R^2 = H$

b) $R^1 = H$; $R^2 = CH_2OH$

29



30

31

[40] (a) Wolff, A.; Böhmer, V.; Vogt, W.; Ugozzoli, F.; Andreetti, G. D. *J. Org. Chem.* **1990**, 55, 5665; (b) Andreetti, G. D.; Böhmer, V.; Jordon, J. G.; Tabatabai, M.; Ugozzoli, F.; Vogt, W.; Wolff, A. *ibid.* **1993**, 58, 4023.

[41] Fu, D.-K.; Xu, B.; Swager, T. M. *J. Org. Chem.* **1996**, 61, 802.

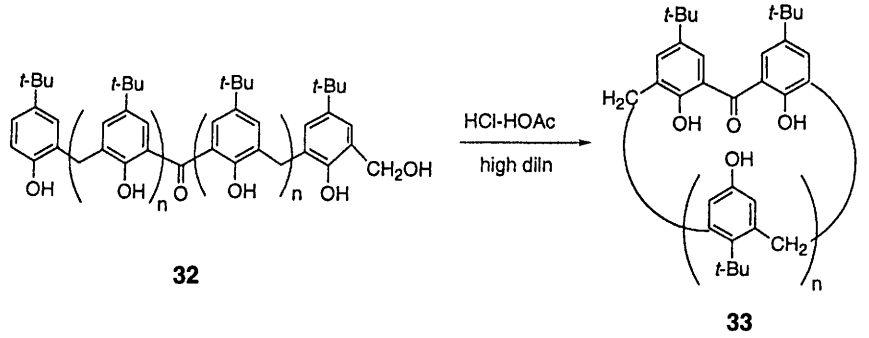
[42] (a) Dahan, E.; Biali, S. E. *J. Org. Chem.* **1989**, 54, 6003; (b) Dahan, E.; Biali, S. E. *ibid.* **1991**, 56, 7269.

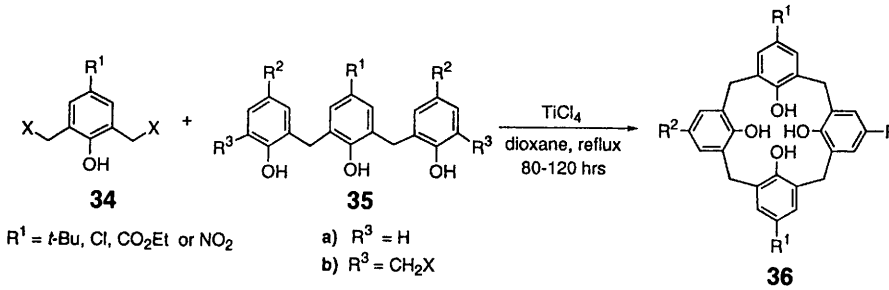
[43] Sartori, G.; Porta, C.; Bigi, F.; Maggi, R.; Peri, F.; Marzi, E.; Lanfranchi, M.; Pellinghelli, M. A. *Tetrahedron* **1997**, 53, 3287.

[44] Tabatabai, M.; Vogt, W.; Böhmer, V.; Ferguson, G.; Paulus, E. F. *Supramol. Chem.* **1994**, 4, 147.

2.2 Fragment Condensation Synthesis of Calixarenes

A nonconvergent stepwise synthesis of a calix[4]arene (see ref. 1, pp. 36–38) was first accomplished by Hayes and Hunter in the 1950s and expanded to include the synthesis of calix[5]-, -[6]-, and -[7]arenes by Kämmerer in the 1970s. A similar approach has recently been used to cyclize linear oligomers **32** carrying a carbonyl group on one of the bridges to the corresponding oxo-calix[4]-, -[5]-, and -[6]arenes **33**.[45] The linear stepwise approach was improved, starting in 1979, by Böhmer and coworkers who introduced the convergent approach aptly called 'fragment condensation'. It continues today to be skillfully exploited by these and other workers with particular utility for the construction of polysub-





[45] Ohba, Y.; Irie, K.; Zhang, F. S.; Sone, T. *Bull. Chem. Soc. Jpn.* **1993**, 66, 828; Ito, K.; Izawa, S.; Ohba, T.; Ohba, Y.; Sone, T. *Tetrahedron Lett.* **1996**, 37, 5959.

stituted, dissymmetric, asymmetric, and bridged calixarenes (see Sections 2.3 and 2.4). Whether in some cases it should actually be classed as a 'one-step' procedure is perhaps a moot point. Examples are shown below[46] of the preparation of polysubstituted calixarenes by (a) a '3 + 1' procedure, combining compounds of the general structures **34** (R = *t*-Bu, Cl, CO_2Et, or NO_2) and **35a** (R = *t*-Bu, Cl, CO_2Et, or NO_2) to give the calix[4]arenes **36** in 25–30% yields (see ref. 1, pp. 38–47) and (b) a '3 + 3' procedure combining **35a** (R^1 = Cl; R^2 = *t*-Bu) with **35b** (R^1 = *t*-Bu; R^2 = Cl; X = Br) to give the calix[6]arene **37** in 9% yield.[47] When **35a** (R^1 = Cl; R^2 = *t*-Bu) is treated with **35b** (R^1 = *t*-Bu; R^2 = Cl; X = OH), however, varying amounts of calix[4]arene are also formed which are postulated to be the result of an acid-catalyzed reversion of the calix[6]arene. Similarly, an attempt to make a calix[5]arene by a '3 + 2' combination yielded only a calix[4]arene.[48] In both of these cases a $TiCl_4$ catalyst was used, and a template effect may be favoring the formation of the calix[4]arene. More recently it has been reported that a '3 + 2' procedure using heat-induced condensation leads successfully to a monodeoxycalix[5]arene and to a fully hydroxylated calix[5]arene in 25% and 19% yield, respectively,[49] as well as to a calix[5]arene carrying three different *p*-substituents in 27–32% yield.[50,51] A fragment condensation that comes even closer to being a true one-step process (*i.e.* none of the aryl rings bridged by methylene groups prior to reaction) involves the combination of two molecules of **34** (R^1 = *t*-Bu, Ph, or CH_2CO_2Et; X = Br) with two molecules of a *p*-substituted phenol to give calix[4]arenes with an ABAB substitution pattern.[52] Although the yields are only 9–11%, the reaction provides a quick way for obtaining compounds that would require numerous steps if made by selective functionalization of $\mathbf{4}^{t\text{-Bu}}$ (see Chapter 5). A similar reaction, leading to a 66% yield of a calix[4]arene with *exo* OH groups (**40**), involves the condensation of mesitol (**38**) with its bis-chloromethylated analog **39a**.[53] Reaction of **38** with **39b**, on the other hand, gives a mixture of products containing one, two, and three OH groups, demonstrating the reversibility of the Friedel–Crafts condensation and the resulting processes of dealkylation and recombination.

A 2 + 2 fragment condensation of **41** and **42** has been employed in the synthesis of calix[4]arenes **43** carrying substituents (R^1 and/or R^2 = Me, Et, *i*-Pr, *t*-Bu, *p*-Ar)[54] on the methylene bridges.[55] The substituents on the methylene

[46] Other recent examples of convergent procedures include the '2 + 2' reaction to give a calix[4]arene with an AABB substitution pattern: No, K.; Hwang, K. L. *Bull. Korean Chem. Soc.* **1993**, 14, 753.

[47] de Mendoza, J.; Nieto, P. M.; Prados, P.; Sánchez, C. *Tetrahedron* **1990**, 46, 671.

[48] Böhmer, V.; Marschollek, F.; Zetta, L. *J. Org. Chem.* **1987**, 52, 3200.

[49] (a) Usui, S.; Deyama, K.; Kinoshita, R.; Odagaki, Y.; Fukazawa, Y. *Tetrahedron Lett.* **1993**, 34, 8127; (b) Haino, T.; Harano, T.; Matsumura, K.; Fukawaza, Y. *ibid.* **1995**, 36, 5793.

[50] No, K.; Kwon, K. M. *Synthesis* **1996**, 1293.

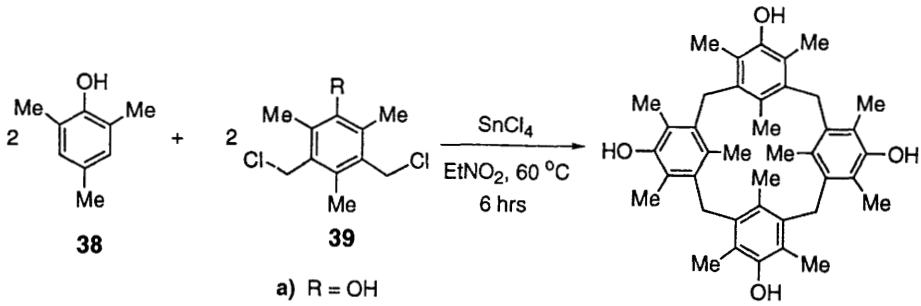
[51] An unpublished '4 + 2' synthesis of a calix[6]arene has been described.[14c (see ref. 34)]

[52] Böhmer, V.; Jung, K.; Schön, M.; Wolff, A. *J. Org. Chem.* **1992**, 57, 790.

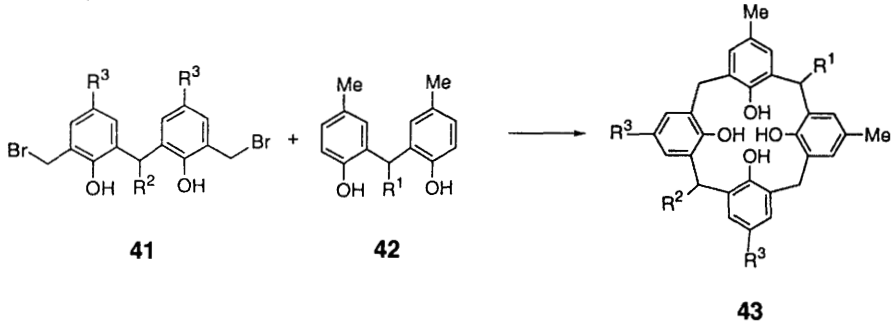
[53] Pappalardo, S.; Ferguson, G.; Gallagher, J. F. *J. Org. Chem.* **1992**, 57, 7102.

[54] For a method of synthesis of unsymmetrical 1,1-bis(2-hydroxyaryl)alkanes, see Katritzky, A. R.; Zhang, Z.; Lang, H.; Lan, X. *J. Org. Chem.* **1994**, 59, 7209.

[55] Grüttner, C.; Böhmer, V.; Vogt, W.; Thondorf, I.; Biali, S. E., Grynszpan, F. *Tetrahedron Lett.* **1994**, 35, 6267; Biali, S. E.; Böhmer, V.; Cohen, S.; Ferguson, G.; Grüttner, C.; Grynszpan, F.; Paulus, E. F.; Thondorf, I.; Vogt, W. *J. Am. Chem. Soc.* **1996**, 118, 12938.



bridges can assume an *exo* (equatorial) or *endo* (axial) orientation, resulting in a mixture of stereoisomers which is separable by column chromatography. In the case of the dialkyl-substituted compounds the *exo-exo* isomers predominate (interconvertible by cone–cone inversion to the higher energy *endo-endo* isomers).



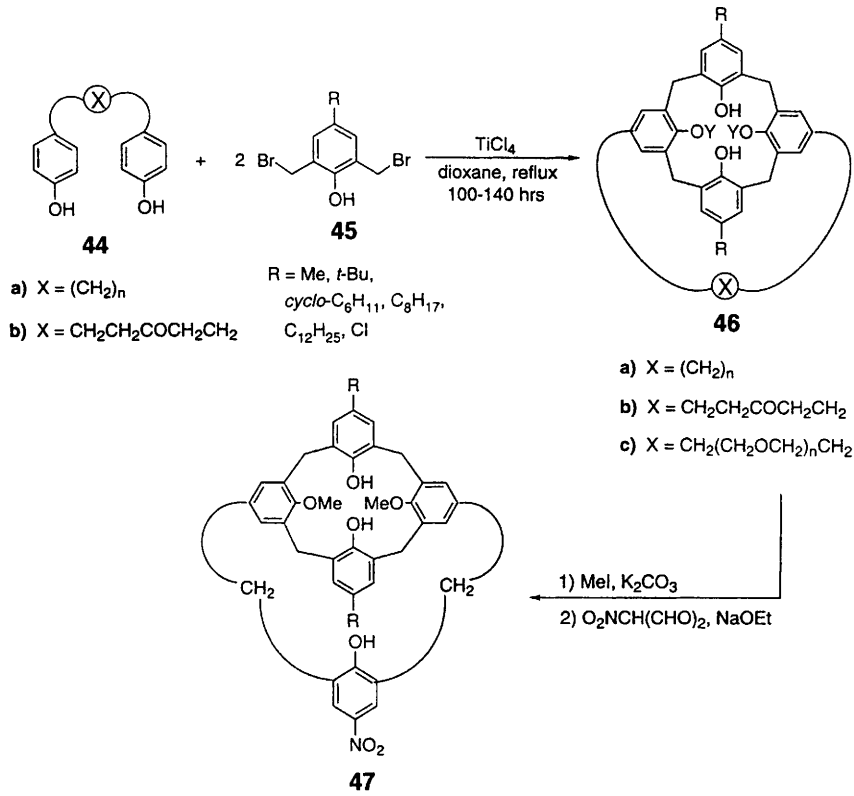
2.3 Synthesis of Bridged Calixarenes

Calixarenes in which bridging is introduced *after* the basic ring structure has been established are discussed in Chapter 5, and only those procedures in which bridging is an *integral* part of the calixarene forming process are discussed in the present section. The classic example of such a process involves the '2 + 1 + 1' fragment condensation of α,ω-bis(*p*-hydroxyphenyl)alkanes (see ref. 1, pp. 42–43) **44a** with **45** (R = Me, *t*-Bu, Ph, cyclo-C_6H_{11}, C_8H_{17}, $C_{12}H_{25}$, $C_{18}H_{37}$, Cl) to give the corresponding **46a** compounds (n = 5–16).[56] This approach has been exploited in an interesting fashion[57] in the condensation of **44b** with **45** (R = Me, *t*-Bu, cyclo-C_6H_{11}, C_8H_{17}) to give 5–37% yields of the corresponding upper rim-bridged calix[4]arenes **46b** (Y = H) to which, by methylation to **46b** (Y = Me)

[56] (a) Böhmer, V.; Goldmann, H.; Vogt, W. *J. Chem. Soc., Chem. Commun.* **1985**, 667; (b) Böhmer, V.; Goldman, H.; Kaptein, R.; Zetta, L. *J. Chem. Soc., Chem. Commun.* **1987**, 1358; (c) Paulus, E.; Böhmer, V.; Goldmann, H.; Vogt, W. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1609; (d) Goldmann, H.; Vogt, W.; Paulus, E.; Böhmer, V. *J. Am. Chem. Soc.* **1988**, 110, 6811; (e) Böhmer, V.; Goldmann, H.; Vogt, W.; Paulus, E. F.; Tobiason, F. L.; Thielman, M. J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1769.

[57] Berger, B.; Böhmer, V.; Paulus, E.; Rodriguez, A.; Vogt, W. *Angew. Chem., Int. Ed. Engl.* **1992**, 31, 96.

followed by treatment with nitromalonaldehyde, another phenolic ring can be constructed in the bridge to produce **47**. In a further elaboration[58] of this general procedure the potential bridge is affixed to a calixarene ring, as in **48** which reacts with **45** (R = Me) to afford the head-to-tail bis-calixarene **49**. In an even more exotic example the reaction of **50** (obtained by de-*tert*-butylation of **18**) with the bis-dibromomethyl dimer **51** produces **52** and **53** in 7–8% yield.[34,59] Upper rim to upper rim single bridging between calixarene moieties has been achieved by the reaction of **59** (R^{3-5} = Me) with the bisphenol **54a** to give **55**.[60] Double and even quadruple bridging have been accomplished, for example from the reaction of **54b** with **56** to give **57**.



2.4 Synthesis of Dissymmetric and Asymmetric Calixarenes: Chiral Calixarenes

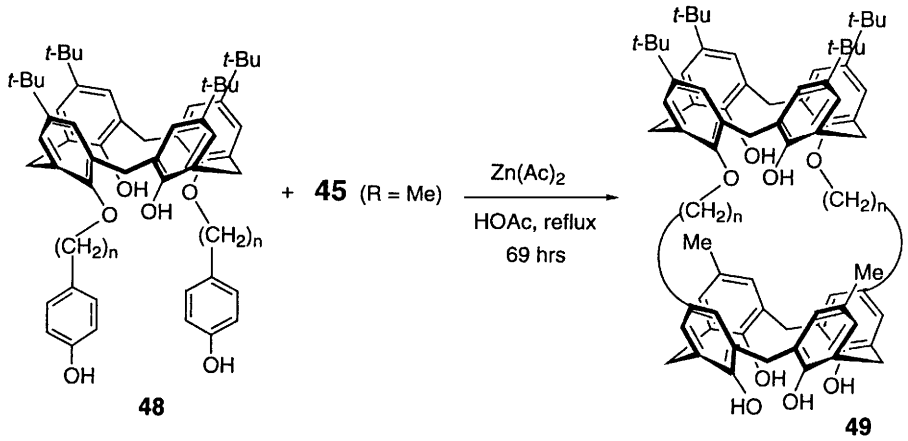
(for a review, see ref. 14c)

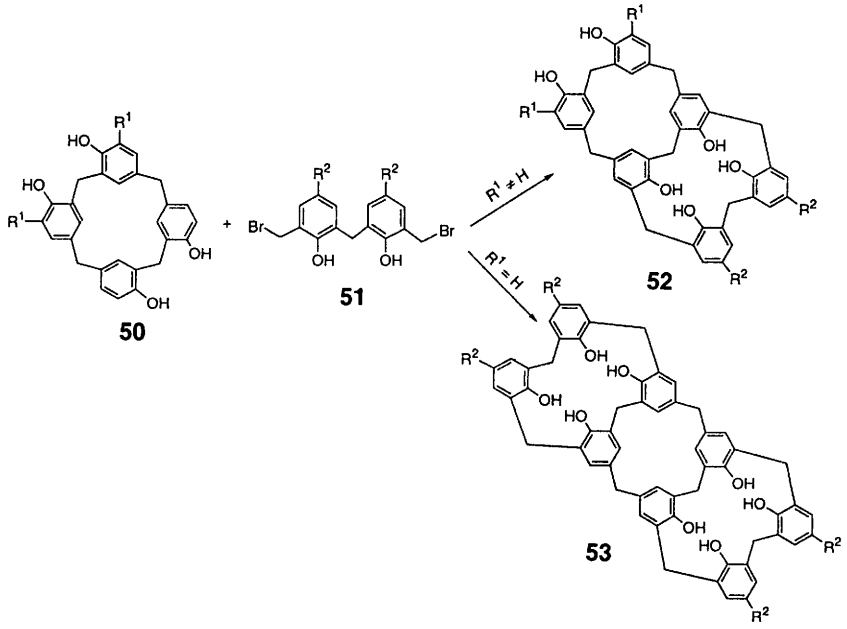
The majority of chiral calixarenes are made either by affixing a chiral moiety to the upper or lower rim of an achiral calixarene or by establishing a dissymmetric

[58] Wasikiewicz, W.; Rokicki, G.; Kielkiewicz, J.; Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 214.

[59] Böhmer, V.; Vogt, W. *Pure Appl. Chem.* **1993**, 65, 403.

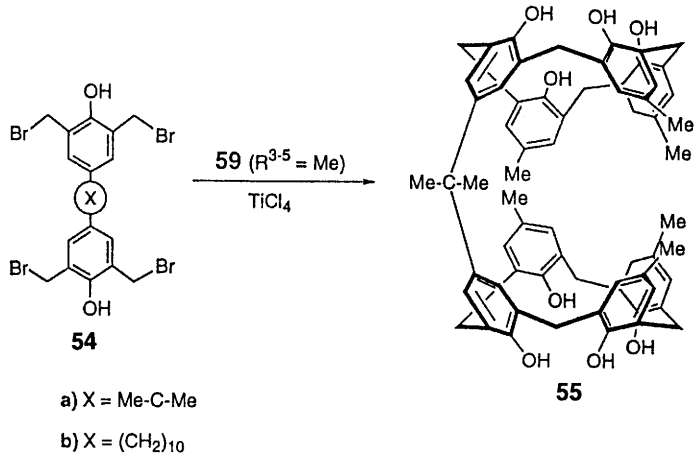
[60] Böhmer, V.; Goldmann, H.; Vogt, W.; Vicens, J.; Asfari, Z. *Tetrahedron Lett.* **1989**, 30, 1391.





or asymmetric pattern of substitution after the basic calixarene ring has been made (see Section 5.5). Direct synthesis of chiral calixarenes by the one-step procedure is possible if the *p*-substituent of the phenol is chiral or if the phenol is unsymmetrically substituted (*e.g.* a substituent in one of the *m*-positions). The one known example of the first case is the condensation of *p*-(−)-menthylphenol to give *p*-(−)-menthylcalix[8]arene (**8**^{menthyl}) in 30% yield.[61] In the second case the products are dissymmetric or asymmetric, depending on the orientation of the individual aryl units in the cyclic array. Compounds **18** with a C_{2v} axis, **10** and **27** with a C_{4v} axis, and **31** with a C_{5v} axis all are examples of dissymmetric

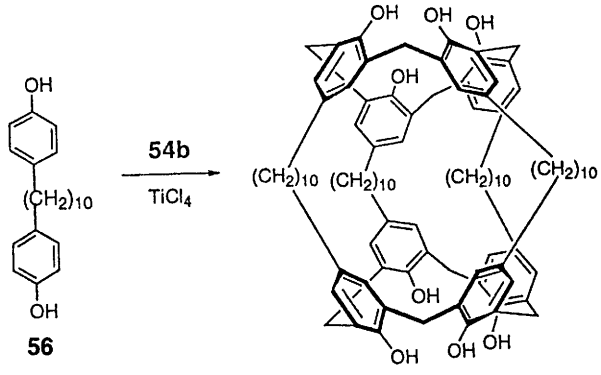
[61] Jauch, J.; Schurig, V. *Tetrahedron: Asymmetry* **1997**, 8, 169.



a) X = Me-C-Me

b) X = $(CH_2)_{10}$

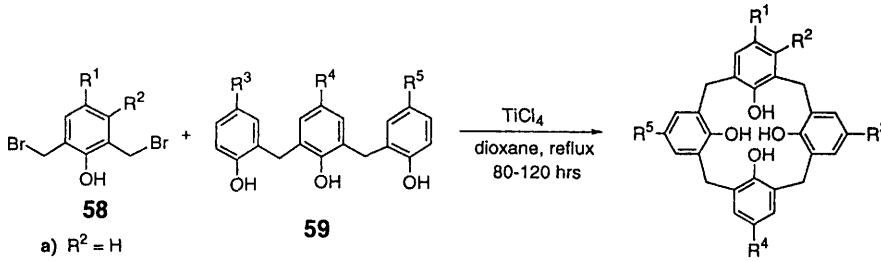
calixarenes obtained in one-step processes (see Section 2.1). Accompanying the product **10** from 1-naphthol and formaldehyde (see Section 2.1.1) are two other isomers,[28] one of which contains the four aryl residues in an asymmetric array. Asymmetrically substituted calixarenes are generally best prepared, however, by fragment condensation (see Section 2.2). For example, the '3 + 1' convergent procedure using various **58** and **59** compounds yields structures **60a** in which ABCD patterns (*e.g.* R^1 = Cyclohexyl, R^2 = H, R^3 = *t*-Bu, R^4 = Me, R^5 = ethoxycarbonyl[62]), AABC pattern (*e.g.* $R^1 = R^3$ = *t*-Bu, R^2 = H, R^4 = Me, R^5 = Ph[62]) and ABAC patterns (*e.g.* $R^1 = R^4$ = Me, R^2 = H, R^3 = *t*-Bu, R^5 = Ph[63]) have been established. A lone *meta*-substituent is also sufficient to confer asymmetry[64] as, for example, in **60b** prepared by the '3 + 1' convergent pathway using **58b** and **59**.



[62] Zetta, L.; Wolff, A.; Vogt, W.; Platt, K. L.; Böhmer, V. *Tetrahedron* **1991**, 47, 1911.

[63] No, K.; Kim, J. E.; Kwon, K. M. *Tetrahedron Lett.* **1995**, 36, 8453.

[64] (a) Casabianca, H.; Royer J.; Satrallah, A.; Taty-C, A.; Vicens, J. *Tetrahedron Lett.* **1987**, 28, 6595; (b) Shinkai, A.; Arimura, T.; Kawabata, H.; Murakami, H.; Iwamoto, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2429.



2.5 Synthesis of Calixarene-related Compounds

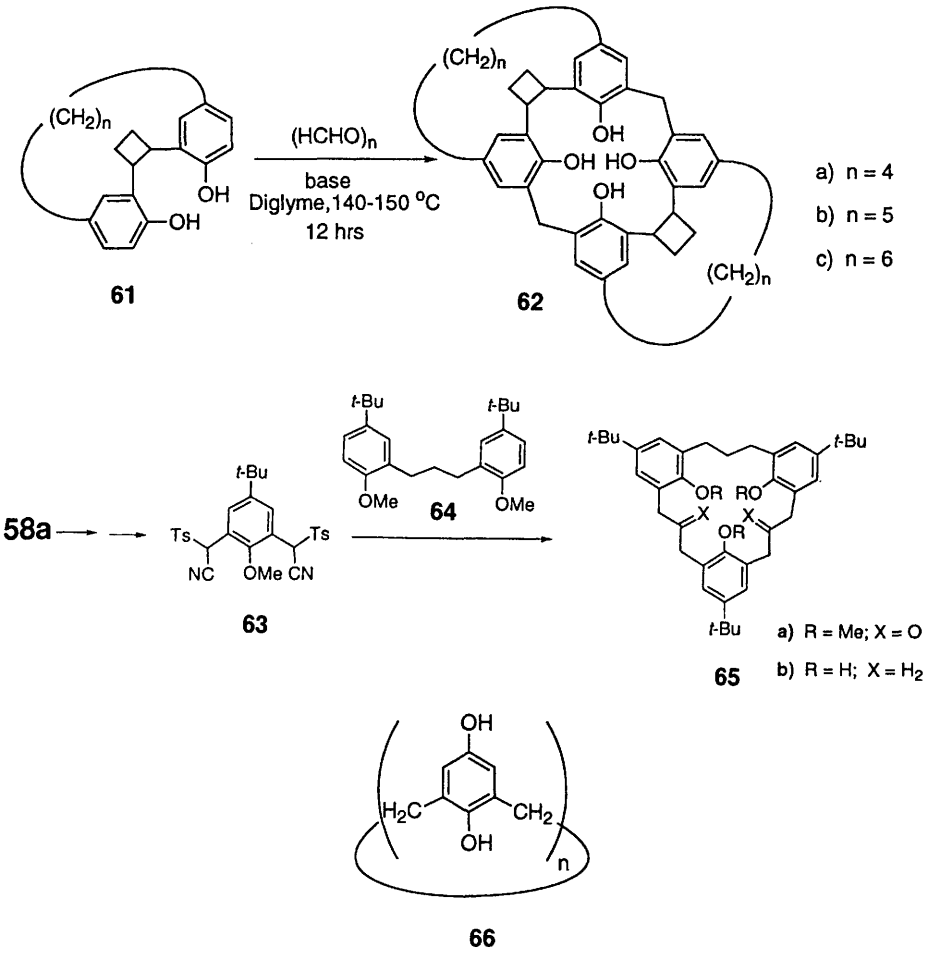
2.5.1 Homocalixarenes

A variety of homocalixarenes have been prepared in which two or more carbons comprise one or more of the bridges between the aryl moeties. For example, a calixarene carrying two 2-carbon bridges has been prepared by treatment of the metacyclophanes **61** (n = 5) with paraformaldehyde[65a] in the presence of LiOH to afford **62b** in 89% yield. With CsOH as the base no product is obtained although, curiously, treatment of **61** (n = 6) under similar conditions[65c] gave a 78% yield of **62c** while **61** (n = 4) failed to produce any of the cyclic tetramer **62a**. Tashiro and coworkers have made a variety of homocalixarenes, representative examples being the hexahomocalix[3]arene **65**[66d] prepared by fragment condensation of **63** with **64** and the tetrahomocalix[4]arene **66** (n = 4)[66a] prepared by a '2 + 2' fragment condensation. *p-tert*-Butylbishomocalix[3]arene has been reported by Yamato and coworkers.[66e] A series of cyclophanes was made many years ago by Jenny and coworkers (for refs. see Vögtle papers) by the action of Na-tetraphenylethene on the methyl ether of **58a** (R^1 = H). Vögtle *et al.*[14d,67] have demethylated these compounds to give **66** (n = 5–10) which they have named 'all-homocalixarenes'.

[65] (a) Okada, Y.; Ishii, F.; Kasai, Y.; Nishimura, J. *Chem. Lett.* **1992**, 755; (b) Okada, Y.; Kasai, Y.; Ishii, F.; Nishimura, J. *J. Chem. Soc., Chem. Commun.* **1993**, 976; (c) Okada, Y.; Nishimura, J. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 41; (d) Okada, Y.; Kasai Y.; Nishimura, J. *Synlett* **1995**, 85.

[66] (a) Tashiro, M.; Tsuge, A.; Sawada, T.; Makishima, T.; Horie, S.; Arimura, T.; Mataka, S.; Yamato, T. *J. Org. Chem.* **1990**, 55, 2404; (b) Yamato, T.; Saruwatari, Y.; Ngayama, S.; Maeda, K.; Tashiro, M. *J. Chem. Soc., Chem. Commun.* **1992**, 861; (c) Sawada, T.; Tsuge, A.; Thiemann, T.; Mataka, S.; Tashiro, M. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 301; (d) Yamato, T.; Doamekpor, L. K.; Koizumi, K.-i.; Kishi, K.; Haraguchi, M.; Tashiro, M. *Liebigs Ann. Chem.* **1995**, 1259; (e) Yamato, T.; Doamekpor, L. K.; Tsuzuki, H. *Liebigs Ann. Chem.* **1997**, 1537; also see Yamato, T.; Saruwatari, Y.; Yasumatsu, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1725.

[67] Brodesser, G.; Güther, R.; Hoss, R.; Meier, S.; Ottens-Hildebrandt, S.; Schmitz, J.; Vögtle, F. *Pure Appl. Chem.* **1993**, 65, 2325; Schmitz, J.; Vögtle, F.; Nieger, M.; Gloe, K.; Stephan, H.; Heitzsch, O.; Buschmann, H.-J.; Hasse, W.; Cammann, K. *Chem. Ber.* **1993**, 126, 2843.



2.5.2 Oxacalixarenes

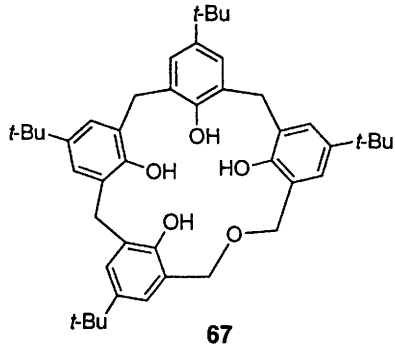
p-tert-Butyldihomooxacalix[4]arene (**67**) is present in varying amounts in the mixtures obtained in the base-induced reaction of *p-tert*-butylphenol and formaldehyde (see ref. 1, pp. 61–62). Although it is rather difficult to isolate in pure form in useful amounts from standard reaction mixtures,[10] if the reaction is quenched before calixarene formation is significant the oxacalixarene can be obtained in as high as 24% yield.[68] Considerable attention has recently been given to obtaining hexahomotrioxacalix[4]arenes **69a** by the thermally induced,[69,70] or, preferably, the high dilution, acid-catalyzed dehydration[71] of

[68] Bavoux, C.; Vocanson, F.; Perrin, M.; Lamartine, R. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1995**, 22, 119.

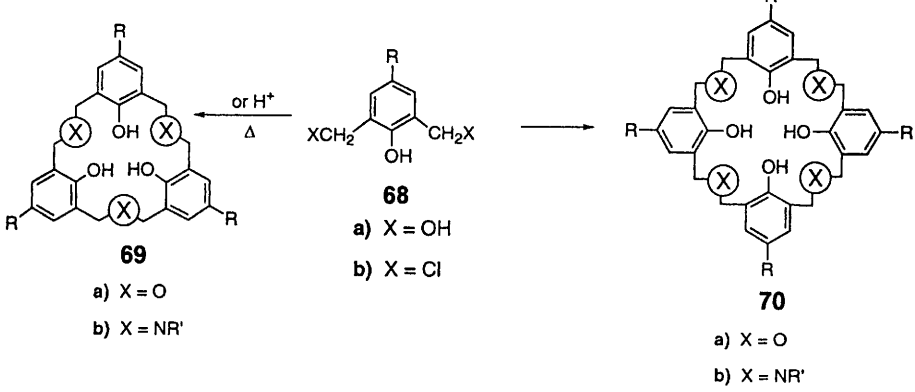
[69] Dhawan, B.; Gutsche, C. D. *J. Org. Chem.*, **1983**, 48, 1536.

[70] (a) Zerr, P.; Mussrabi, M.; Vicens, J. *Tetrahedron Lett.* **1991**, 32, 1879; (b) Suzuki, K.; Minami, H.; Yamagata, Y.; Fujii, S.; Tomita, K.-I.; Asfari, Z.; Vicens, J. *Acta Crystallogr.* **1992**, *C*48, 350.

2,6-bishydroxymethyl-4-alkyl-phenols (**68**). The reaction provides **69a** (R = *t*-Bu, *i*-Pr, Et, Me, Cl) in 12–32% yields accompanied by very small amounts of the corresponding octahomotetraoxacalix[4]arenes **70a**. It is curious that no calixarenes are formed under these conditions, whereas at higher concentrations they become virtually the exclusive product (see Section 2.1.2).



67



69

a) X = O

b) X = NR'

68

a) X = OH

b) X = Cl

70

a) X = O

b) X = NR'

2.5.3 Azacalixarenes

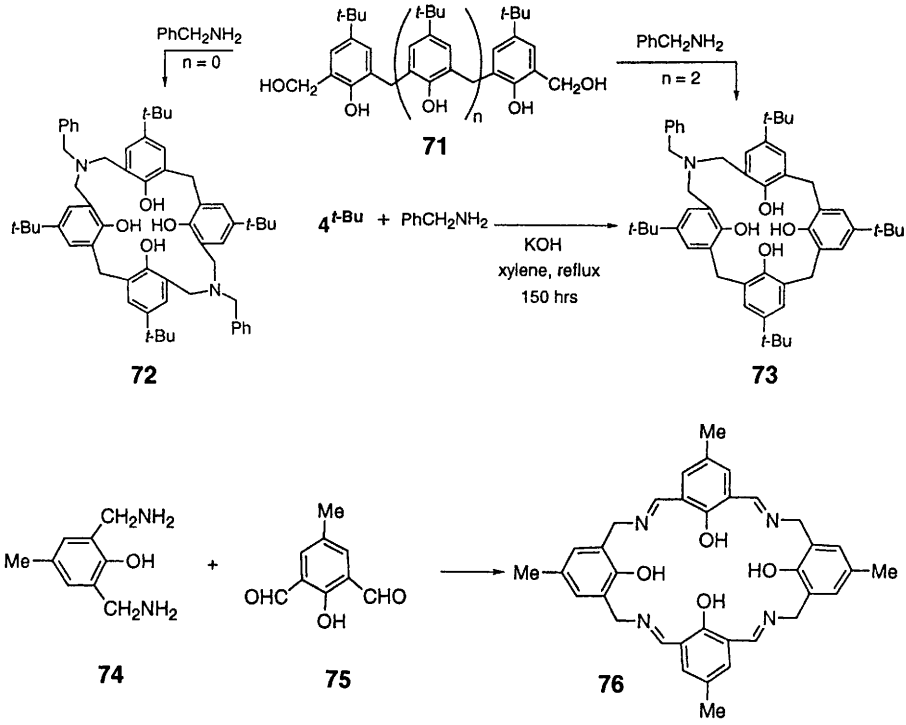
The azacalixarenes **69b** and **70b** have been made by condensing 2,6-bishydroxymethylphenols **68a**[72] or 2,6-bischloromethylphenols **68b**[73] with various amines including benzylamine, α-picolylamine, methyl glycinate, and (*S*)-(−)-α-methylbenzylamine; the latter gives a chiral calixarene **70b** (R = Me; R′ = α-methylbenzyl) in 53% yield.[72c] In similar fashion the tetrahomobisazacalix[4]arene **72** and dihomoazacalix[4]arene **73** have been synthesized in *ca.* 20% yield starting with the bishydroxymethyl compounds **71** ($n = 0$ and 2).

[71] (a) Hampton, P. D.; Bencze, Z.; Tong, W.; Daitch, C. E. *J. Org. Chem.* **1994**, 59, 4838; (b) Hampton, P. D.; Daitch, C. E.; Duesler, E. N. *New J. Chem.* **1996**, 20, 427.

[72] (a) Takemura, H.; Yoshimura, K.; Khan, I. U.; Shinmyozu, T.; Inazu, T. *Tetrahedron Lett.* **1992**, 33, 5775; (b) Khan, I. U.; Takemura, H.; Suenaga, M.; Shinmyozu, T.; Inazu, T. *J. Org. Chem.* **1993**, 58, 3158; (c) Takemura, H.; Shinmyozu, T.; Miura, H.; Khan, I. U.; Inazu, T. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 193.

[73] Hampton, P. D.; Tong, W.; Wu, S.; Duesler, E. N. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1127.

Compound **73** was also obtained, although in only 8% yield, from $\mathbf{4}^{t\text{-Bu}}$ by prolonged treatment with benzylamine in the presence of KOH.[72c] Aza-homocalix[4]arenes have been prepared by the condensation of 2,6-bis(aminomethyl)phenols (**74**) with 2,6-diformylphenols (**75**) to yield Schiff bases (**76**), which can be reduced to the corresponding saturated compounds.[74]



2.5.4 Calixarene-like Cyclooligomers

Although cyclooligomers containing furan residues have been known almost as long as the calixarenes,[75] they have commanded much less attention and have been the subject of only occasional research in recent years. By acid-catalyzed condensation of aldehydes or ketones (**77**) with furan[76a] or with linear oligomers of furan (**78**),[76b] cyclic oligomers **79** with $n = 4$, 5, and 6 have been prepared. For the formaldehyde-derived compounds, $H_2C(OMe)_2$ is the reagent of choice, leading to linear oligomers **78** (n = 1–6) of which only the linear tetramer can be

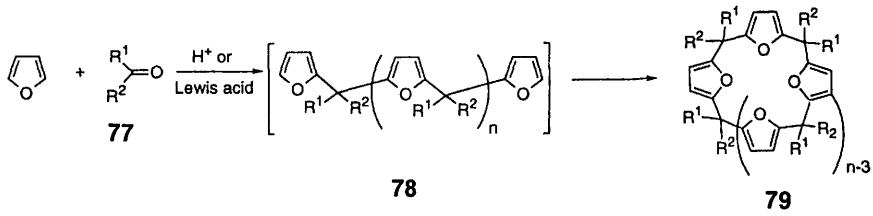
[74] Grannas, M. J.; Hoskins, B. F.; Robson, R. *Inorg. Chem.* **1994**, 33, 1071.

[75] (a) Ackerman, R. G.; Brown, W. H.; Wright, G. F. *J. Org. Chem.* **1955**, 20, 1147; (b) Brown, W. H.; French, W. N. *Can. J. Chem.* **1958**, 38, 537; (c) Chastrette, M.; Chastrette, F. *J. Chem. Soc., Chem. Commun.* **1973**, 534; (d) Timkom, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1974**, 96, 7159; (e) Kobuke, Y.; Hanji, K.; Horiguchi, K.; Asada, M.; Nakayama, Y.; Furukawa, J. *J. Am. Chem. Soc.* **1974**, 98, 7414.

[76] (a) Healy, M. de S.; Rest, A. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 973; (b) Musau, R. M.; Whiting, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1029; (c) Musau, R. M.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2881.

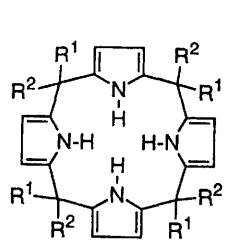
converted to the cyclic tetramer **79** ($n = 4$) in reasonable yield.[76b,c]

Over a century ago, Baeyer isolated a cyclic tetramer (**80**) from the acid-catalyzed condensation of pyrrole and acetone, and these compounds have been recently studied as anion binders and given the name 'calix[4]pyrroles'.[77] Compounds that have acquired the name 'calix[3]indoles' can be prepared by

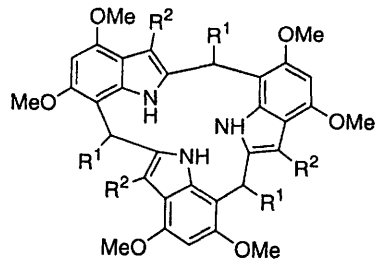


77 **78** **79**

acid-catalyzed condensation of 4,6-dimethoxy-3-R^2-indoles with aryl aldehydes[78a] to give **81** (R^1 = Ar; R^2 = Me) and by acid-catalyzed condensation of hydroxymethylindoles to give **81** (R^1 = H; R^2 = Ar).[78b,c]

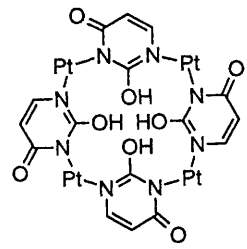


80



R^1 = H or Aryl **81**

R^2 = Alkyl or Aryl



82

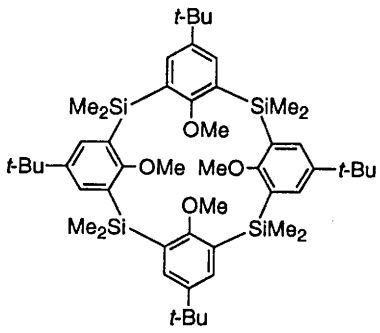
Other cyclooligomers to which the name calixarene has been affixed include a metal analog (**82**),[79a] silacalixarenes **83**[79b] and **84a–c**,[79b] a pentahomothiazacalix[3]arene (**85**),[79c] a uracil-based calix[4]arene,[79d] and a calix[5]arene analog in which one of the aryl residues is connected at the *p*-positions.[80d] Calixarene-like compounds containing nitrogen bridges[80b] and sulfur bridges[80c] in place of methylene bridges have recently come on the scene.

[77] Gale, P. A.; Sessler, J. L.; Král, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, 118, 5140; see this journal article for earlier references to these compounds.

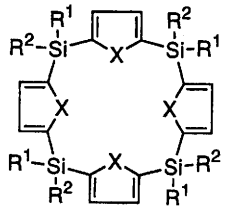
[78] (a) Black, D. St. C.; Craig, D. C.; Kumar, N. *J. Chem. Soc., Chem. Commun.* **1989**, 425; (b) Black, D. St. C.; Bowyer, M. C.; Kumar, N.; Mitchell, P. S. R. *ibid.* **1993**, 819; (c) Black, D. St. C.; Craig, D. C.; Kumar, N.; McConnell, D. B. *Tetrahedron Lett.* **1996**, 37, 241.

[79] (a) Rauter, H.; Hillgeris, E. C.; Erxleben, A.; Lippert, B. *J. Am. Chem. Soc.* **1994**, 116, 616; (b) König, B.; Rödel, M.; Bubenitschek, P.; Jones, P. G. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 661; (c) Ito, K.; Ohba, Y.; Sone, T. *Chem. Lett.* **1996**, 183; (d) König, B.; Rödel, M.; Bubenitschek, P.; Jones, P. G.; Thondorf, I. *J. Org. Chem.* **1995**, 60, 7406.

[80] (a) Kumar, S.; Paul, D.; Singh, H. *Tetrahedron Lett.* **1997**, 38, 3607; (b) Graubaum, H.; Lutze, G.; Costisella, B. *J. Prakt. Chem.* **1997**, 339, 266; (c) Kumagai, H.; Hasagawa, M.; Miyanari, S.; Sugawa, Y.; Sato, Y.; Hori, T.; Veda, S.; Kamiyama, H.; Miyano, S. *Tetrahedron Lett.* **1997**, 38, 3971; Sone, T.; Ohba, Y.; Moriya, K.; Kumada, H.; Ito, K. *Tetrahedron* **1997**, 53, 10689; (d) Haino, T.; Yamada, K.; Fukazawa, Y. *Synlett* **1997**, 673.



83

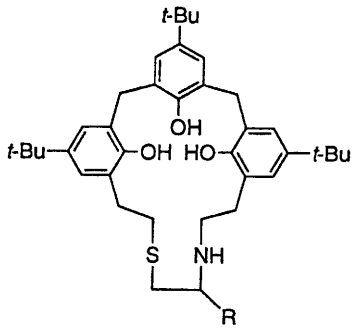


84

a) X = O

b) X = S

c) X = NMe



85

2.6 Mechanism of Calixarene Formation

The mechanism of the base-induced transformation of *p*-alkylphenols and formaldehyde to calixarenes is discussed in considerable detail in the previous volume (see ref. 1, pp. 50–59), where it was postulated that the calix[8]arene is the product of kinetic control and may arise from a pair of linear tetramers forming a hydrogen-bonded cyclic dimer (a hemicalixarene)[81] which then extrudes H_2O and HCHO to produce the cyclic octamer. A study[82] has been carried out in which aliquotes were removed at various times during a synthesis of **8**$^{t\text{-Bu}}$ by the *Organic Synthesis*[10c] procedure. The samples were analyzed for the presence of linear oligomers (non-hydroxymethylated, mono-hydroxymethylated, and bis-hydroxoymethylated) and cyclic oligomers and were found to contain linear oligomers no longer than six units in any significant amount, thus providing support for the hemicalixarene route for calix[8]arenes. The proposed corollary to the hemicalixarene route to calix[8]arenes is that the cyclic tetramer is the product of thermodynamic control and is formed from the cyclic octamer in a

[81] The X-ray crystal structure of the complex between benzene and the linear tetramer from *p*-cresol shows the benzene to be in a cavity formed by two intermolecularly hydrogen-bonded linear tetramers: Usui, S.; Deyama, K.; Fukazawa, Y.; Sone, T.; Ohba, Y. *Chem. Lett.* **1991**, 1387.

[82] Vocanson, F.; Lamartine, R. *Supramol. Chem.* **1996**, 7, 19.

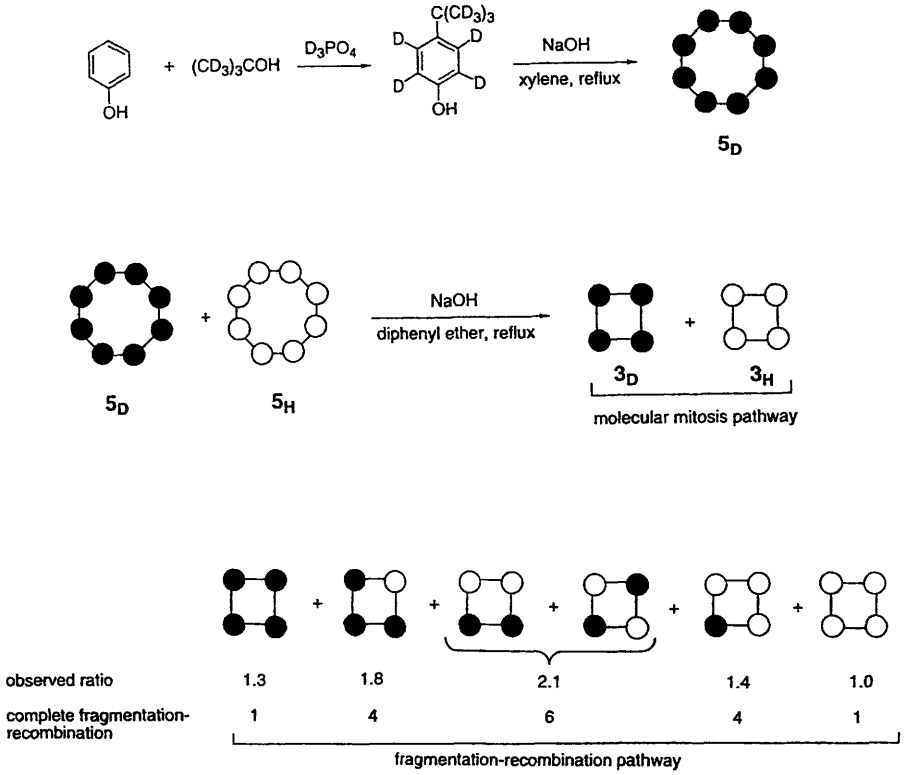


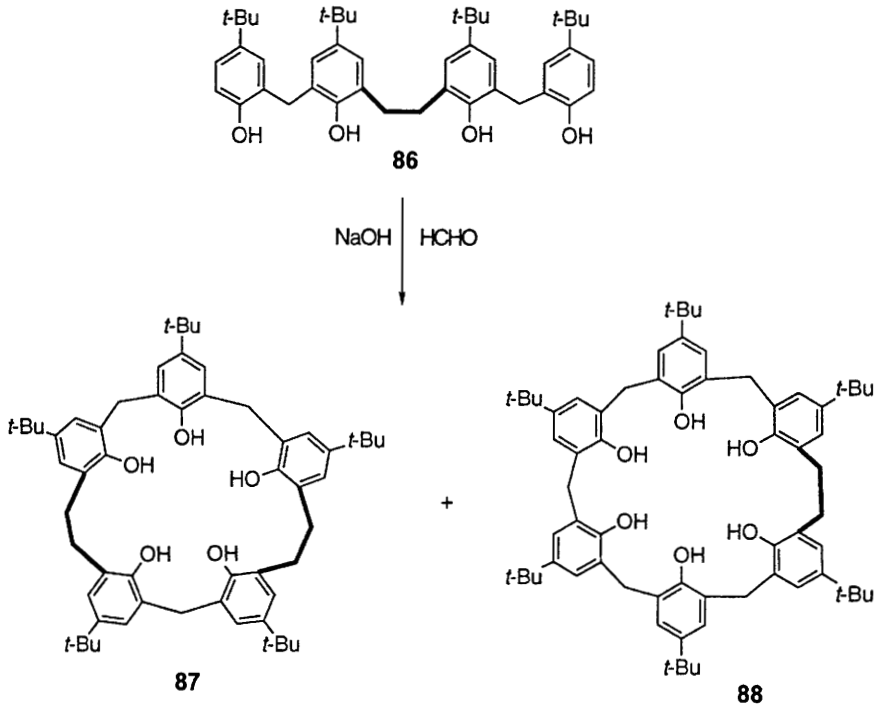
Figure 2.1 *Test for molecular mitosis pathway (filled circles, deuterated residues; open circles, proteated residues)*

process viewed as 'molecular mitosis' wherein the cyclic octamer pinches in the middle and then splits into two cyclic tetramers. To test this hypothesis[83] a deuterated sample of $[\mathbf{8}^{t\text{-Bu}}]_D$ was mixed with an equal amount of ordinary $[\mathbf{8}^{t\text{-Bu}}]_H$ and subjected to treatment with base at elevated temperature, which induces the conversion of the cyclic octamer $\mathbf{8}^{t\text{-Bu}}$ to the cyclic tetramer $\mathbf{4}^{t\text{-Bu}}$ in *ca.* 85% yield.[84] If molecular mitosis occurs as the exclusive pathway the product should consist only of fully deuterated and fully proteated cyclic tetramer $[\mathbf{4}^{t\text{-Bu}}]_D$ and $[\mathbf{4}^{t\text{-Bu}}]_H$. However, if fragmentation–recombination processes occur the deuterium will be distributed among six products (two of which are isomeric) and, if randomization is complete, these will be present in a 1:4:6:4:1 ratio, as depicted in Figure 2.1. The observed ratio is somewhere between these two extremes and thus does not completely negate the molecular mitosis pathway but clearly indicates that fragmentation–recombination is a very significant pathway. That fragmentation even of the cyclic tetramer can occur is also indicated by the obtention of **73** from treating $\mathbf{4}^{t\text{-Bu}}$ with benzylamine (*vide*

[83] Gutsche, C. D.; Johnston, D. E., Jr., unpublished results.

[84] Gutsche, C. D.; Iqbal, M.; Stewart, D. *J. Org. Chem.* **1986**, 51, 742; Dhawan, B.; Chen. S.-I.; Gutsche, C. D. *Makromol. Chem.* **1987**, 188, 921.

supra[71c]). Still another piece of evidence for fragmentation–recombination comes from the reaction of **86** (carrying one ethylene bridge) with HCHO and NaOH in refluxing xylene. The product contains none of the expected cyclic octamer but comprises 35% of the cyclic pentamer **87** and 25% of the cyclic hexamer **88** in which the ethylene-bridged moieties are retained.[85]



A hemicalixarene precursor to the calixarenes has also been suggested for the genesis of the $\mathbf{6}^{t\text{-Bu}}$ (see ref. 1, p. 56), but recent experiments[86] may refute this possibility. A reaction employing the *Organic Synthesis*[10b] conditions for preparing $\mathbf{6}^{t\text{-Bu}}$ was monitored by GC and TLC which showed that at the end of the first step relatively little linear trimer and tetramer are present but that significant amounts of the linear hexamer have formed, suggesting that the immediate precursor for $\mathbf{6}^{t\text{-Bu}}$ is a pseudocalixarene (*i.e.* a linear hexamer) rather than a hemicalixarene (*i.e.* a pair of linear trimers).

Until recently, the acid-catalyzed synthesis of calixarenes was limited to the calixresorcarenes. A kinetic and molecular modeling study[87] of the acid-catalyzed reaction of acetaldehyde and resorcinol comes to the conclusions that (a) ring closure to the calix[4]resorcarene is at least as fast as chain propagation;

[85] Yamato, T.; Yasumatsu, M.; Doamekpor, L. K.; Nagayama, S. *Liebigs Ann. Chem.* **1995**, 285.
[86] Vocanson, F.; Lamartine, R.; Perrin R. *Supramol. Chem.* **1994**, 4, 153. For a comparison of HPLC and supercritical fluid chromatography, see Graham, B. F.; Harrowfield, J. M.; Trengove, R. D.; Rodriguez, I.; Li, S. F. Y. *J. Chromatogr. Sci.* **1997**, 35, 232.
[87] Weinelt, F.; Schneider, H.-J. *J. Org. Chem.* **1991**, 56, 5527.

(b) the macrocyclic products are the thermodynamic sink of the reactions; and (c) linear oligomers longer than four aryl units depolymerize fast in comparison with ring opening, thus promoting the formation of cyclic tetramer. Although the reaction of resorcinol with RCHO appears to yield only calix[4]resorcarenes, reaction with HCHO (from trioxane) yields mixtures containing both calix[4]- and calix[6]resorcarenes.[88] Also it is now known that *p-tert*-butylphenol and $(CH_2O)_3$ yield calixarenes under acid catalysis (see Section 2.1.2), but significantly the calix[4]arene is not a major product in this case. Larger cyclic oligomers are formed in preference, and the more concentrated the solution the greater is their proportion. Thus, in contrast to resorcinol, chain propagation of the linear oligomers is faster than cyclization to the cyclic tetramer.

[88] Konishi, H.; Ohata, K.; Morikawa, O.; Kobayashi, K. *J. Chem. Soc., Chem. Commun.* **1995**, 309.

CHAPTER 3

Proving the Baskets: The Characterization and Properties of Calixarenes

'What if one does say the same things, – of course in a little different form each time, – over and over? If he has anything to say worth saying, that is just what he ought to do'

Oliver Wendell Holmes, Sr., *Over the Teacups*

3.1 Separation and Purification of Calixarenes

For the successful characterization of a compound it is generally necessary to obtain it in pure form. Calixarenes, especially when made by one-step procedures, are often produced as a mixture requiring the separation of its components. In some instances, *e.g.* the one-step syntheses of *p-tert*-butylcalix[4]-, -[6]-, and -[8]arenes, simple recrystallization suffices. In many other instances, however, chromatographic procedures are necessary, principally flash chromatography and HPLC. The latter, discussed in the previous volume (see ref. 1, pp. 84–85), has been applied to mixtures of the parent calixarenes.[89] The reverse phase HPLC technique is particularly useful for following the separation of the larger members of the family, a typical example of which is shown in Figure 3.1.[24] Calixarenes carrying phosphoryl groups on the lower rim have been separated by this technique,[90] and chiral calix[4]arenes have been resolved by the use of enantioselective columns.[91] Still another separation technique that has been occasionally used is capillary zone electrophoresis, *e.g.* for the separation of *p*-sulfonatocalixarenes.[92] Most recently, calixarenes have been separated on a

[89] Vocanson, F.; Lamartine, R.; Duchamp, C.; Regnouf de Vains, J. B. *Chromatographia* **1995**, 41, 204.

[90] Kalchenko, O. I.; Lipkowski, J.; Nowakowski, R.; Kalchenko, V. I.; Visotsky, M. A.; Markovsky, L. N. *J. Chromatogr. Sci.* **1997**, 35, 49.

[91] (a) Shinkai, S.; Arimura, T.; Kawabata, H.; Murakami, H.; Iwamoto, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2429; (b) Caccamese, S.; Pappalardo, S. *Chirality* **1993**, 5, 159.

[92] Zhang, Y.; Warner, I. M. *J. Chromatogr. A* **1994**, 688, 293.

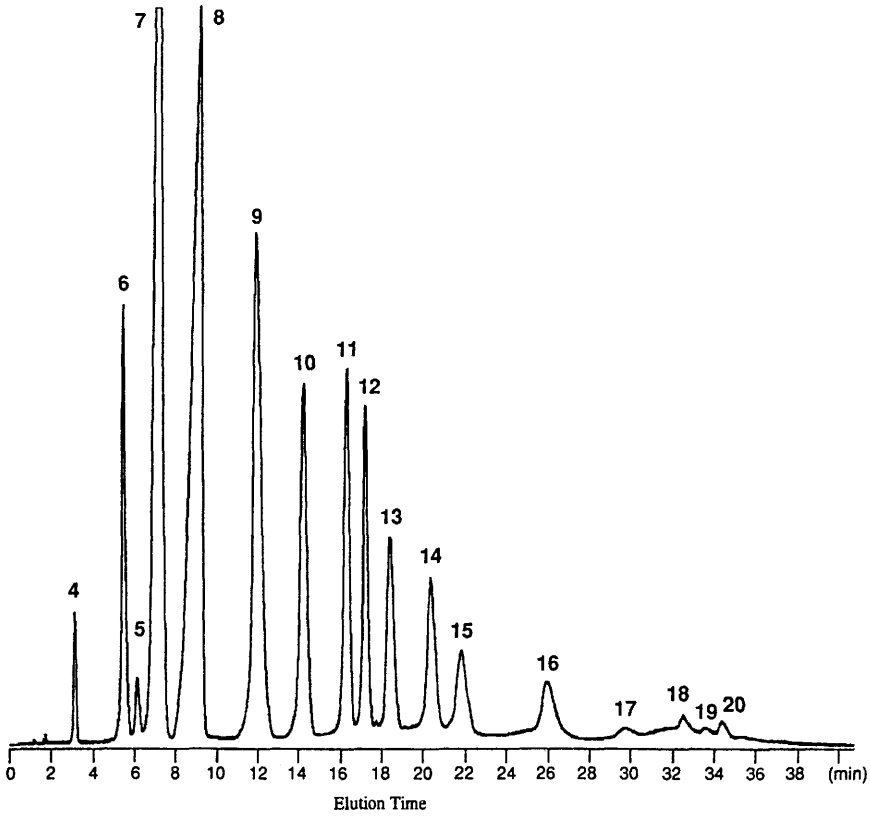


Figure 3.1 *HPLC of a* p-tert-*butylcalix*[n]*arene mixture. The numbers above the peaks indicate the value of* n

diol column using supercritical fluid chromatography with MeOH/$CHCl_3$-modified CO_2 as the mobile phase.[93]

3.2 Melting Points of Calixarenes

(see ref. 1, pp. 74–75)

For the melting points of the parent calixarenes, see data in Table 3.3.

3.3 X-Ray Crystallography: The Ultimate Proof of Structure

(for a review, see ref. 13c)

By 1989, when the previous volume was published, all doubts concerning the structures of the three major and two minor *p-tert*-butylcalixarenes had been

[93] Glennon, J. D.; Hutchinson, S.; Harris, S. J.; Walker, A.; McKervey, M. A.; McSweeney, C. C. *Anal. Chem.* **1997**, 69, 2207.

dispelled. In addition to the chemical and spectral data that had been adduced by that time, the X-ray crystallographic work of the Parma group of Andreetti, Pochini, and Ungaro had provided unequivocal proof of structure (see ref. 1, pp. 67–72). Today, several hundred X-ray crystallographic determinations of calixarenes have been reported from numerous research groups throughout the world. The great majority of these involve calix[4]arenes, and relatively few X-ray structures have been reported for the larger calixarenes. Numerous examples of X-ray crystallographic structures are presented in the following chapters dealing with conformation and complexation.

3.4 pK_a Values of Calixarenes

The calixarenes are considerably stronger acids than their monomeric phenolic counterparts, but the accurate measurement of their pK_a values has posed some difficuties. Some of the values reported at the time of the first volume (see ref. 1, pp. 77–78) have been revised, and several more determinations have since been published.[93–102] Using both potentiometric and spectrophotometric methods, Reinhoudt and Shinkai and their respective coworkers measured the pK values in water of calix[4]arenes carrying $SO_2N(CH_2CH_2OH)_2$ or NO_2 groups in the *p*-positions. They compared these values with those of the analogous monomers and trimers, with the results shown in Table 3.1. It is interesting to note that the pK_1 values for the linear trimers fall between those of the calix[4]arenes and the monomers and, in the case of the *p*-nitro series, quite close to the former. The

Table 3.1 *pK_a values of calix[4]arenes and their linear trimer and monomer counterparts*

Compound	pK_1	pK_2	pK_3	pK_4
4$^{SO_2N(CH_2CH_2OH)_2}$	0.8 ± 0.3	9.7 ± 0.1	*ca.* 12.5	> 14
Linear trimer	4.71 ± 0.05	8.27 ± 0.05	11.61 ± 0.1	
Monomer	8.25 ± 0.03			
4^{NO_2}	2.9 ± 0.3	10.9 ± 0.1	12.3 ± 0.2	> 14
Linear trimer	3.6 ± 0.1	10.6 ± 0.1	*ca.* 12.5	
Monomer	8.67 ± 0.03			

[94] Araki, K.; Iwamoto, K.; Shinkai, S.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **1990**, 63, 3480.

[95] Grootenhuis, P. D. J.; Kollman, P. A.; Groenen, L. C.; Reinhoudt, D. N.; van Hummel, G. J.; Ugozzoli, F.; Andreetti, G. D. *J. Am. Chem. Soc.* **1990**, 112, 4165.

[96] Shinkai, S.; Araki, K.; Grootenhius, P. D. J.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1883.

[97] Scharff, J.-P.; Mahjoubi, M.; Perrin, R. *New J. Chem.* **1991**, 15, 883.

[98] Arena, G.; Cali, R.; Lombardo, G. G.; Rizzarelli, E.; Sciotto, D.; Ungaro, R.; Casnati, A. *Supramol. Chem.* **1992**, 1, 19.

[99] Araki, K.; Murakami, H.; Ohseto, F.; Shinkai, S. *Chem. Lett.* **1992**, 539.

[100] Yoshida, I.; Yamamoto, N.; Sagara, F.; Ishii, D.; Ueno, K.; Shinkai, S. *Bull. Chem. Soc. Jpn.* **1992**, 65, 1012.

[101] Atwood, J. L.; Clark, D. L.; Juneja, R. K.; Orr, G. W.; Robinson, K. D.; Vincent, R. L. *J. Am. Chem. Soc.* **1992**, 114, 7558.

[102] Ray, K. B.; Weatherhead, R. H.; Pirinccioglu, N.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 83.

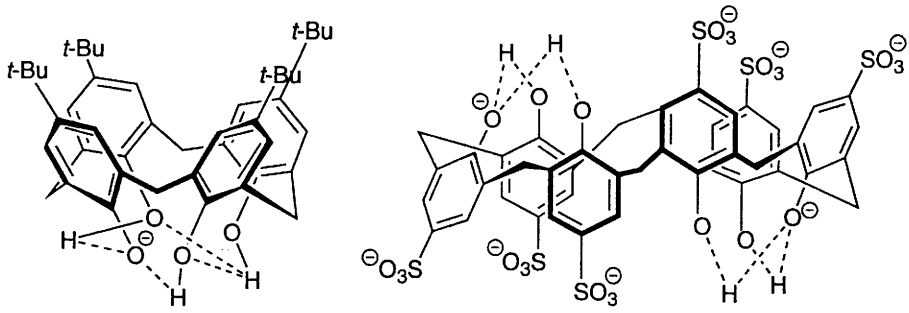


Figure 3.2 *Stabilization of calixarene anions*

unusual ease with which the first dissociation of the calix[4]arenes occurs is attributed to stabilization of the monoanion relative to the parent species, and semiempirical calculations[95] indicate that the monoanion is strongly hydrogen-bonded to its flanking OH groups which, in turn, are stabilized by a bifurcated hydrogen bond with the fourth OH group, as depicted in Figure 3.2. A somewhat analogous stabilization can be achieved in the linear trimers, accounting for their considerably enhanced acidity. The dissociation of the second proton of the calix[4]arenes, on the other hand, is slightly less facile than that of the corresponding linear trimer. Although calculations indicate that hydrogen bonding still contributes to the stabilization of the dianion in this case,[95] unfavorable electrostatic repulsions appear to be the dominant factor.

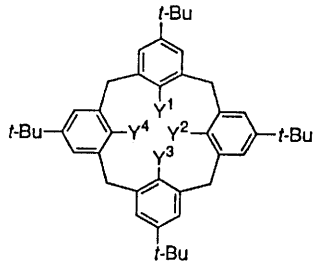
Determination of the pK_a values for the water soluble *p*-sulfonatocalixarenes has been a particularly thorny problem because of the difficulty in distinguishing between the strongly acidic calixarene OH and SO_3H groups. Early measurements on *p*-sulfonato-calix[4]arene (see ref. 1, pp. 77–78) indicated a pK_1 value of less than 1, but more recent measurements have raised this above 3 (3.26,[100] 3.34[98]). Also, the values for pK_2 and pK_3 have been significantly raised to 12.3 and 12.9, respectively, with pK_4 of 13.6 remaining close to its previously determined level. Potentiometric titration (a) of *p*-sulfonatocalix[5]arene[103] gives values of $pK_1 = 4.31$, $pK_2 = 7.63$, and $pK_3 = 10.96$; (b) of *p*-sulfonatocalix[6]arene gives values of $pK_1 = 3.45$[97] (3.44[101]) and $pK_2 = 5.02$[97] (4.76[101]) in a high ionic strength medium, but $pK_1 = 4.16$ and $pK_2 = 5.90$ in a low ionic strength medium; (c) of *p*-sulfonatocalix[8]arene gives even higher values[97] with $pK_1 = 7.70$ and $pK_2 = 9.10$. The pK_1 in the last case, however, is still somewhat lower than the pK of 8.68 for the OH of *p*-hydroxybenzenesulfonic acid. The enhanced acidity in the calix[6]arene[101] is interpreted in terms similar to those applied to the calix[4]arene, positing two sets of triads with each one forming a monoanion stabilized by adjacent OH groups, as shown in Figure 3.2.

The problem of determining the pK_a values of water insoluble calixarenes has been addressed by Shinkai and coworkers,[94] who used the tetramethylammonium salts of 4-nitrophenol, 2,4-dinitrophenol, and 2,4,6-trinitrophenol (pic-

[103] Steed, J. W.; Johnson, C. P.; Barnes, C. L.; Juneja, R. K.; Atwood, J. L.; Reilly, S.; Hollis, R. L.; Smith, P. H.; Clark, D. L. *J. Am. Chem. Soc.* **1995**, 117, 11426.

ric acid) as the titrants in THF solution. The 'apparent pK_1' values for $\mathbf{4}^{t\text{-Bu}}$, $\mathbf{6}^{t\text{-Bu}}$, and $\mathbf{8}^{t\text{-Bu}}$ obtained in this fashion were found to be 4.11, 3.62, and 4.05, respectively. As a reference point, the pK_a of *p-tert*-butylphenol was determined by this method and found to be 10.9, while those of a linear dimer, trimer, and tetramer were 7.92, 6.9, and 5.3, respectively. The pK_a values for *p*-nitrocalix[8]arene have been determined to be $pK_1 < 0$, $pK_2 = 2.6$, $pK_3 = 7.2$, $pK_4 = 10.2$, and $pK_{5\text{-}8} > 12$.[104]

The acidities of calix[4]arenes carrying fewer than four OH groups on the lower rim have been measured in several systems. By means of 4-nitrophenolate titration in THF the pK_a values for the monomethyl (**89a**), dimethyl (**89b**), and trimethyl (**89c**) ethers of $\mathbf{4}^{t\text{-Bu}}$ have been determined to be 6.95, 12.1, and 12.5, respectively, although there is some question about the first of these values which ranged downward to 3.98 when picrate was used as the titrant. Picrate titration of the A,C-diamino-*p-tert*-butylcalix[4]arene **89d** in THF[99] indicated an apparent pK_a value of 9.17 for the dissociation of the first OH group, *ca.* 5 pK units higher than the value of 4.11 for pK_1 quoted above for $\mathbf{4}^{t\text{-Bu}}$ as determined in the same fashion. Spectrophotometric titration of the monobenzoates (**89e**) of $\mathbf{4}^{t\text{-Bu}}$ using hydroxide in ethanol/water[102] gave $pK_1 = 6.84$, $pK_2 = 12.14$, and $pK_3 > 14$.



89

a) Y^1 = OMe; $Y^{2\text{-}4}$ = OH

b) $Y^{1,3}$ = OMe; $Y^{2,4}$ = OH

c) $Y^{1\text{-}3}$ = OMe; Y^4 = OH

d) $Y^{1,3}$ = NH_2; $Y^{2,4}$ = OH

e) Y^1 = OCOAr; $Y^{2\text{-}4}$ = OH

3.5 Dipole Moments of Calixarenes

Rather little attention has been given to the measurement and calculation of dipole moments of calixarenes. The most comprehensive experimental study[105] includes data on nine calix[4]arenes with examples of each of the four 'up-down' conformations, as shown in Table 3.2. As anticipated from simple inspection of molecular models, the sequence of decreasing dipole moment is cone > partial cone > 1,2-alternate > 1,3-alternate. A computational study[107] affirms the sequence of decreasing dipole moment as cone > partial cone > 1,2-alternate > 1,3-alternate but yields a value of only 0.46 D for $\mathbf{4}^{t\text{-Bu}}$ and values of 1.46, 6.4, and 12.6 D for the cone conformers of $\mathbf{4}^{H}$, $\mathbf{4}^{Br}$, and $\mathbf{4}^{CN}$, respectively.

[104] Bünzli, J.-C. G.; Ihringer, F. *Inorg. Chim. Acta* **1996**, 246, 195.

[105] de Mendoza, J.; Prados, P.; Campillo, N.; Nieto, P. M.; Sánchez, C.; Fayet, J.-P.; Vertut, M. C.; Jaime, C.; Elguero, J. *Recl. Trav. Chim. Pays-Bas* **1993**, 112, 367.

[106] Kelderman, E.; Derhaeg, L.; Heesink, G. J. T.; Verboom, W.; Engbersen, J. F. J.; vanHulst, N. F.; Persoons, A.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1992**, 31, 1075.

[107] Iwamoto, K.; Ikeda, A.; Araki, K.; Harada, T.; Shinkai, S. *Tetrahedron Lett.* **1993**, 49, 9937.

Table 3.2 *Dipole moments of calix[4]arenes*

Lower rim	*Upper rim*	*Conformation*[a]	*Dipole moment, D*	*Ref.*
OH	*t*-Bu	Cone	4.19	105
OPr	NO_2	Cone	13.8	106
OPr	NO_2	Partial cone	6.7	106
OPr	NO_2	1,3-Alternate	0.0	106
OAc	*t*-Bu	Partial cone	2.57	105
OAc	*t*-Bu	1,2-Alternate	2.21	105
OAc	*t*-Bu	1,3-Alternate	1.58	105
OH/OMe	*t*-Bu	Pinched cone	3.75	105

[a]See Section 4.4.1 for nomenclature of conformers.

3.6 Spectral Characteristics of Calixarenes

3.6.1 Infrared Spectra

The complete IR spectra of *p-tert*-butylcalix[4]- to -[9]arenes were shown in the previous volume (see ref. 1, pp. 78–80), their most distinctive feature being the position of the OH stretching band in the 3100–3500 cm^{-1} region. These values, along with newer data for the larger calixarenes, are collected in Table 3.3. Analogous data for calixarenes variously substituted on the lower rim are discussed in Chapter 4 dealing with conformations. The considerably lowered stretching constants for the OH bonds in all of the parent calixarenes is attributed to intramolecular hydrogen bonding, which is most strongly manifested in the calix[4]-, -[6]-, and -[8]arenes. The calix[5]arene posseses a more open cone conformation than the calix[4]arene, and the calix[7]arene possesses an interrupted pleated loop conformation in comparison with the completed pleated loop conformation of calix[8]arene. As a consequence they are somewhat more weakly intramolecularly hydrogen-bonded. With larger numbers of aryl residues in the cyclic array, *e.g.* **9** ($n > 8$), the flexibility continues to increase, and intramolecular hydrogen bonding diminishes to some extent.

3.6.2 Ultraviolet Spectra

The UV spectra of the calix[4]- to -[8]arenes are tabulated in the previous volume (see ref. 1, pp. 79–81). The trend of increasingly large extinction coefficients for the absorptions at 280 and 288 nm, however, reaches a plateau at the calix[8]arene, the larger calixarenes showing little, if any, further escalation in absorptivity.

3.6.3 NMR Spectra

NMR spectra, discussed in some detail in the previous volume (see ref. 1, pp. 81–83), continue to play a pivotal role in calixarene chemistry. The position of

Table 3.3 *Melting points, IR stretching frequences and NMR resonances for the O–H bond in calixarenes*

Compound	*Mp*, °C	ν_{OH}, cm^{-1}	δ_{OH}	*Ref.*
$\mathbf{4}^{t\text{-Bu}}$	342–344	3179[a]	10.34	94
$\mathbf{4}^{SO_3H}$		3232, 3411	8.36[b]	97
$\mathbf{5}^{t\text{-Bu}}$	310–312		9.64	24
$\mathbf{6}^{t\text{-Bu}}$	372–374	3120	10.53	94
$\mathbf{6}^{SO_3H}$		3393[c]	5.13[b]	97
$\mathbf{7}^{t\text{-Bu}}$	249 (dec 290)		10.34	24
$\mathbf{8}^{t\text{-Bu}}$	418–420	3190	9.60	94
$\mathbf{8}^{SO_3H}$		3242, 3426	4.78[b]	97
p-tert-Butylcalix[9]arene	317–318		9.78	24
p-tert-Butylcalix[10]arene	308–310		9.24	24
p-tert-Butylcalix[11]arene	200–250		9.50	24
p-tert-Butylcalix[12]arene	294–295		9.53	24
p-tert-Butylcalix[13]arene	313–314		9.45	24
p-tert-Butylcalix[14]arene	317–320		9.32	24
p-tert-Butylcalix[15]arene	227–295		9.13	24
p-tert-Butylcalix[16]arene	310–312		9.02	24
p-tert-Butylcalix[17]arene			9.02	24
p-tert-Butylcalix[18]arene			8.98	24
p-tert-Butylcalix[19]arene			9.06	24
p-tert-Butylcalix[20]arene	290–292		8–10	24
Monodeoxy-*p-tert*-butylcalix[4]arene			7.5[d]	108
p-tert-Butylhexahomotrioxacalix[3]arene		3369	8.57	71a

[a]Values of 3150 cm^{-1} for the solid state spectrum at 300 K and 3190 and 3140 cm^{-1} for spectra measured in CS_2 and CCl_4, respectively, have been reported.[109]
[b]Value for OH and SO_3H in D_2O.
[c]Values of 3165 and 3150 cm^{-1} for spectra measured in CS_2 and CCl_4, respectively, have been reported.[110]
[d]At − 90 °C the value is δ 8.8.

the resonance(s) arising from the OH group(s) in the ^1H NMR spectra, for example, provides valuable information concerning the shapes of the molecules, a point that is discussed in more detail in Chapter 4. For the parent calixarenes listed in Table 3.3 the δ_{OH} value is taken to be a measure of the strength of intramolecular hydrogen bonding: the greater the value the stronger is the hydrogen bond. Thus, intramolecular hydrogen bonding is particularly strong in the calix[4]- and -[6]arenes, slightly less so in the calix[8]arene, and still less so in the calix[5]- and -[7]arenes. It is interesting to note that for a number of the very large calixarenes ($n > 8$) there are several OH resonances at low temperature, and a similar situation exists for a calix[6]arene at low temperatures, as

[108] Fukazawa, Y.; Deyama, K.; Usui, S. *Tetrahedron Lett.* **1992**, 33, 5803.
[109] Groenen, L. C.; Steinwender, E.; Lutz, B. T. G.; van der Maas, J. H.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1893.
[110] Lutz, B. T. G.; Astarloa, G.; van der Maas, J. H.; Janssen, R. G.; Verboom, W.; Reinhoudt, D. N. *Vib. Spectrosc.* **1995**, 10, 29.

discussed in Chapter 4. While there is generally a parallelism between δ_{OH} and ν_{OH}, this is not true in all cases. For example, while the ν_{OH} of 3150 cm^{-1} for **18** (R = *t*-Bu) is, surprisingly, comparable with that of $\mathbf{4}^{t\text{-Bu}}$, the δ_{OH} is only 6.33.

^{13}C NMR spectra have been brought to bear on the conformational identification of calix[4]arenes by de Mendoza and coworkers,[111a] who have shown that the resonance arising from the bridge methylene carbon is near δ 31 when the attached aryl groups are in the *syn* orientation (*i.e.* both groups 'up' or both groups 'down')[111b] and near δ 37 when they are in the *anti* orientation (*i.e.* one group 'up' and one group 'down'). The application of the 'de Mendoza rule' has been extended to calix[5]arenes[112] and calix[6]arenes[113] and appears to be applicable with reasonable accuracy. Another ^{13}C NMR rule has been proposed by Pappalardo and coworkers, which states that the OCH_2 resonances of pyridylmethyl ethers appear at *ca.* δ = 71 when both adjacent aryl moieties are *anti* to one another and at δ = 77 when they are *syn*.[114] A ^{17}O NMR investigation of calix[4]arene and calix[6]arene yields values supporting the stronger hydrogen bonds in the former.[115] The ^{1}H NMR and ^{13}C NMR relaxation times for calix[4]-, -[6]-, and -[8]arenes have been measured[116] as well as the ^{23}Na NMR longitudinal magnetization recovery times for some Na^+ complexes.[117] Solid state ^{13}C NMR measurements (^{13}C CP-MAS NMR) on parent calixarenes and some of their ethers[118] generally corroborate the solution state conformations, and similar measurments on complexes of $\mathbf{4}^{t\text{-Bu}}$ with alkylbenzenes have been used to establish their structures.[119]

3.6.4 Mass Spectra

Mass spectra (see ref. 1, pp. 83–84) continue to be useful in calixarene chemistry, primarily for the determination of the molecular weights of compounds such as the parent calixarenes with $n > 8$ and numerous other large calixarene-derived compounds (*e.g.* 'a rigid cavity of nanosize dimensions'[120]). Mass spectral deter-

[111] (a) Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P. M.; Sánchez, C. *J. Org. Chem.* **1991**, 56, 3372; (b) with A,C-diesters in the cone conformation the resonance position is closer to δ 33–34: Magrans, J. O.; de Mendoza, J.; Pons, M.; Prados, P. *J. Org. Chem.* **1997**, 62, 4518; also see ref. 282.

[112] Stewart, D. R.; Krawiec, M.; Kashyap, R. P.; Watson, W. H.; Gutsche, C. D. *J. Am. Chem. Soc.* **1995**, 117, 586.

[113] Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1994**, 59, 3871.

[114] Pappalardo, S.; Giunta, L.; Foti, M.; Ferguson, G.; Gallagher, J. F.; Kaitner, B. *J. Org. Chem.* **1992**, 57, 2611.

[115] Cerioni, G.; Biali, S. E.; Rappoport, Z. *Tetrahedron Lett.* **1996**, 37, 5797.

[116] (a) Yamada, A.; Murase, T.; Kikukawa, K.; Matsuda, T.; Shinkai, S. *Chem. Lett.* **1990**, 455; (b) Ikeda, A.; Nagasaki, T.; Arimura, T.; Shinkai, S. *Chem. Express* **1991**, 6, 491; (c) Yamada, A.; Murase, T.; Kikukawa, K.; Arimura, T.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **1991**, 793; (d) Antony, J. H.; Doelle, A.; Fliege, T.; Geiger, A. *J. Phys. Chem. A*, **1997**, 101, 4517.

[117] Jin, T.; Ichikawa, K. *J. Phys. Chem.* **1991**, 95, 2601.

[118] Liang, T.-M., Laali, K. K. *Chem. Ber.* **1991**, 124, 2637.

[119] Yamanobe, T.; Nakamura, I.; Hibino, K.; Komoto, T.; Kurosu, H.; Ando, I.; Nakamoto, Y.; Ishida, S.-i. *J. Mol. Struct.* **1995**, 355, 15.

[120] Timmerman, P.; Verboom, W.; van Veggel, F. C. J. M.; van Hoorn, W. P.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 1292; Timmerman, P.; Nierop, K. G. A.; Brinks, E. A.; Verboom, W.; van Veggel, F. C. J. M.; van Hoorn, W. P.; Reinhoudt, D. N. *Chem. Eur. J.* **1995**, 1, 132.

minations have provided good evidence that the larger calixarenes may form aggregation oligomers through intermolecular hydrogen bonding. Using secondary ion mass spectrometry (SIMS), Shinkai and coworkers[121] have measured the [dimer]/[monomer] and [trimer]/[monomer] ratios, respectively, for several calixarenes and have concluded that the calix[7]arenes and calix[8]arenes aggregate as dimers and trimers. The temperature dependent value of δ_{OH} for the monodeoxy-*p-tert*-butylcalix[4]arene (see Table 3.1) has been attributed to aggregation *via* intermolecular hydrogen bonding,[108] although mass spectrometry detected 0.1% or less of the dimer.[121]

[121] Inokuchi, F.; Shinkai, S. *J. Chem. Soc., Perkin Trans.* 2 **1996**, 601.

CHAPTER 4

Shaping the Baskets: Conformations of Calixarenes

'Some problems are so complex that you have to be highly intelligent and well informed just to be undecided about them'

Harvey G. Cox, *On Not Leaving It to the Snake*

The calixarenes are often compared with cyclodextrins, and, indeed, there are a number of structural similarities between the two families of compounds. There are significant differences with respect to their conformational flexibility, however. Whereas the cyclodextrins are quite rigid molecules, capable of a mild degree of flexing but lacking the ability to undergo ring inversions, the parent calixarenes are highly flexible molecules, capable not only of minor flexing but also possessing the ability to undergo complete ring inversions. Flexibility endows the calixarenes with a dimension that at times can be frustrating but that also makes possible the fashioning of cavities of highly varied shapes and contours.

4.1 Conformational Representation and Nomenclature

The calix[4]arenes were first recognized by Cornforth[7] as being capable of assuming four conformations, with various numbers of aryl groups projecting upward ('u') or downward ('d') relative to an average plane defined by the bridge methylene groups. These were later named by Gutsche[122] as 'cone' (u,u,u,u), 'partial cone' (u,u,u,d), '1,2-alternate' (u,u,d,d), and '1,3-alternate' (u,d,u,d), as illustrated in Figure 4.1. As the number of aryl groups in the cyclic array escalates (*i.e.* as *n* in **9** increases) the number of conformations likewise escalates. While calix[5]arenes can have only four true 'up/down' conformers, calix[6]arenes have eight, calix[8]arenes have sixteen, *etc.* Additionally, with all of the calixarenes there can be departures from the true 'up/down' orientations. For example, the aryl rings can project outward ('o'), and the likelihood of outward projecting aryl residues increases as the flexibility of the system increases. This

[122] Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, 39, 409.

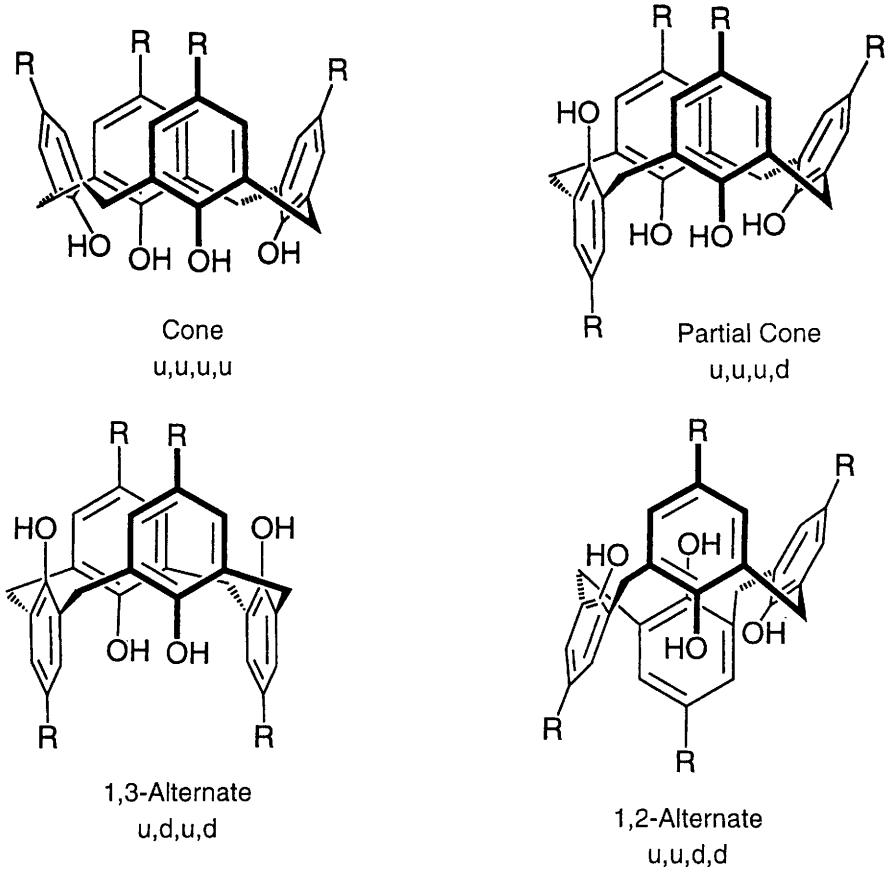


Figure 4.1 *Conformations of calix*[4]*arenes*

adds significantly to the total number of possible conformers and to the task of representing them in a simple pictorial (iconographic) or linear fashion. The 'up,down,out' designations[123] suffice reasonably well for the calix[4]arenes, calix[5]arenes, and to some extent the calix[6]arenes, but beyond this point they lose all precision. When applied to calixarene derivatives such as ethers and esters it is necessary for the 'up' and 'down' designations to accommodate the manner of substitution. To do this a *reference aryl group* is chosen by applying the Cahn–Ingold–Prelog priority rules. For example, the *p-tert*-Bu-ArOMe ring takes precedence over a *p-tert*-Bu-ArOH ring, a *p-tert*-Bu-ArOH ring takes precedence over a *p*-MeArOH ring, an $ArSO_2$ ring takes precedence over an ArCO ring, *etc.* If two or more aryl rings are identical, the one that is flanked by the greater number of higher priority aryl rings is chosen. For example, in the trimethyl ether of *p-tert*-butylcalix[4]arene the ArOMe ring flanked on *both* sides by ArOMe rings is chosen as the reference group. The reference group is

[123] Other designations that have been employed for the up/down orientation of the aryl groups are '+ and −' and 'α and β'.

indicated by a bold-faced or underlined **u** or **d** (or both) and can be arbitrarily assigned an 'up' orientation in most instances. Since mirror image sequences designate identical constitutions, however, it makes no difference which orientation is chosen unless the absolute configuration of the calixarene is being defined. The other aryl groups in the cyclic array are then designated by proceeding around the ring along the pathway that encounters the groups of higher priority (*i.e.* the 'outward exploration' concept of the Cahn–Ingold–Prelog rules). A representative example is depicted in Figure 4.2 where the priority of the rings is established by OBz > OPr > H and the aryl ring *syn* to the reference ring takes precedence over the aryl ring *anti* to the reference ring.

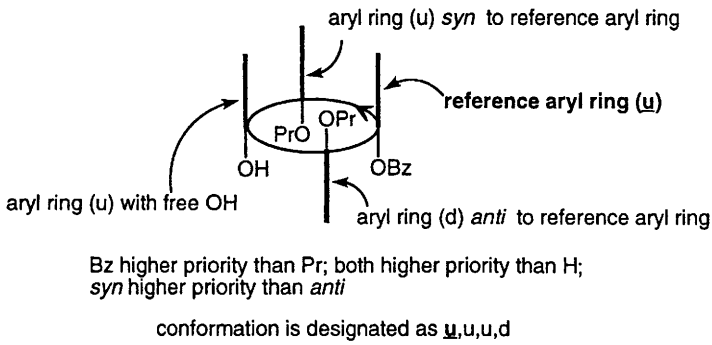


Figure 4.2 *'up/down' Designation of an O-substituted calix*[4]*arene*

The pictorial depiction of the conformations of calixarenes has been considered in a variety of ways. Representative examples of the pseudo-three-dimensional, iconographic, and linear representations of four of the conformations of a calix[6]arene are shown in Figure 4.3.[124] The iconographic representations, rendered in two dimensions, are derived from the shadow that is projected when light is cast downward from the upper rim of the calixarene. A cross-hatched circle denotes a group projecting *toward* the light (a 'u' group); a solid circle denotes a group projecting *away* from the light (a 'd' group); a circle cross-hatched in the half outside the calixarene ring denotes a group projecting up and outward (a 'uo' group); a circle cross-hatched in the half inside the calixarene ring denotes a group projecting up and inward (a 'ui' group); a circle solid-filled in the half outside the calixarene ring denotes a group projecting down and outward (a 'do' group; a circle solid-filled in the half inside the calixarene ring denotes a group projecting down and inward (a 'di' group); and an unfilled circle denotes a group projecting outward (an 'o' group). Another iconographic representation that has been proposed is illustrated in Figure 4.4 for calix[5]arenes in which the aryl groups are shown as rectangles or squares depending on their orientation as 'up/down' or 'out', respectively.

The most definitive conformational representation of a calixarene is derived from X-ray crystallography, although even these pictures sometimes fail to

[124] Kanamathareddy, S.; Gutsche, C. D. *J. Am. Chem. Soc.* **1993**, 115, 6572.

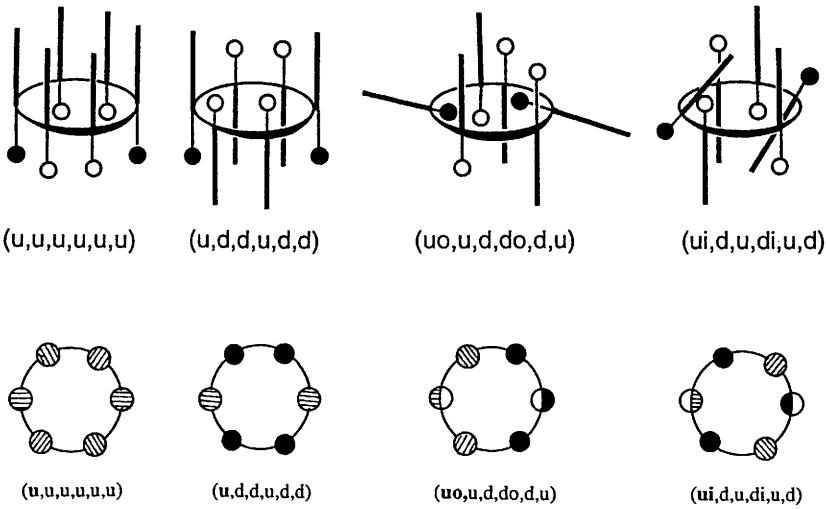


Figure 4.3 *Pseudo-three-dimensional, iconographic, and linear representations of calix[6]arene conformations*

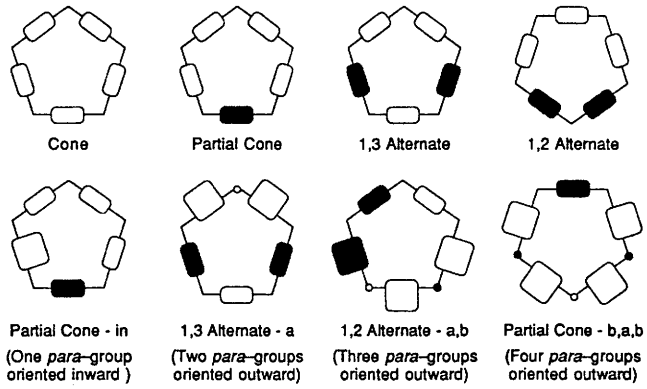


Figure 4.4 *Iconographic representations of calix[5]arene conformations*

readily convey the intended information because of the difficulty of presenting the molecule on the printed page in an orientation suitable for easy visual comprehension. As presaged by earlier workers and later detailed by Andreetti and coworkers,[125] the most critical feature in determining the conformation of a calixarene is the value of the dihedral angles ϕ and χ as defined by the sequences C_1–C_2–C_3–C_4 and C_2–C_3–C_4–C_5, respectively, shown in Figure 4.5. When the two adjacent aryl rings are in the A-orientation, the signs of ϕ and χ are opposite; when they are in the B-orientation, the signs of ϕ and χ are the same. For the precise designation of a calixarene conformation the values as well as the signs for all of these dihedral angles must be given, as illustrated by the data[125] in

[125] Ugozzoli, F.; Andreetti, G. D. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, 13, 337.

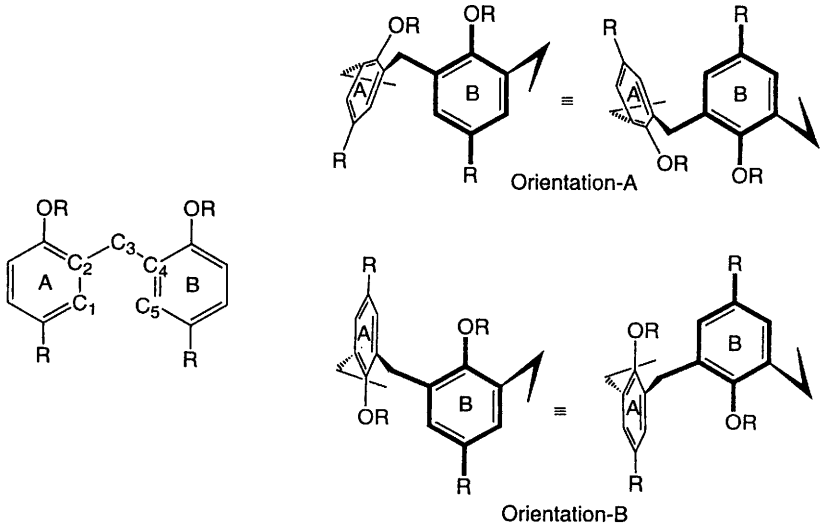


Figure 4.5 *Dihedral angles between adjacent aryl groups of a calixarene*

Table 4.1. For a qualitative linear designation, however, only the signs need be given. Thus, the four 'up/down' conformers of a calix[4]arene can be represented in linear fashion as follows: cone (+ − , + − , + − , + −); partial cone (+ − , + − , + + , − −); 1,2-alternate (+ − , + + , − + , − −); 1,3-alternate (+ + , − − , + + , − −). These can be further refined and, in some cases, condensed by including the Schönflies point symmetry designation. For example, the symmetrical cone conformation of a calix[4]arene is C_4 + − ; the distorted cone conformation of a calix[4]arene is C_2 + − ; the cone conformation of a calix[5]arene lacking symmetry is C_1 + − , + − , + − , + − , + − ; the pleated loop conformation of *p-tert*-butylcalix[8]arene is C_4 − + , + − .[126] In selecting the sequence for the calculations of the *n* pairs of dihedral angles around the macrocyclic ring, the 'top side' is defined as the one containing the maximum number of phenolic oxygens. The sequence of dihedral angles is then obtained by proceeding counterclockwise around the macrocyclic ring. It should be recognized, however, that the 'top ring', as defined in this manner, is actually the *lower rim* as defined by the now generally accepted convention (see Figure 1.6).

[126] The connection between the 'up,down' designations and the Ugozzoli and Andreetti designations is made by focusing on the relative signs as one progresses from one pairwise designation to the next. In a + − , + − sequence the sign changes from − to + and designates an 'up' aryl residue (*i.e.* 'u'); in a − + , − + sequence the sign changes from + to − and designates a 'down aryl residue' (*i.e.* 'd'); in a − + , + − sequence the sign remains the same and designates an 'up and out' aryl residue (*i.e.* 'uo'); in a + − , − + sequence the sign remains the same and designates a 'down and out' group (*i.e.* 'do').

Table 4.1 *Dihedral angles for ϕ and χ in calixarenes from selected examples cited in ref.* 125

Compound	*Conformation*	*Adjacent groups*	*Dihedral angles/°* ϕ	χ
p-tert-Butylcalix[4]arene (1:1 complex with toluene)	Symmetrical cone	A–B	+ 88.9	− 89.4
		B–C	+ 88.9	− 89.4
		C–D	+ 88.9	− 89.4
		D–A	+ 88.9	− 89.4
1,3-Dimethyl ether of *p-tert*-butylcalix[4]arene	Distorted cone	A–B	+ 74	− 124
		B–C	+ 102	− 63
		C–D	+ 64	− 107
		D–A	+ 116	− 58
1,3-Diethyl ether of *p-tert*-butylcalix[4]arene-crown-5	Partial cone	A–B	+ 91	− 67
		B–C	+ 75	− 101
		C–D	+ 156	+ 115
		D–A	− 130	− 137
1,3-Diethyl ether of *p-tert*-butylcalix[4]arene-crown-5	1,3-Alternate	A–B	+ 161	+ 110
		B–C	− 131	− 126
		C–D	+ 131	+ 128
		D–A	− 130	− 149
[Methyl ether of *p-tert*-butylcalix[4]arene][$MeAlMe_2$]$_2$	1,2-Alternate	B–A	+ 81	− 63
		A–D	+ 116	+ 140
		D–C	− 81	+ 63
		C–B	− 116	− 140
Calix[5]arene	Cone	A–B	+ 96	− 81
		B–C	+ 76	− 96
		C–D	+ 77	− 88
		D–E	+ 98	− 82
		E–A	+ 85	− 88
p-tert-Butylcalix[8]arene	Pleated loop	A–B	− 41.6	+ 35.6
		B–C	+ 101.5	− 83.1
		C–D	− 87.9	+ 87.9
		D–E	+ 85.6	− 86.5
		E–F	− 102.3	+ 71.9
		F–G	+ 103.2	− 87.3
		G–H	− 90.8	+ 88.3
		H–A	+ 88.8	− 102.8

4.2 Computational Studies of Calixarene Conformations[127]

One of the most significant changes in calixarene chemistry since the appearance of the previous volume in 1989 is the degree to which computational studies have been used to interpret and predict experimental results. One group of papers features molecular mechanics and dynamics calculations as their central focus,[95,128-136] while another group employs these techniques as an adjunct to

[127] For a review, see Ungaro, R. *et al.* in *Computational Approaches in Supramolecular Chemistry*; Wipff, G., Ed.; Nato ASI Series, Series C; Kluwer: Dordrecht; **1994**, Vol. 371, p. 277.

[128] Roger, J.; Bayard, F.; Decoret, C. *J. Chim. Phys.* **1990**, 87, 1695.

experimental data,[42b,105,108,111a,137-148] including complexation phenomena.[128,149-158] One of the earliest studies in the first category was carried out by the Reinhoudt group[95] and deals with calculations of structural, energetical, and acid–base properties of calix[4]arenes carrying H, Me, and *t*-Bu groups on the upper rim and various numbers of OH and OMe groups on the lower rim. The results are in generally good agreement with experiment with respect to the relative conformational stabilities, although some discrepancies were noted. For example, the stability sequence for the parent calix[4]arene was correctly predicted by calculation to be cone > partial cone > 1,2-alternate > 1,3-alternate, but the tetramethyl ether was incorrectly predicted by calculation to favor the 1,3-alternate rather than the partial cone conformation. Problems of this sort plagued computational results for several years and inspired studies in which various computational methods were compared,[95,131,132] leading one group[131] to declare 'these methods (*i.e.* MM2, AMBER, OPLSA, CHARMm,

[129] Harada, T.; Rudzinski, J. M.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2109.
[130] Harada, T.; Rudzinski, J. M.; Osawa, E.; Shinkai, S. *Tetrahedron* **1993**, 49, 5941.
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[133] Thondorf, I.; Brenn, J.; Brandt, W.; Böhmer, V. *Tetrahedron Lett.* **1995**, 36, 6665.
[134] Harada, T.; Ohseto, F.; Shinkai, S. *Tetrahedron* **1994**, 50, 13377.
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[139] McMurry, J. E.; Phelan, J. C. *Tetrahedron Lett.* **1991**, 32, 5655.
[140] van Loon, J.-D.; Heida, J. F.; Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1992**, 111, 353.
[141] Neri, P.; Ferguson, G.; Gallagher, J. F.; Pappalardo, S. *Tetrahedron Lett.* **1992**, 33, 7403.
[142] Pappalardo, S. *New J. Chem.* **1996**, 20, 465.
[143] Neri, P.; Foti, M.; Ferguson, G.; Gallagher, J. F.; Kaitner, B.; Pons, M.; Molins, M. A.; Giunta, L.; Pappalardo, S. *J. Am. Chem. Soc.* **1992**, 114, 7814.
[144] Molins, M. A.; Nieto, P. M.; Sánchez, C.; Prados, P.; de Mendoza, J.; Pons, M. *J. Org. Chem.* **1992**, 57, 6924.
[145] Neri, P.; Rocco, C.; Consoli, G. M. L.; Piatelli, M. *J. Org. Chem.* **1993**, 58, 6535.
[146] Coffer, J. L.; Chandler, R. R.; Gutsche, C. D.; Alam, I.; Pinizzotto, R. F.; Yang, H. *J. Phys. Chem.* **1993**, 97, 696.
[147] Moran, J. K.; Georgiev, E. M.; Yordanov, A. T.; Mague, J. T.; Roundhill, D. M. *J. Org. Chem.* **1994**, 59, 5990.
[148] Cunsolo, F.; Piattelli, M.; Neri, P. *J. Chem. Soc., Chem. Commun.* **1994**, 1917.
[149] Perrin, R.; Bourakhoudar, M.; Perrin, M.; Oehler, D.; Gharnati, F.; Lecocq, S.; Royer, J.; Decoret, C.; Bayard, F. *C. R. Acad. Sci., Ser. II*, **1991**, 312, 1135.
[150] Miyamoto, S.; Kollman, P. A. *J. Am. Chem. Soc.* **1992**, 114, 3668.
[151] Guilbaud, P.; Wipff, G. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1993**, 16, 169.
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[156] Asfari, Z.; Astier, J.-P.; Bressot, C.; Estienne, J.; Pepe, G.; Vicens, J. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 291.
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[158] Wipff, G.; Engler, E.; Guilbaud, P.; Lauterbach, M.; Troxler, L.; Varnek, A. *New J. Chem.* **1996**, 20, 403.

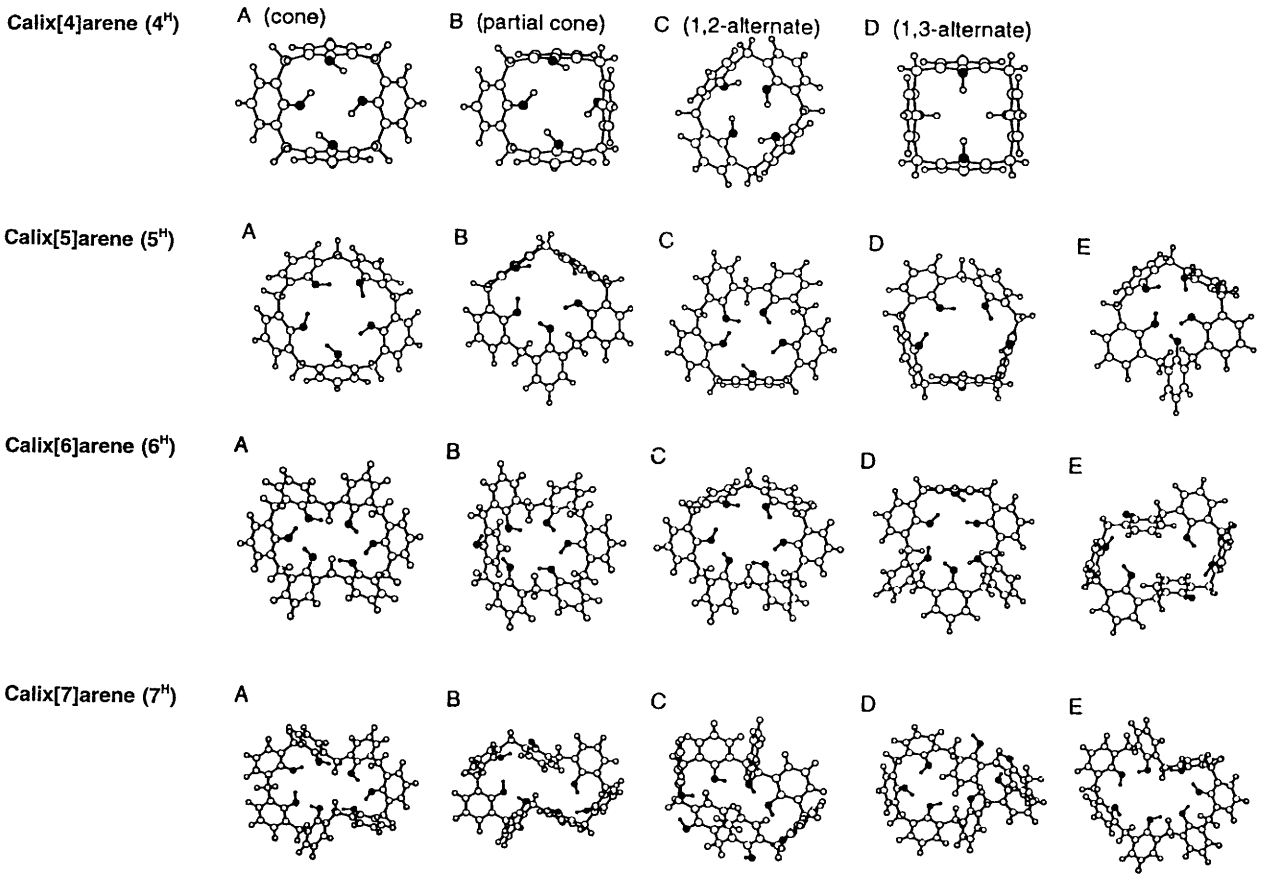

Figure 4.6 *MM3(92)-optimized conformers for calix[4]arene, calix[5]arene, calix[6]arene, and calix[7]arene (Taken from Harada and Shinkai*[136]*). The conformers are pictured in order of increasing energy from left to right*

MOPAC6AM1, MOPAC6PM3, AMPACAM1, AMPACPM3) to be ineffective and unreliable computational tools for predicting calixarene conformer stability'. They cautioned 'others to refrain from placing too much significance in such computed energies'. Computational techniques are improving rapidly, however, and the now frequently used MM3 program[106,129,130,133,134,136] and improved CHARMm program[135] appear to yield results that are usually in quite good agreement with experiment.

An extensive study of the conformational energies of the parent calixarenes[136] uses the MM3(92) program and yields four energy optimized structures for the calix[4]arenes, 10 for the calix[5]arenes, 90 for the calix[6]arenes, and 651 for the calix[7]arenes. Several of the lower energy forms for each of these four types of calixarene are shown in Figure 4.6. The lowest energy structure for the calix[4]arenes and calix[5]arenes is calculated to be the cone conformer; for the calix[6]arenes and calix[7]arenes it is the 'double cone pinched' conformer. In all of the lowest energy conformers the OH groups form hydrogen bonds with neighboring OH groups and show a regular distance and angle. In the higher energy conformers the OH bonds are longer and/or partially or completely cleaved. The calix[8]arene remains beyond present computational capabilities.

The subtle question has been addressed in some detail as to whether the cone conformers of calix[4]arenes exist in solution as time-invariant structures with C_4 symmetry or as rapidly interconverting structures with C_2 symmetry, as illustrated in Figure 4.7.

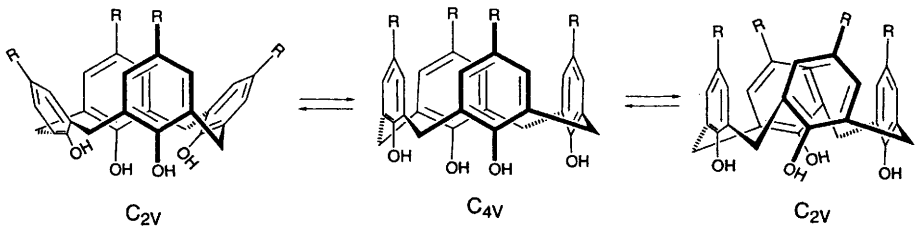

Figure 4.7 *Pinched cone–pinched cone interconversion of a calix*[4]*arene*

The first experimental data to suggest rapid interconversion of C_2 structures came from Böhmer's studies[62] with the bridged calixarenes **46a** in which the ^{1}H NMR resonance for the OH group diminishes from δ10.19 for the compound with a 16-methylene bridge to δ6.93 for the compound with a 5-methylene bridge as the result of the increasing distortion imposed on the system by the shorter bridge. Several other observations appear also to support this view, including the effect of Ag^+ on the ^{1}H NMR spectrum[154] as well as the effect of hydrogen bonding groups attached to the *p*-positions.[159–161] The tetra-CH_2CO_2Et ether

[159] Arduini, A.; Fabbi, M.; Mantovani, M.; Mirone, L.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Org. Chem.* **1995**, 60, 1454.

[160] Scheerder, J.; Vreekamp, R. H.; Engbersen, J. F. J.; Verboom, W.; van Duynhoven, J. P. M.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, 61, 3476.

[161] Conner, M.; Janout, V.; Regen, S. L. *J. Am. Chem. Soc.* **1991**, 113, 9670.

of **27a** shows broad ^{1}H NMR signals at room temperature which sharpen at lower temperatures to a pattern commensurate with C_2 pinched cone symmetry for the molecule. Temperature dependent ^{1}H NMR measurements give a $\Delta G^{\ddagger}$ of 13.4 kcal mol^{-1} for the pinched cone–pinched cone interconversion *via* a transition state with C_4 symmetry,[40b] comparable to the 14.1 kcal mol^{-1} value obtained with the *n*-octyl ether of **4**$^{t\text{-Bu}}$.[161] Upon complexation with Na^+ the system becomes much more rigid, adopting a C_4 symmetry similar to its counterpart, the Na^+ complex of the CH_2CO_2Et ether of **4**$^{t\text{-Bu}}$.[116c] Computational studies,[162,163a] indicate that this is true for the parent compound as well, the calculated energy favoring the C_2 conformer by *ca.* 0.8 kcal mol^{-1}. Similarly, the lowest energy conformers of the larger calixarenes lack complete symmetry: that of calix[5]arene is calculated to be C_1 but approaching C_5 (which is 0.3 kcal mol^{-1} less stable), while those of calix[6]arene (calculated to be C_2) and calix[7]arene (calculated to be C_1) are far more stable than their conformers with C_6 and C_7 symmetries, respectively. Another subtle aspect of calix[*n*]arene structure is the question of whether the intramolecular hydrogen bonds are permanently oriented or engage in 'flip-flop' reorientation. The question has been addressed only for the calix[4]arenes, where the computational studies appear to favor the former alternative.[95] Whether this also prevails for the larger calixarenes, particularly the calix[8]arene in the pleated loop conformation, remains to be explored.

The major focus of the computational studies of the calixarenes has been on conformational energies, but a few attempts have been made to calculate other properties of these compounds. Using free energy perturbation methods, the relative acidities of *p*-methylcalix[4]arene and an acyclic analog were calculated.[95] The calixarene was estimated to be the more acidic by 9–11 pK_a units, in qualitative agreement with experimental data (see Section 3.4). The puzzling prediction from the calculations that the dissociation to calix[4]arene anions should become progressively easier with increasing deprotonation, however, led the authors to suggest several possible flaws in the method of calculation. Dipole moment calculations[105,107] are in quite good agreement with experimentally observed values (see Section 3.5) and correctly predict the sequence to be: cone > partial cone > 1,2-alternate > 1,3-alternate.

4.3 Conformations of Calixarenes in the Solid State

4.3.1 Calix[4]arenes

Calix[4]arenes containing four *endo*-OH groups exist in the cone conformation in the solid state.[164,165] The first X-ray structure of a calix[4]arene to show this

[162] Dickert, F. L.; Schuster, O. *Adv. Mater.* **1993**, 5, 826.

[163] van Hoorn, W. P., Ph.D. Thesis, Universiteit Twente, Enschede, Netherlands, **1997** (a) p. 44; (b) p. 38.

[164] A lone exception has been reported[165] describing the isolation of two crystalline forms of *p*-hexanoylcalix[4]arene which, on the basis of CP-MAS ^{13}C NMR spectral measurements, are assigned cone (one C=O resonance) and partial cone (3 C=O resonances) stuctures.

[165] Shinkai, S.; Nagasaki, T.; Iwamoto, K.; Ikeda, A.; He, G.-X.; Matsuda, T.; Iwamoto, M. *Bull. Chem. Soc. Jpn.* **1991**, 64, 381.

was that of *p-tert*-butylcalix[4]arene,[166] and this observation has since been confirmed with a number of other calix[4]arenes, including **4**$^{1,1,3,3\text{-tetramethylbutyl}}$,[167] **4**$^{i\text{-Pr}}$ as a 1:1 toluene complex,[168] **4**^{Ph} as a 1:1 $CHCl_3$ complex,[169] **4**$^{N=NPh}$,[170] and **4**^{COMe}.[171] *p-tert*-Butylcalix[4]arene (as its 1:1 toluene complex) is a cone with almost perfect C_4 symmetry (u,u,u,u), as also is its counterpart **18** containing four *exo*-OH groups (as an acetonitrile complex).[34] Introduction of four or eight methyl groups into the *m*-positions (**27a**,[40] R^1 = Me and **29**[42a]) causes the cone to change its symmetry from C_4 to approximately C_2 (u,uo,u,uo) to give a conformation variously called 'flattened cone', 'pinched cone', or 'boat'.[42b] Imposing a bridge between the A,C *p*-positions on the upper rim [*via* a '2 + 2' convergent synthesis (see ref. 1, pp. 42–43)] to give **46a** (n = 4–16) changes the symmetry in a similar fashion, the magnitude of the change increasing with decreasing values of n.[56c,d,e] The introduction of a single *m*-methyl group (**60b**, $R^{1,3,4,5}$ = *i*-Pr), however, causes relatively little distortion.[172] Molecular mechanics calculations[34] on the 'annulated' calixarene **52** ($R^{1,2}$ = H) suggest that it has two conformations nearly equal in energy, one in which both the *exo* and *endo* portions are cones and the other in which the *endo* part is a cone and the *exo* part is a 1,2-alternate. Calix[4]arenes in which one or more of the hydrogens of the OH groups on the lower rim are replaced by other groups also frequently exist in the cone conformation in the solid state. An example of an *O*-monosubstituted compound is the monomethyl ether of **4**$^{t\text{-Bu}}$ which is most stable in the cone conformation.[173] Examples of disubstituted cone conformers include both the A,B- and A,C-di-*O*-substituted calix[4]arenes such as the A,B-di(ethoxycarbonylmethyl) compound, **90b**,[174,175] the A,C-dimethyl ether **90c**,[95] the A,C-dicyanomethyl cone conformers **90d**,[176] and the A,C-bridged compound **90e**.[177] Examples of trisubstituted compounds include the trimethyl ether **90f**[95] and the mixed pyridylmethyl/benzyl ether **90g**.[178] X-Ray structures of tetra-*O*-substituted calix[4]arenes showing cone conforma-

[166] Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1005.
[167] Andreetti, G. D.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1773.
[168] Ohtsuchi, M.; Suzuki, K.; Armah, A. E.; Yamagata, Y.; Fujii, S.; Tomita K.-I.; Asfari, Z.; Vicens, J. *Acta Crystallogr.* **1993**, *C*49, 639.
[169] Juneja, R. K.; Robinson, K. D.; Johnson, C. P.; Atwood J. L. *J. Am. Chem. Soc.* **1993**, 115, 3818.
[170] Ehlinger, N.; Lecocq, S.; Perrin, R.; Perrin, M. *Supramol. Chem.* **1993**, 2, 77.
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[172] Ueda, Y.; Fujiwara, T.; Tomita, K.-I.; Asfari, Z.; Vicens, J. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1993**, 15, 341.
[173] Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R. *Gazz. Chim. Ital.* **1989**, 119, 335.
[174] Groenen, L. C.; Ruël, B. H. M.; Casnati, A.; Timmerman, P.; Verboom, W.; Harkema, S.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron Lett.* **1991**, 32, 2675.
[175] An X-ray structure of the corresponding de-*tert*-butyl compound **90c** ($R^{1,2}$ = H)[95] showed this compound to also exist in a cone conformation, indicating that the *p*-substituent has little effect on the solid state conformation of calix[4]arenes.
[176] Collins, E. M.; McKervey, M. A.; Madigan, E.; Moran, M. B.; Owens, M.; Ferguson, G.; Harris, S. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3137.
[177] Böhmer, V.; Ferguson, G.; Gallagher, J. F.; Lough, A. J.; McKervey, M. A.; Madigan, E.; Moran, M. B.; Phillips, J.; Williams, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1521.
[178] Ferguson, G.; Gallagher, J. F.; Giunta, L.; Neri, P.; Pappalardo, S.; Parisi, M. *J. Org. Chem.* **1994**, 59, 42.

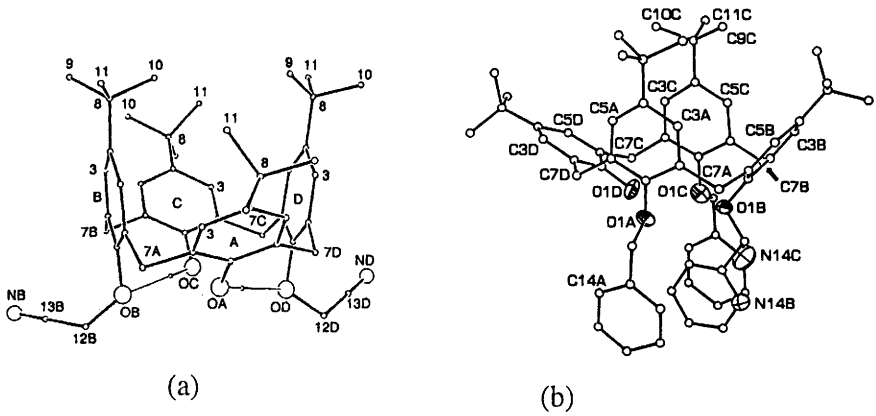

Figure 4.8 *X-Ray crystallographic structures of* (a) *A,C-dicyanomethyl ether of* $\mathbf{4}^{t\text{-}Bu}$ *and* (b) *A,B-dipyridyl-C-benzyl ether of* $\mathbf{4}^{t\text{-}Bu}$ *(Taken from Collins* et al.[176] *and Ferguson* et al.[178])

tions are numerous, typical examples including the tetramethyl ether **90h**,[95] the tetraacetonyl ether **90i**,[179] the tetrapropyl ether **90j**,[180] the bis-crown ether-bridged calix[4]arene **90k**,[181] and several phosphate-bridged[182–184] and phosphorus-bridged[185] calix[4]arenes. In a number of the calix[4]arenes which possess the cone conformation, two of the aryl groups are almost parallel to one another while the other two are splayed outward to give the 'pinched cone' ('flattened cone') conformation; representative examples are shown in Figure 4.8. In the case of the tetrapropyl ether of A,C-bis(acetamido)calix[4]arene, both of the pinched cone conformations are present in the solid state, as revealed by X-ray crystallography.[186]

Relatively few X-ray structures of calix[4]arenes in the partial cone conformation have been reported (see ref. 1, pp. 106–107), most of them involving tetra-*O*-

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[184] Neda, I.; Plinta, H.-J.; Sonnenburg, R.; Fischer, A.; Jones, P. G.; Schmutzler, R. *Chem. Ber.* **1995**, 128, 267.

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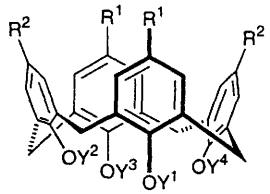


90

a) Y^1 = Me; Y^{2-4} = H; $R^{1,2}$ = *t*-Bu

b) $Y^{1,2}$ = CH_2CO_2Et; $Y^{3,4}$ = H ; $R^{1,2}$ = H

c) $Y^{1,3}$ = Me; $Y^{2,4}$ = H; $R^{1,2}$ = *t*-Bu

d) $Y^{1,3}$ = CH_2CN; $Y^{2,4}$ = H; $R^{1,2}$ = *t*-Bu

e) Y^1,Y^3 = $CH_2CONH(CH_2)_2NHCOCH_2$; $Y^{2,4}$ = H, $R^{1,2}$ = *t*-Bu

f) Y^{1-3} = Me; Y^4 = H; $R^{1,2}$ = *t*-Bu

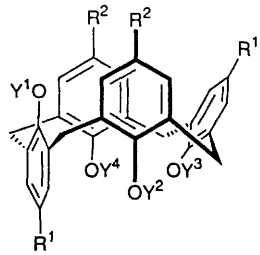
g) $Y^{1,2}$ = CH_2Py; Y^3 = CH_2Ph; Y^4 = H; $R^{1,2}$ = *t*-Bu

h) Y^{1-4} = Me; $R^{1,2}$ = *t*-Bu

i) Y^{1-4} = CH_2COCH_3; $R^{1,2}$ = *t*-Bu

j) Y^{1-4} = Pr; R^1 = NHCOMe; R^2= H

k) Y^1,Y^2 =Y^3,Y^4 = $(CH_2)_2O(CH_2)_2$; $R^{1,2}$ = Cyclohexyl



91

a) Y^{1-4} = Me; $R^{1,2}$ =CH_2SCH_3

b) Y^{1-4} = Et; $R^{1,2}$ = *t*-Bu

c) Y^{1-4} = CH_2Py; $R^{1,2}$ = *t*-Bu

d) $Y^{1,3}$ = $CH_2CH{=}CH_2$; $Y^{2,4}$ = Me; R^1 = H; R^2 = *t*-Bu

e) $Y^{1,3}$ = $CH_2CH{=}CH_2$; $Y^{2,4}$ = COPh; $R^{1,2}$ = H

f) $Y^{1,3}$ = CH_2CN; $Y^{2,4}$ = Me; $R^{1,2}$ = *t*-Bu

g) $Y^{1,3}$ = CH_2COEt; $Y^{2,4}$ = CH_2Py; $R^{1,2}$ = *t*-Bu

h) $Y^{1,2,4}$ = Me; Y^3 = COMe; $R^{1,2}$ = H

i) $Y^{1,2}$ = Et; $Y^{3,4}$ = H; $R^{1,2}$ = *t*-Bu

j) Y^{1-4} = Me; $R^{1,2}$ = CN

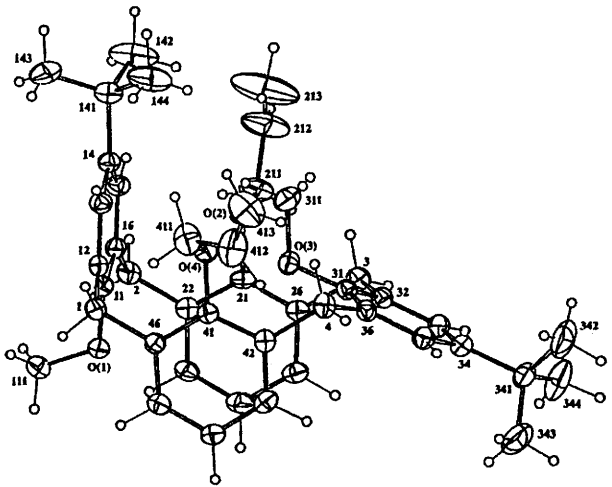
substituted compounds such as the symmetrically-substituted tetramethyl (**91a**, **91j**),[187,188] tetraethyl (**91b**),[189] and tetrapyridylmethyl (**91c**)[190] ethers. For the

[187] Hamada, F.; Bott, S. G.; Orr, G. W.; Coleman, A. W.; Zhang, H.; Atwood, J. L. *J. Inclusion Phenom.* **1990**, 9, 195.

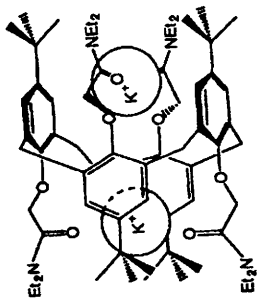
[188] Hamada, F.; Orr, G. W.; Zhang, H.; Atwood, J. L. *J. Crystallogr. Spectrosc. Res.* **1993**, 23, 681.

[189] (a) Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, 56, 4955; (b) Araki, K.; Iwamoto, K.; Shinkai, S.; Matsuda, T. *Chem. Lett.* **1989**, 1747.

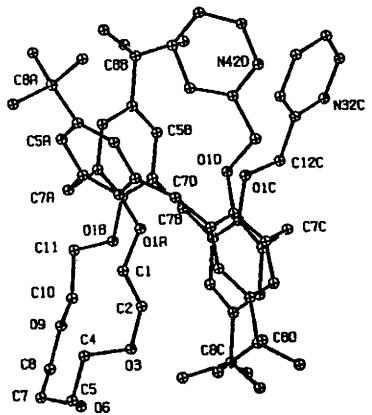
[190] Ferguson, G.; Gallagher, J. F. *Acta Crystallogr.* **1993**, *C*49, 1537.



91d



92b

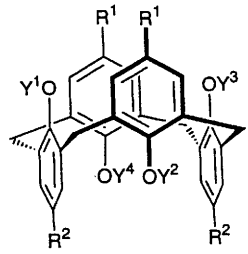


94d

Figure 4.9 *X-Ray crystallographic structures of* (a) *partial cone conformer* **91d** (*Taken from Harrowfield* et al.[191a]); (b) 1,3-*alternate conformer* **92b** (*Taken from Beer* et al.[155]); *and* (c) 1,2-*alternate conformer* **94d** (*Taken from Pappalardo* et al.[198])

tetrasubstituted calix[4]arenes **91d–i**[191] in which two different substituents are attached to the oxygens, two different partial cone structures are possible depending on which pair of A,C aryl residues are *anti* to one another. An example of a di-*O*-substituted calix[4]arene in the partial cone conformation is the A,B-diethyl ether **91i**.[192] In most of these examples the conformation is more or less distorted from a true partial cone into what is sometimes referred to as a 'flattened partial cone', as illustrated in Figure 4.9 for structure **91d** and by the 'doubly flattened partial cone' structure of the $AlMe_3$ complex of the A,C-dimethyl ether of $\mathbf{4}^{t\text{-Bu}}$.[193]

Numerous examples of 1,3-alternate conformers of calix[4]arenes are known, but relatively few have been established by X-ray crystallography. In addition to earlier examples,[194] more recent ones include the tetra-*O*-substituted[195] **92a** and **92b** (as a K^+ complex)[155] (see Figure 4.9), the doubly-bridged **92c**,[196] the bis-calixarene **93**,[197] and the calix[4]arene **40** containing four extraannular OH groups.[53]



92

a) $Y^{1,3} = CH_2CO_2Et$; $Y^{2,4} = CH_2Py$; $R^{1,2} = t\text{-Bu}$

b) $Y^{1\text{-}4} = CH_2CONEt_2$; $R^{1,2} = t\text{-Bu}$

c) $Y^1Y^3 = Y^2Y^4 = CH_2CH_2(OCH_2CH_2)_2OCH_2CH_2$; $R^{1,2} = t\text{-Bu}$

Among the four conformations of the calix[4]arenes, the least often encountered is the 1,2-alternate. The first reported example[194b] is the complex obtained by treatment of the tetramethyl ether of $\mathbf{4}^{t\text{-Bu}}$ with $AlMe_3$. More recent examples, include the tetraethyl ether **94a**,[138] the tetrakis(2-pyridylmethyl) ether **94b**,[198] the dimethyl ether diphosphate **94c** of $\mathbf{4}^{t\text{-Bu}}$,[199] and the bridged ether

[191] (a) Harrowfield, J. M.; Mocerino, M.; Skelton, B. W.; Whitaker, C. R.; White, A. H. *Aust. J. Chem.* **1994**, 47, 1185; (b) Georgiev, E. M.; Mague, J. T; Roundhill, D. M. *Supramol. Chem.* **1993**, 2, 53; (c) Guelzim, A.; Khrifi, S.; Baert, F.; Loeber, C.; Asfari, Z.; Matt, D.; Vicens, J. *Acta Crystallogr.* **1993**, *C*49, 72; (d) Park, Y. J.; No, K.; Song, B.-H.; Rhim, S. K. *Bull. Korean Chem. Soc.* **1994**, 15, 1108; (e) Shinkai, S.; Fujimoto, K.; Otsuka, T.; Ammon, H. L. *J. Org. Chem.* **1992**, 57, 1516.

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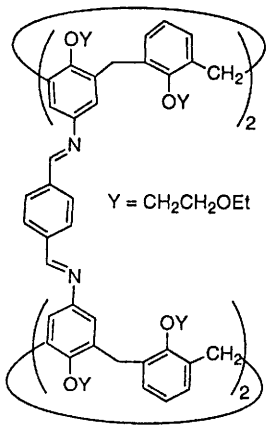
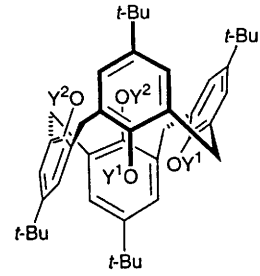
[199] Ting, Y.; Verboom, W.; Groenen, L. C.; van Loon, J.-D.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1990**, 1432.



93



94

a) $Y^{1,2}$ = Et

b) $Y^{1,2}$ = CH_2Py

c) Y^1 = Me; Y^2 = $PO(OEt)_2$

d) Y^1Y^1 = $CH_2CH_2(OCH_2CH_2)_3$; Y^2 = CH_2Py

94d,[198] illustrated in Figure 4.9. Another unusual conformation is that of the $Cr(CO)_6$ complex of the tetra-*n*-propyl ether of $\mathbf{4}^{H}$, which is described as a 'bis-roof'.[200]

Replacement of the OH groups of the calix[4]arenes with hydrogens yields a series of OH-depleted calix[4]arenes whose X-ray structures have been determined. The monodeoxy compound **95a**[201] (as a pyridine complex) retains the cone conformation in the solid state, whereas the other members of the series assume non-cone conformations, *viz.* a 1,2-alternate conformation for the dideoxy compound **95b**,[201] a 1,3-alternate conformation for its diethyl ether **95c**,[202] a 1,2-alternate conformation for the tetradeoxy compound, **95d**,[139,201] and a 'chair' conformation for its analog **95e** lacking the *p-tert*-butyl groups,[139] as illustrated in Figure 4.10. In the terminology discussed in Section 4.1 the chair form would be designated as a (u,o,d,o) conformation.

One, two, three, or all four of the OH groups of $\mathbf{4}^{t\text{-Bu}}$ have been replaced by SH groups,[203] and X-ray structures have been obtained for these compounds as well as the precursor compound **95f**. The monothiol **95g** assumes the cone conformation,[203] while the 1,3-dithiol **95h** (as a Hg complex),[204] the trithiol **95i**,[203] and the tetrathiol **95j**[205] all assume the 1,3-alternate conformation. The precursor **95f**

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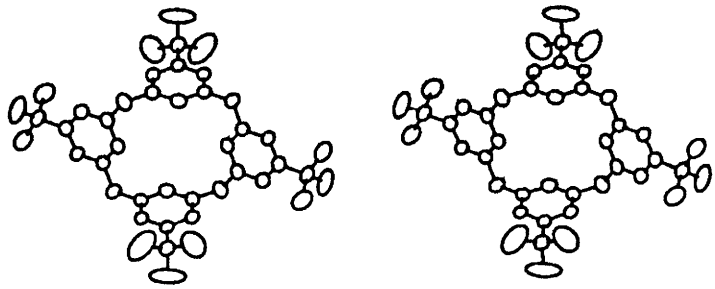
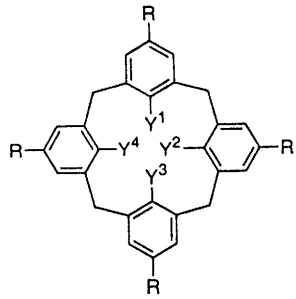


Figure 4.10 *X-Ray crystallographic structure of tetradeoxy*-p-tert-*butylcalix*[4]*arene* **95d** (*Taken from Grynszpan* et al.[201a])



95

a) Y^{1-3} = OH; Y^4 = H; R = *t*-Bu

b) $Y^{1,3}$ = OH; $Y^{2,4}$ = H; R = *t*-Bu

c) $Y^{1,3}$ = OEt; $Y^{2,4}$ = H; R = *t*-Bu

d) Y^{1-4} = H; R = *t*-Bu

e) Y^{1-4} = H; R = H

f) Y^{1-4} = $SCONMe_2$; R = *t*-Bu

g) Y^1 = SH; Y^{2-4} = OH; R = *t*-Bu

h) $Y^{1.3}$ = SH; $Y^{2,4}$ = OH; R = *t*-Bu

i) Y^{1-3} =SH; Y^4 = OH; R = *t*-Bu

j) Y^{1-4} = SH; R = *t*-Bu

k) Y^{1-4} = Me; R = H

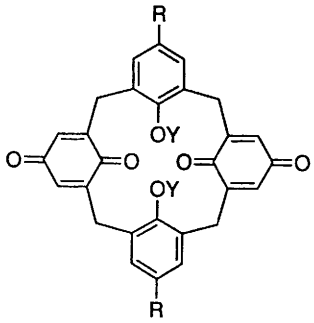
exists as the 1,2-alternate conformer but undergoes conformational conversion to the 1,3-alternate conformer on hydrogenolysis.[203]

The X-ray structure of calix[4]arene tetraquinone[206a,b] shows it to be in a flattened partial cone conformer. Similarly, the dialkyl ether diquinones **96a**, **96b**, and **96c** all assume the partial cone conformation[207] but differ with respect to the orientation of the four residues in the cyclic array: in **96a** and **96b** the alkoxyaryl

[206] (a) Morita, Y.; Agawa, T.; Kai, Y.; Kanehisa, N.; Kasai, N.; Nomura, E.; Taniguchi, H. *Chem. Lett.* **1989**, 1349; (b) Morita, Y.; Agawa, T.; Nomura, E.; Taniguchi, H. *J. Org. Chem.* **1992**, 57, 3658; (c) Timmerman, P.; Harkema, S.; Van Hummel, G. J.; Verboom, W.; Reinhoudt, D. N. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1993**, 16, 189.

[207] Casnati, A.; Comelli, E.; Fabbi, M.; Bocchi, V.; Mori, G.; Ugozzoli, F.; Lanfredi, A. M. M.; Pochini, A.; Ungaro, R. *Recl. Trav. Chim. Pays-Bas* **1993**, 112, 384.

moieties are *anti*, whereas in **96c** the quinone moieties are *anti*. On the other hand, the O,O′-bridged diquinone **96d** (as a Na^+ complex),[208] the monoketal of a calix[4]arene monoquinone,[206c] and the calix[4]arene monoquinoneimine all exist as pinched cone (flattened cone) conformers.



96

a) Y = Me; R = H

b) Y = Et; R = *t*-Bu

c) Y = i-Pr; R = H

d) Y,Y = $CH_2CH_2(OCH_2CH_2)_2OCH_2CH_2$; R = *t*-Bu

4.3.2 Calix[5]arenes

Several X-ray structures of the parent *p*-substituted calix[5]arenes have been obtained, including $\mathbf{5}^{t\text{-Bu}}$ as the acetone complex,[209] the tetralin complex,[210] the ethyl acetate complex,[211] and the 'self' complex;[212] $\mathbf{5}^{1,1,3,3\text{-tetramethylbutyl}}$ as the toluene complex[213] (see Figure 4.11); and $\mathbf{5}^{SO_3H}$ as the pyridine *N*-oxide complex.[103] In all of these cases the conformation is a somewhat distorted shallow cone, but when one of the OH groups is replaced by a hydrogen to give a monodeoxycalix[5]arene the conformation changes to a partial cone.[49a] Calix[5]arene ethers and esters assume a variety of conformations, depending on the degree and nature of substitution. While the pentaethoxycarbonylmethyl ether **97a**,[214] the 1,2,3-triethers **97c**,[215] and **97d**,[216] and the monoether **97e**[112] all retain a distorted cone conformation (typically u,u,uo,uo,uo), the pentaisopropyl ether **97b**[112] is a flattened 1,2-alternate (u,uo,u,d,d) conformation. Several of these compounds show self complexation; *e.g.* an isopropoxy group fills the cavity in the case of **97b** and a *tert*-butyl group in the case of **97a** and **97e**, as illustrated in Figure 4.11.

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[216] Arnecke, R.; Böhmer, V.; Ferguson, G.; Pappalardo, S. *Tetrahedron Lett.* **1996**, 37, 1497.

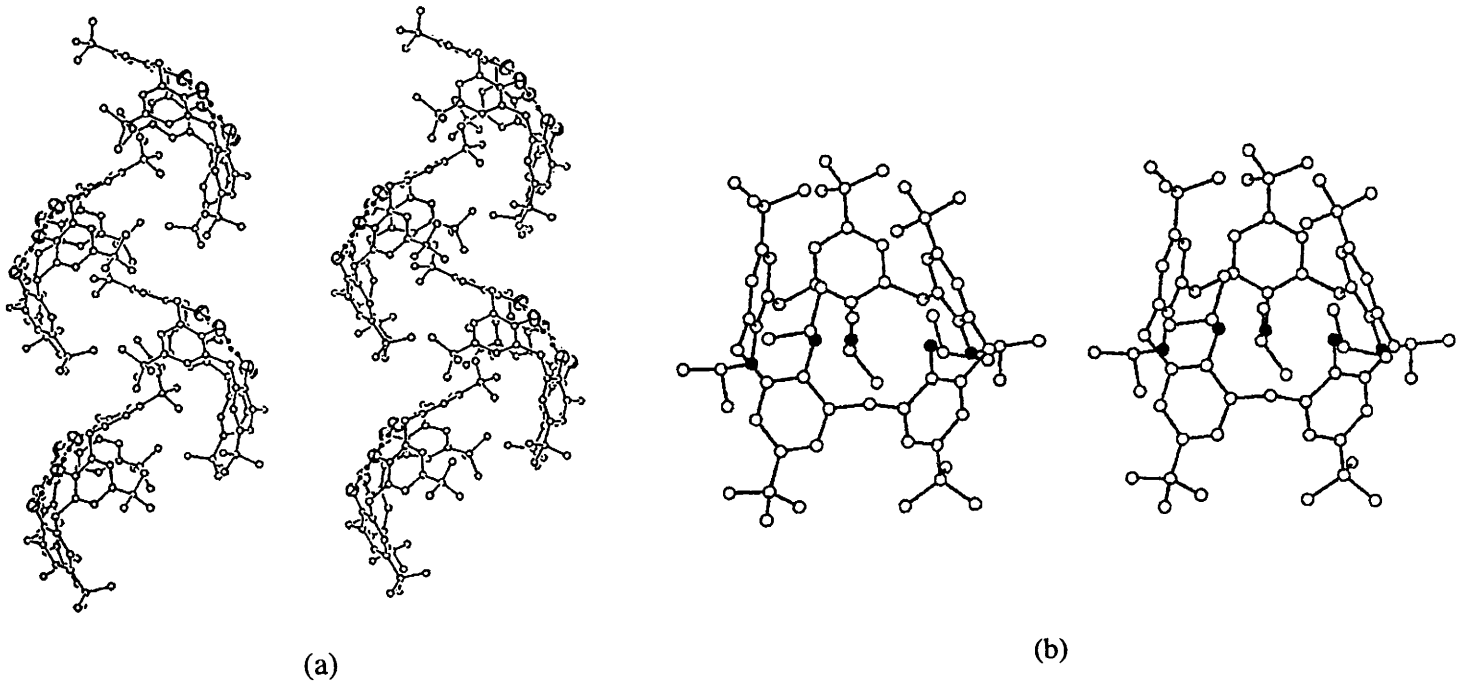
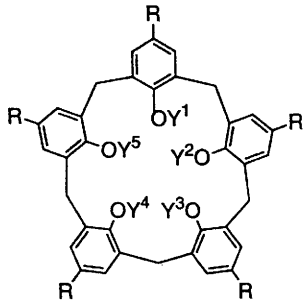


Figure 4.11 *X-Ray crystallographic structures of* (a) $\mathbf{5}^{t\text{-}Bu}$ *intermolecularly self-complexed (Taken from Gallagher* et al.[212]*) and* (b) *the penta-i-propyl ether of* $\mathbf{5}^{t\text{-}Bu}$ *intramolecularly self-complexed (Taken from Stewart* et al.[112])



97

a) $Y^{1\text{-}5}$ = CH_2CO_2Et; R = *t*-Bu

b) $Y^{1\text{-}5}$ = i-Pr; R = *t*-Bu

c) $Y^{1,2,3}$ = CH_2Py; $Y^{4,5}$ = H; R = *t*-Bu

d) $Y^{1,2}$ = $CH_2(CH_2OCH_2)_3CH_2$; Y^3 = CH_2Py; $Y^{4,5}$ = H; R = *t*-Bu

e) Y^1 = *i*-Pr; $Y^{2\text{-}5}$ = H; R = *t*-Bu

4.3.3 Calix[6]arenes

The conformations of the parent calix[6]arenes have been variously described as distorted cone [**6**$^{t\text{-Bu}}$],[217] double partial cone [**6**^{cumyl} [218] and **6**^{SO_3H} [101]], winged [**6**$^{t\text{-Bu}}$ as its tetrachloroethylene complex[219]], hinged (see ref. 1, p. 97), pinched cone [**6**$^{i\text{-Pr}}$ as its benzene complex,[220,221] and **6**$^{t\text{-Bu}}$ as its acetonitrile complex[222]], 1,2,3-alternate [**6**$^{t\text{-Bu}}$ as its DMSO complex[221]], and distorted 1,2,3-alternate cone [**6**^{H} as a doubly deprotonated dianion[223a]]. A recent study by Bott and coworkers[221] has shown that the conformation in the solid state is a function of the solvent from which the compound is crystallized. When the solvent (*e.g.* benzene) cannot engage in hydrogen bonding with the OH groups of the calixarene the result is a pinched cone conformation (designated as C_2 − +, + −, + −, − +, + −, + − or [uo,u,uo,uo,u,uo]) in which all of the OH groups are intramolecularly hydrogen-bonded in a cyclic array. However, when the solvent (*e.g.* acetone, DMSO) can disrupt the intramolecular hydrogen bonding the calixarene assumes a distorted 1,2,3-alternate conformation (designated as C_i + −, − +, − +, − +, + −, + − or [u,u,uo,d,d,do]), as illustrated in Figure 4.12.

Replacement of all of the phenolic hydrogens has the same effect as a hydrogen

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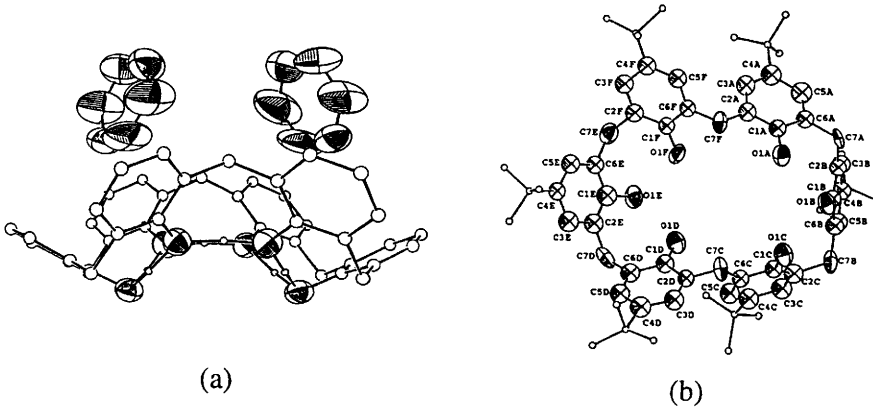
[223] (a) Thuéry, P.; Keller, N.; Lance, M.; Vigner, J.-D.; Nierlich, M. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1995**, 20, 89; (b) also see Taniguchi, H.; Nomura, E.; Hinomoto, R. *Chem. Express* **1992**, 7, 853.



(a) (b)

Figure 4.12 *X-Ray crystallographic structures of* $\mathbf{6}^{t\text{-}Bu}$ *in* (a) *pinched cone conformation and* (b) 1,2,3-*alternate conformation* (*Taken from Wolfgong* et al.[221])

bond-breaking solvent, resulting in distorted 1,2,3-alternate conformations as in **98a**.[224] When only four of the OH groups are replaced, however, some intramolecular hydrogen bonding remains, and the solid state conformation becomes u,d,do,d,u,uo (designated by one group of authors[143] as 1,2,4,5-alternate) as in **98b**[225] and **98c**.[143] With only two OH groups replaced, intramolecular hydrogen bonding remains even stronger, and the A,C-disubstituted *p-tert*-butylcalix[6]arene **98d** exists in the pinched cone conformation.[226] Bridging between the phenolic residues imposes additional steric demands on the system, but seems generally to result in cone-like conformations [*cf.* structures **150d**[227] and **157** (R = *t*-Bu)[228]]. A pentaaluminum complex of $\mathbf{6}^{H}$ has been shown to exist in the solid state in a conformation in which all six of the oxygen atoms are essentially coplanar.[229] The solid state structure of calix[6]hexaquinone is best described as a (u,d,o,d,u,o) conformation.[230]

4.3.4 Calix[7]arenes

An X-ray structure[231] of $\mathbf{7}^{t\text{-}Bu}$ shows that the molecule adopts a flattened conformation designated as C_i + −, − +, + −, + −, + +, − +, + − or

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[227] (a) Saiki, T.; Goto, K.; Tokitoh, N.; Goto, M.; Okazaki, R. *Tetrahedron Lett.* **1996**, 37, 4039; (b) Saiki, T.; Goto, K.; Tokitoh, N.; Okazaki, R. *J. Org. Chem.* **1996**, 61, 2924.
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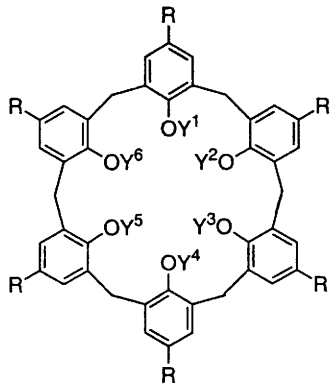
[231] Andreetti, G. D.; Ugozzoli, F.; Nakamoto, Y.; Ishida, S.-I. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1991**, 10, 241.



98

a) $Y^{1\text{-}6}$= CH_2CH_2OMe; R = *t*-Bu

b) $Y^{1,2,4,5}$ = $(CH_2CH_2O)_2Me$; $Y^{3,6}$= H; R = *t*-Bu

c) $Y^{1,2,4,5}$ = CH_2Py; $Y^{3,6}$ = H; R = *t*-Bu

d) $Y^{1,3}$ = $P(O)(OEt)_2$; $Y^{2,4,5,6}$ = H; R = *t*-Bu

e) $Y^{1,4}$ = $P(O)(OEt)_2$; $Y^{2,3,5,6}$ = H; R = *t*-Bu

f) $Y^{1,2,4}$ = $P(O)(OEt)_2$; $Y^{3,5,6}$ = H; R = *t*-Bu

g) $Y^{1\text{-}6}$= $P(O)(OEt)_2$; R = *t*-Bu

h) $Y^{1,4}$ = $P(S)(OEt)_2$; $Y^{2,3,5,6}$= H; R =*t*-Bu

i) Y^1Y^4 = CH_2ArCH_2; $Y^{2,3,5,6}$= Me; R = Br or H

j) $Y^{1\text{-}5}$ = $P(S)(OEt)_2$; Y^6 = H; R = *t*-Bu

[u,u,uo,u,u,u,uo], as illustrated in Figure 4.13. An X-ray structure of $\mathbf{7}^{Et}$,[232] on the other hand, shows a conformation that is calculated[136] to be 5.4 kcal mol^{-1} less stable in which two of the phenolic residues are inverted, possibly a consequence of the combined influences of the *p*-substituent and crystal packing forces.

4.3.5 Calix[8]arenes

An early X-ray structure of $\mathbf{8}^{t\text{-}Bu}$ crystallized from pyridine indicated it to have a 'pleated loop' conformation (see ref. 1, p. 70),[233] and rather similar conformations have been observed for its complexes with calcium[234] and uranyl[235] cations. In a more recent study,[236] however, the X-ray structure of a complex of $\mathbf{8}^{t\text{-}Bu}$ with eight pyridine molecules showed it to assume a twisted conformation, something approaching the 'pinched' conformation suggested in the early 1980s before an X-ray structure had been obtained.[237] Complexes of $\mathbf{8}^{t\text{-}Bu}$ with various metal ions, including lanthanides,[238] thorium,[239] and molybdenum,[240] also reveal a conformation different from a pleated loop and approximately described as a 1,2,3,4-alternate.

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[240] Gibson, V. C.; Redshaw, C.; Clegg, W.; Elsegood, M. R. J. *J. Chem. Soc., Chem. Commun.* **1995**, 2371.

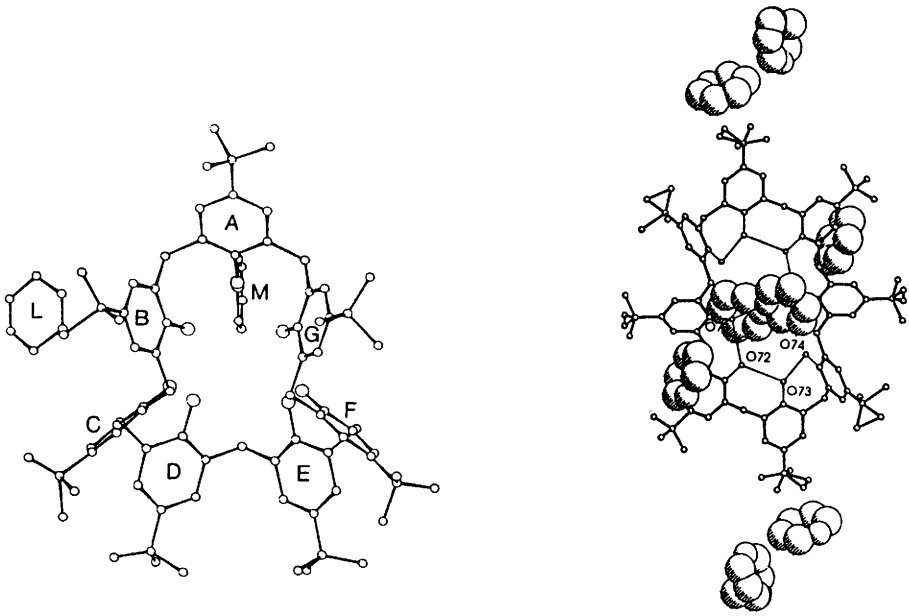


Figure 4.13 *X-Ray crystallographic structures of* (a) p-tert-*butylcalix*[7]*arene* (*with two pyridine molecules, L and M, of crystallization*) (*Taken from Andreetti* et al.[231] *and* (b) p-tert-*butylcalix*[8]*arene* (*with 8 pyridine molecules of crystallization* (*Taken from Czugler* et al.[236])

4.4 Conformations of Flexible Calixarenes in Solution

4.4.1 Conformational Mobility of Calix[*n*]arenes

All of the *p*-alkylphenol-derived calixarenes, regardless of ring size, are conformationally flexible in solution at room temperature on the ^{1}H NMR time scale. The rate at which they undergo conformational interconversion is most easily studied by ^{1}H NMR spectroscopy, and the essential details of the application of this technique are discussed in the previous volume (see ref. 1, pp. 87–101). The data contained therein, showing the dependence of conformational mobility on ring size and solvent, have been supplemented by the more recent data shown in Figure 4.14 which reveal a periodicity in conformational mobility. Calix[4*n*] arenes (n = 1–4) are more stable than their immediate neighbors, probably the result of stronger intramolecular hydrogen bonding in these members of the family. The two types of conformations most conducive to strong intramolecular hydrogen bonding are the cone (when n = 1) and pleated loop (when n = 2). It is postulated that the other calixarenes seek conformations which possess as much cone and/or pleated loop character as their geometry permits, an idea that finds support in the computer-generated structures.[24] The calix[6]arene system, however, does not readily assume either of these, and its conformation both in the

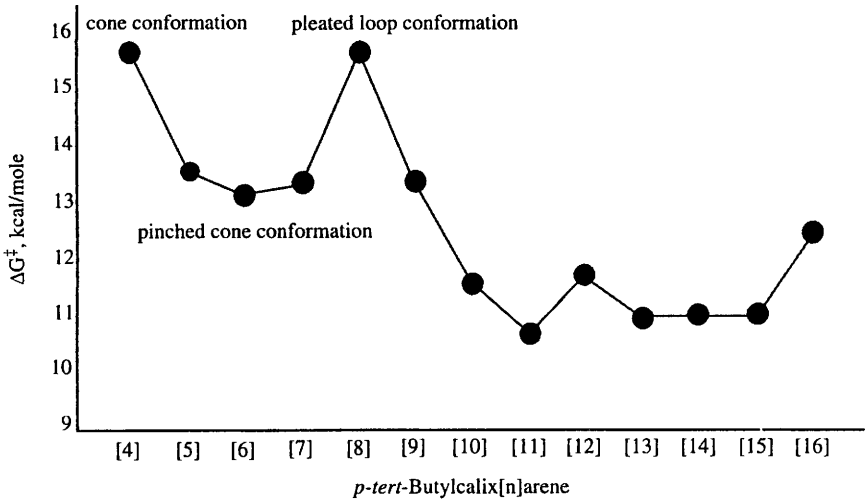


Figure 4.14 *Plot of* $\Delta G^{\ddagger}$ *values for* p-tert-*butylcalix*[4–16]*arenes in* $CDCl_3$[24]

solid state and in solution has been the subject of considerable study and some controversy. A detailed ^1H NMR and molecular mechanics study of a calix[6]arene carrying upper rim *tert*-butyl groups and Cl atoms on alternate rings led to the conclusion that the conformation is best described as a winged cone that is made asymmetric by the clockwise or anticlockwise sense of the cyclic array of hydrogen bonds.[144] A later study, however, came to the conclusion that the solution state conformation is a pinched cone, the same as in the solid state, and that it is more stable than the winged conformation by 16.2 kcal mol^{-1}.[241] The significant difference between these two conformations is that the winged conformation has all six methylene groups pointing outward from the cavity, whereas the pinched conformation has two of them pointing inward. The latter provides a better geometry for optimal intramolecular hydrogen bond formation. The calculated dynamical properties also are in better agreement with the pinched cone than the winged cone conformation.

Computer-assisted simulations[242] of the ^1H NMR spectra of $\mathbf{4}^{t\text{-Bu}}$ and $\mathbf{8}^{t\text{-Bu}}$ in $CDCl_3$ reveal that the inversion process is dominated by the $\Delta H^{\ddagger}$ term (15.9 and 17.4 kcal mol^{-1}, respectively), while the $\Delta S^{\ddagger}$ term ($-$ 1.7 and 2.0 cal $mol^{-1}K^{-1}$, respectively) is small. This accords with the premise that hydrogen bonding is largely responsible for maintaining the conformation, and it is corroborated by the isokinetic temperature (202 °C) and by the lower value (14.3 kcal mol^{-1}) of $\Delta H^{\ddagger}$ for $\mathbf{4}^{t\text{-Bu}}$ in C_5D_5N as compared with $CDCl_3$.

Since the calixarenes form complexes with a variety of guests (see Chapter 5) it is not surprising that their conformational mobility is influenced by cations.

[241] van Hoorn, W. P.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, 61, 7180.
[242] Araki, K.; Shinkai, S.; Matsuda, T. *Chem. Lett.* **1989**, 581.

Table 4.2 *Conformational mobility of calixarenes with one or more hydroxyls replaced by other groups*

Ring size	*Lower rim groups*	*Solvent*	$\Delta G^{\ddagger}$, kcal mol^{-1}	T_c, °C	*Ref.*
4	3 OH, 1 H	$CD_2Cl_2/CDCl_3$	9.6	− 60	246
4	2 OH (1,3), 2 H (2,4)	$CDCl_2F$	9.6	− 71	246
4	2 OH (1,2), 2 H (3,4)	$CDCl_2F$	10.6	− 34 to − 52	247a
4	1 OH, 3 H	CD_2Cl_2	9.7	− 63	134
4	4 H	$CD_2Cl_2/CDCl_3$	< 9.5	< − 85	139, 201b
4	3 OH, 1 NH_2	$CDCl_3$	14.8	39	247a
4	3 OH, 1 NH_3^+	$CD_3C_6D_5$	16.4	82	417
4	2 OH (1,3), 2 NH_2 (2,4)	$CDCl_3$	13.9		417
4	2 OH (1,3), 1 H, 1 NH_2	$CD_2Cl_2/CDCl_3$	11.6	37	248
4	3 SH, 1 H	$C_2D_2Cl_4$	19.2	135	203c
4	2 OH (1,3), 2 SH (2,4)	$C_2D_2Cl_4$	17.6	105	203b
8	8H	$CD_2Cl_2/CDCl_3$	< 9.0	< − 85	201b

Typical examples are the *p*-sulfonatocalixarenes, which become somewhat less mobile in the presence of metal ions such as Na^+ and considerably less mobile in the presence of ammonium ions such as phenyltrimethylammonim.[243]

The ^{1}H NMR spectra of the oxyanions generated by the action of BuLi on *p*-allylcalix[4]arene in DMSO suggest that the conformations of the mono- and tetra-anions are cone, while those of the di- and tri-anions are less clear[244] (see ref. 1, pp. 124–126). However, X-ray crystal structures of the monosodium and dilithium salts of **4**$^{t\text{-Bu}}$, generated by the action of NaH or BuLi on the calixarene followed by treatment with MeOH, show both to be in the cone conformation in the solid state.[245]

Replacing the lower rim hydroxyls with other groups such as H, NH_2, or SH changes the conformational mobility, as illustrated by the data in Table 4.2.

The conformations adopted by flexible calixarenes in solution depend primarily on the ring size and the substituents on the lower rim. As discussed in Section 4.2, the cone conformers are the lowest energy structures for the parent calix[4]arenes and calix[5]arenes, and the double cone pinched conformers are the lowest energy structures for the parent calix[6]arenes and calix[7]arenes. Whether the parent calix[8]arenes exist in solution as pleated loops, pinched

[243] Shinkai, S.; Araki, K.; Matsuda, T.; Manabe, O. *Bull. Chem. Soc. Jpn.* **1989**, 62, 3856; Shinkai, S.; Araki, K.; Kubota, M.; Arimura, T.; Matsuda, T. *J. Org. Chem.* **1991**, 56, 295.

[244] Gutsche, C. D.; Iqbal, M.; Nam, K. S.; See, K.; Alam, I. *Pure Appl. Chem.* **1988**, 60, 483; Nam, K. C.; Kim, D. S.; Kim, J. M. *Bull. Korean Chem. Soc.* **1997**, 18, 636. Tetralithiation of **4**$^{t\text{-Bu}}$ in HMPA gives a monomeric complex in which LiOH is incorporated into a Li_5O_5 core based on an isolated square pyramid of Li atoms or a dimeric LiOH-free Li_8O_8 species: Davidson, M.G.; Howard, J. A. K.; Lamb, S.; Lehmann, C. W. *J. Chem. Soc., Chem. Commun.* **1997**, 1607.

[245] Hamada, F.; Robinson, K. D.; Orr, G. W.; Atwood, J. L. *Supramol. Chem.* **1993**, 2, 19.

[246] Grynszpan, F.; Biali, S. E. *Tetrahedron Lett.* **1991**, 32, 5155.

[247] (a) Aleksiuk, O.; Grynszpan, F.; Biali, S. E. *J. Chem. Soc., Chem.Commun.* **1993**, 11; (b) Litwak, A. M.; Biali, S. E. *J. Org. Chem.* **1992**, 57, 1943.

[248] Grynszpan, F.; Aleksiuk, O.; Biali, S. E. *J. Org. Chem.* **1994**, 59, 2070.

double cones, or some other type of conformer remains uncertain. Experimental data (see ref. 1, pp. 90–97) as well as computational studies,[95,130] indicate that in most cases a *p*-substituent plays a relatively minor role in determining the conformation and the conformational mobility of the parent calixarenes, although there are indications that a *tert*-butyl group may destabilize 1,2- and 1,3-alternate conformations.[130,249] For example, removal of two of the *p-tert*-butyl groups from the A,C-bis(3,5-dinitrobenzoyl) ester of **4**$^{t\text{-Bu}}$ changes the conformation from pinched cone to 1,3-alternate.[250] *m*-Substituents, however, can have a more pronounced effect, the eight Me groups in **29**, for example, forcing the compound into a pinched cone (flattened cone; boat[42b]) conformation and lowering the conformational inversion barrier to 10.9 kcal mol^{-1} as a result of the increased energy of the ground state structure. A surprisingly large substituent effect is noted in the calix[5]arene **31** carrying *p*-benzoyl and *m*-hydroxyl groups, the $\Delta G^{\ddagger}$ for inversion being 17.3 kcal mol^{-1}.[44] Solvent also plays a relatively minor role in the conformational characteristics of the parent calix[4]arenes but may play a more dominant role in the larger calixarenes. This is dramatically illustrated by the effect that the change of solvent from $CDCl_3$ to pyridine-d_5 has on the temperature dependent ^{1}H NMR spectrum of **8**$^{t\text{-Bu}}$ (see ref. 1, pp. 94–96), where the energy barrier to conformational inversion is lowered from 15.7 kcal mol^{-1} to less than 9 kcal mol^{-1}. An interesting contrast, however, is the octamethylcalix[4]arene **29** where the conformational barrier is *increased*[42b] from 10.9 kcal mol^{-1} in $CD_2Cl_2/CDCl_3$ to 11.8 kcal mol^{-1} in pyridine-d_5.

4.4.2 Conformational Mobility of Calixarene Methyl Ethers, Ethyl Ethers, Deoxycalixarenes, Calixquinones, and Calixarenethiols

Whereas all of the parent calixarenes are conformationally flexible in solution at room temperature, space filling molecular models of calix[4]arenes indicate that any group larger than OH should curtail this mobility. Surprisingly, however, OMe groups are not sufficiently large to do this, the tetramethyl ether of **4**$^{t\text{-Bu}}$ having a conformational inversion barrier almost identical with that of the parent compound.[251] Even OEt groups are not quite large enough, equilibration among the conformers of the tetraethyl ether of **4**$^{t\text{-Bu}}$ being observable at elevated temperatures.[138,189] These substituent effects vanish in the larger calixarenes where the pentamethyl and pentaethyl ethers of **5**$^{t\text{-Bu}}$, for example, have $\Delta G^{\ddagger}$ values that are lower than 9.3 kcal mol^{-1} and 11.1 kcal mol^{-1}, respectively.[112] With intramolecular hydrogen bonding playing no part in the tetramethyl ether of **4**$^{t\text{-Bu}}$, all four conformers are present in equilibrium in $CDCl_3$ solution in the amounts of 85.6% partial cone, 5.5% cone, 6.1% 1,2-alternate, and 2.8% 1,3-

[249] However, the amount of 1,2- and 1,3-alternate conformers in the equilibrium mixture of the tetramethyl ethers of **4** is greater for **4**$^{t\text{-Bu}}$ than **4**^{H}.[129]

[250] See, K. A.; Fronczek, F. R.; Watson, W. H.; Kashyap, R. P.; Gutsche, C. D. *J. Org. Chem.* **1991**, 56, 7256.

[251] Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, 39, 409.

alternate.[129] However, the conformer distribution depends on the *p*-substituent as well as the solvent, and the relative stability for the conformers of the Me ether of $\mathbf{4}^{H}$ is partial cone > cone > 1,2-alternate > 1,3-alternate. In both cases the proportion of cone conformer increases with increasing solvent polarity as the result of the greater dipole moment of the cone conformer compared with the other conformers.[107,109,252] With the tetramethyl ether of $\mathbf{4}^{SO_3H}$, on the other hand, it is the 1,3-alternate conformer that predominates.[253] Molecular mechanics calculations employing an early version of the CHARMm program[138] and the more recent MM3 program[130] both correctly predict the partial cone to be the most stable conformer but predict less accurately for the other three conformers. A kinetic study of the conformational interconversion of the tetramethyl ethers finds that the partial cone $\rightleftharpoons$ cone, partial cone $\rightleftharpoons$ 1,2-alternate, and partial cone $\rightleftharpoons$ 1,3-alternate processes have almost identical enthalpies of activation (14 ± 0.7 kcal mol^{-1}) but entropies of activation of -3.82, -16.7, and -6.93 cal mol^{-1}K^{-1}, respectively, leading to the conclusion that the conformational interconversion is under entropic control.[254] A similar situation exists for the tetraethyl ethers of calix[4]arenes which, although conformationally stable at room temperature, form an equilibrium mixture at higher temperatures.[138,189] When heated for 2 h in $CHCl_2CHCl_2$ (bp 147 °C) an equilibrium mixture was obtained containing 45% 1,2-alternate, 49% partial cone, 6% cone, and less than 1% 1,3-alternate.[189a]

The effects of *p*-substituents and solvent have also been studied in the trimethyl ethers of monodeoxycalix[4]arenes carrying various combinations of Me and *t*-Bu groups in the *p*-positions.[255] The (u,u,d) conformer (only ArOR rings designated) was found in all cases to be the most stable, with increasing preponderance as the *p*-substituents changed from Me to *t*-Bu. It is postulated that in the (u,u,d) conformer one of the OMe groups is oriented inward in the cavity created by the other three aromatic rings.

Replacement of two or more of the OH groups with other groups such as H, Me, SH, and NH_2 similarly affects the order of conformational stability. For example, molecular mechanics calculations using the MM3 program predict the stability sequences for the tetradeoxy compound **95e** to be cone > partial cone > 1,3-alternate > 1,2-alternate and that of the tetramethyl compound **95k** to be 1,3-alternate ≫ partial cone > 1,2-alternate > 1,3-alternate.[130]

In contrast to the A,C-dimethyl ether of $\mathbf{4}^{t\text{-}Bu}$, the calix[4]arenediquinone dimethyl ether **96a** is conformationally mobile at room temperature. At -70 °C, however, it assumes a partial cone conformation in which one of the OMe groups points inward into the calix.[207] Similarly, the diethyl ether **96b** is formed in the partial cone conformation, but this has been shown to be a kinetic product which in the presence of Na^+ very slowly (many hours at room temperature) converts to the cone conformer.[256] The calix[4]arenetetraquinone and

[252] Shinkai, S.; Iwamoto, K.; Araki, K.; Matsuda, T. *Chem. Lett.* **1990**, 1263.
[253] Nagasaki, T.; Sisido, K.; Arimura, T.; Shinkai, S. *Tetrahedron* **1992**, 48, 797.
[254] Blixt, J.; Detellier, C. *J. Am. Chem. Soc.* **1994**, 116, 11957.
[255] Fukazawa, Y.; Yoshimura, K.; Sasaki, S.; Yamazaki, M.; Okajima, T. *Tetrahedron* **1996**, 52, 2301.
[256] Gómez-Kaifer, M.; Reddy, P. A.; Gutsche, C. D.; Echegoyen, L. *J. Am. Chem. Soc.* **1997**, 119, 5222.

calix[6]arenehexaquinone are even more conformationally flexible than the diquinone.[230]

Molecular mechanics calculations on the calix[4]arenetetrathiol **95k** using the CHARMm program indicates the stability sequence to be 1,3-alternate > partial cone > 1,2-alternate > cone.

4.4.3 Conformational Mobility of Calixarene-related Compounds

The dihomooxacalix[4]arene **67** favors the cone conformation but is more conformationally mobile than its calix[4]arene analog, showing a conformational barrier of *ca.* 13 kcal mol^{-1}.[257] The azacalix[4]arene **73**, on the other hand, shows a temperature dependent ^{1}H NMR spectrum which the authors interpret in terms of a major 1,2-alternate conformer accompanied by a small amount of cone conformer,[72c], although MM3 calculations show the latter to be 10 kcal mol^{-1} more stable.

4.4.4 Pathways for Cone–Cone Interconversion

The means by which the cone conformer (u,u,u,u) of a calix[4]arene is transformed to its inverted cone conformer (d,d,d,d) remains somewhat uncertain, although it clearly involves a 'lower rim through the annulus' pathway (see Section 4.5.1). One possibility is that the process is concerted (a 'continuous chain pathway') without intermediates and only one transition state. Another possibility is that the process is stepwise (a 'broken chain pathway') with intermediates and two or more transition states, *e.g.* cone → partial cone → 1,2- or 1,3-alternate → inverted partial cone → inverted cone. Although arguments based on the Arrhenius plot for the rate of inversion of calix[4]arene[242] and on the conformational behavior of the calix[4]arene methyl ethers[109] have been proposed in support of the first alternative, computational studies of **4**$^{t\text{-Bu}}$,[135] its conformationally flexible tetramethyl ether,[95] and the *endo*-OH calix[4]arene **18** ($R^1 = R^2 = t$-Bu)[133] provide quite compelling evidence in favor of the second alternative. Experimental evidence from the NMR study of the tetramethyl ether also supports a stepwise process, although the lack of intramolelcular hydrogen bonding makes the pathway in this case not directly comparable.

4.5 Conformationally Immobile Calixarenes

4.5.1 Minimum Structural Requirements for Conformational Immobility of Unbridged Calixarene Ethers and Esters

4.5.1.1 *Fully Etherified and Esterified Calixarenes*

Two pathways are available to a calixarene for conformational inversion. One involves the 'upper rim through the annulus' and the other involves the 'lower

[257] Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, 107, 6052.

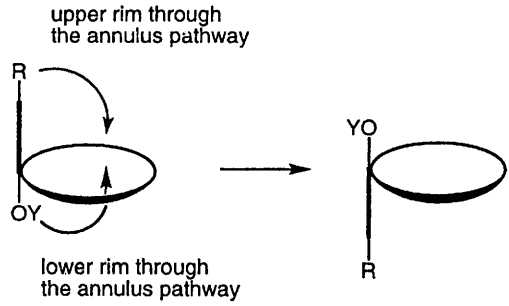


Figure 4.15 *Pathways for conformational inversion of calix*[n]*arenes*

rim through the annulus', as illustrated in Figure 4.15. If conformational inversion is to be curtailed it is necessary that *both* pathways be precluded, either by the incorporation of sufficiently large groups on the rims or a bridge across one or both rims. In the case of the calix[4]arenes the 'upper rim through the annulus' pathway is so hindered that even the *p*-H compound can engage only in 'lower rim through the annulus' conformational inversion. This is not true for larger calixarenes, however, where groups even as bulky as *tert*-butyl may not suffice to curtail the 'upper rim through the annulus' pathway.

Realizing that only the 'lower rim through the annulus' pathway is available for the interconversion of calix[4]arene conformers, attention has focused on the minimum size of OR group that is necessary to curtail this pathway. The tetramethyl ethers of calix[4]arenes are surprisingly flexible (see Section 4.4.2), and even the tetraethyl ether[189] as well as the tetrakis(cyanomethyl) ether[258] can undergo conformational interconversion. The tetra-*n*-propyl ether, however, is conformationally fixed even at elevated temperatures, as are all other tetraethers containing groups larger than *n*-propyl. Tetraacetates and higher esters of calix[4]arenes are similarly conformationally inflexible.

In the calix[5]arenes it is not yet known whether the *p*-H compound can engage in 'upper rim through the annulus' conformational inversion, but it seems quite certain that the *p-tert*-butyl compound cannot do so at temperatures ordinarily encountered in laboratory procedures. As anticipated, larger OR groups are necessary to curtail conformational interconversion of calix[5]arenes than for the calix[4]arenes; it has been determined that the threshold size requires a group slightly more bulky than *n*-butyl ($\Delta G^{\ddagger}$ of penta-*n*-butyl ether of $\mathbf{5}^{t\text{-Bu}} = 15.5\,\text{kcal mol}^{-1}$) for ethers and *n*-butanoyl ($\Delta G^{\ddagger}$ for penta-*n*-butanoate of $\mathbf{5}^{t\text{-Bu}} = 17.5\,\text{kcal mol}^{-1}$) for esters.[112] For example, the pentaisobutanoate of $\mathbf{5}^{t\text{-Bu}}$ ($\Delta G^{\ddagger} > 20\,\text{kcal mol}^{-1}$)[112] and the pentakis(ethoxycarbonyl)methyl ether of $\mathbf{5}^{t\text{-Bu}}$ [259] are conformationally inflexible at ordinary laboratory temperatures.

tert-Butyl groups on the upper rim are not quite sufficient to completely curtail conformational transformation *via* the 'upper rim through the annulus' pathway in the calix[6]arenes. This has been demonstrated by placing very large

[258] Guelzim, A.; Khrifi, S.; Baert, F.; Loeber, C.; Asfari, Z.; Matt, D.; Vicens, J. *Acta Crystallogr.* **1993**, *C*49, 72.

[259] Souley, B.; Asfari, Z.; Vicens, J. *Pol. J. Chem.* **1993**, 67, 763.

groups (*e.g.* cholesteryl[260] and *p*-phenylbenzyl[261]) on the lower rim and finding that slow conformational interconversion still occurs. The barrier to conformational interconversion via this 'upper rim through the annulus' pathway[261] is 21 kcal mol^{-1} at 55 °C, appreciably higher than the 15.7 kcal mol^{-1} value for $\mathbf{4}^{t\text{-Bu}}$ or its tetramethyl ether. Thus, *p-tert*-butylcalix[6]arenes carrying large OR substituents can be classed as marginally conformationally flexible. Presumably, substituents larger than *tert*-butyl (*e.g.* 1,1,3,3-tetramethylbutyl or adamantyl) would eliminate the 'upper rim through the annulus' pathway, but this has yet to be experimentally demonstrated. Accepting the fact that the 'upper rim through the annulus' pathway is available to *p-tert*-butylcalix[6]arenes, the threshold sizes of groups necessary to curtail the 'lower rim through the annulus' pathway can nevertheless be established. For example, the hexabenzyl ether of *p-tert*-butylcalix[6]arene has been shown to be conformationally flexible *via* this pathway, whereas the hexa *p*-cyanobenzyl ether is not.[113] Inspection of space filling molecular models shows that it is indeed possible to force a benzyloxy moiety through the annulus but not a *p*-cyanobenzyloxy moiety. A detailed study of the conformational flexibility of hexa-*O*-alkylated calix[6]arenes[261] shows the system to be a slowly interconverting (*vide supra*) mixture of pinched cone and 1,2,3-alternate conformers (energy difference 0.5–1.56 kcal mol^{-1}). The special stabilizing effect of methoxyl groups in the 1,3,5-positions has been attributed to their orientation inward to occupy space inside the annulus.

The conformational characteristics of calix[7]arenes have not yet been explored, but it is known that calix[8]arenes carrying *p-tert*-butyl groups and $OSiMe_3$ groups are conformationally flexible with a $\Delta G^{\ddagger} = 13.2$ kcal mol^{-1} inversion barrier (see ref. 1, pp. 112–113). It is possible that very large groups on the upper and lower rims can curtail conformational flexibility in this system, but this remains to be studied.

4.5.1.2 *Partially Etherified and Esterified Calixarenes*

It is a curious fact that partially etherified and esterified calixarenes are often less conformationally flexible than their fully etherified or esterified counterparts. The simplest examples occur with the methyl ethers of calix[4]arenes where the monomethyl ether, 1,2-dimethyl ether, 1,3-dimethyl ether, and trimethyl ether all are conformationally less flexible than the parent compound or the tetramethyl ether, as illustrated by data in Table 4.3. This is the result of the synergistic interplay of intramolecular hydrogen bonding and steric factors. In the parent compound, hydrogen bonding is at a maximum, holding the compound firmly in a cone conformation. In the tetramethyl ether, hydrogen bonding is nonexistent, and only the steric interference arising from the OMe groups determines the conformational mobility. In the partially methylated

[260] (a) Otsuka, H.; Araki, K.; Shinkai, S. *Chem. Express* **1993**, 8, 479; (b) Otsuka, H.; Araki, K.; Sakaki, T.; Nakashima, K.; Shinkai, S. *Tetrahedron Lett.* **1993**, 34, 7275.

[261] van Duynhoven, J. P. M.; Janssen, R. G.; Verboom, W.; Franken, S. M.; Casnati, A.; Pochini, A.; Ungaro, R.; de Mendoza, J.; Nieto, P. M.; Prados, P.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1994**, 116, 5814.

Table 4.3 *Comparison of conformational barriers, IR stretching frequencies, and conformations of parent calixarenes and their fully and partially etherified derivatives*

[*n*]	R in OR	$\Delta G^{\ddagger}$/kcal mol^{-1}	ν_{OH} (solid)[a]	*Major conformer*
4	4 H	15.7[1(p92),b]	3150[1(p92)]	u,u,u,u
	3 H, 1 Me	$\gg$ 16[c]	3270, 3142[109,173]	u,u,u,u
	2 H (1,2), 2 Me (3,4)	> 16[b]	3438, 3367[109]	
	2 H (1,3), 2 Me (2,4)	$\gg$ 16[b]	3456[109]	uo,u,uo,u
	1 H, 3 Me	*ca.* 18[b]	3452[109]	uo,u,uo,u
	4 Me	*ca.* 15.7		u,u,u,d
5	5 H	13.2[1(p98)]		u,u,u,u,u
	4 H, 1 *n*-Pr	19.9[112]		u,u,u,u,ui
	5 *n*-Pr	12.6[112]		u,u,d,d,d or u,u,u,u,d
6	6 H	13.3[1(p98)]		
	5 H, 1 Bz	> 18[113]		u,u,u,u,u,u
	6 Bz	12.9[113]		
	4 H, 2 Bz-*t*-Bu	*ca.* 26[145]		u,**u**,u,d,d,d/ d,**d**,u,u,u,u

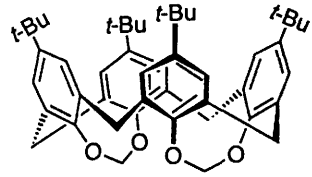
[a]See ref. 109 for a detailed discussion of the ν_{OH} values in the solid state as well as in CCl_4 and CS_2 solution.
[b]A higher value of 16.4 kcal mol^{-1} has been reported,[242] but a more recent[541] line shape analysis of the temperature dependent ^{1}H NMR spectrum of **4**$^{t\text{-Bu}}$ confirms the earlier value obtained from the coalescence temperature approximation.
[c]Extrapolated from data in ref. 163.

compounds, both hydrogen bonding and steric interference reduce the conformational mobility, the two effects combining to reach a probable maximum at the mono substitution stage. Since a group as small as methyl exerts this 'mono substituent effect', it is to be expected that all other substituents will act in like fashion in calix[4]arene systems. The same phenomenon is also observed with the calix[5]arenes and calix[6]arenes, the only difference being that larger OR groups are necessary to achieve similar results in these cases. While a methyl group is insufficient in the calix[5]arene, a single propyl group proves effective in curtailing complete inversion of the system[112] and adds 6.7 kcal mol^{-1} to $\Delta G^{\ddagger}$. Even a benzyl group is not quite large enough in the calix[6]arenes, but a slight extension in its length, *e.g.* *p*-cyanobenzyl, becomes sufficient.[113] A careful ^{1}H NMR study of the dynamical properties of a series of phosphorylated and thiophosphorylated *p-tert*-butylcalix[6]arenes[262] shows that at least three processes are at play. Ranked in order of increasing effect on the activation barrier they are: hydrogen bond array reversal, pinched conformer interconversion, and macrocyclic ring interconversion. The greatest increase in the barrier for macrocyclic ring interconversion occurs upon monosubstitution with a bulky substituent (*i.e.* mono ether effect) and generally decreases with increasing extent of substitution.

[262] Janssen, R. G.; van Duynhoven, J. P. M.; Verboom, W.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1996**, 118, 3666.

4.5.2 Conformational Immobilization *via* Bridging

A wide variety of lower rim-bridged calix[4]arenes are known, the syntheses for which are discussed in Chapter 5. The result of bridging across the lower rim of a calix[4]arene in most cases is to prevent complete conformational interconversion. An exception to this generality is noted in the doubly-bridged calix[4]arene **99** which exists as an equilibrium mixture of cone and 1,2-alternate conformers (differing by 0.43 kcal mol^{-1}) and which shows a barrier of 18.2 kcal mol^{-1} for conformational interconversion.[141] An early example of an upper rim-bridged calix[4]arene (**46a**) is discussed in the previous volume (see ref. 1, pp. 42–43), and several others have been added more recently, including **47**, **52**, **53**, and **62**. The bridges in these are sufficient to prevent cone–cone interconversion regardless of the substituents on the lower rim, but they do not necessarily prevent rotation of one or more of the aryl groups between 'up' and 'down' orientations. Although the polymethylene-bridged calix[4]arenes **46a** exist only as conformationally inflexible cones,[56] the tetramethyl ethers of the upper rim-bridged calix[4]arenes **46c** exist in solution as mixtures of partial cone and cone conformers, the ratio varying from 4.0 ($n = 0$) to 1.7 ($n = 4$) as the bridge lengthens.[263] By means of 2-D chemical exchange (2-D EXSY) NMR experiments it was established that the interconversion between these two conformers occurs primarily *via* a higher energy 1,3-alternate conformer, with the three conformers kinetically related as shown in Figure 4.16. The faster rates for **46c** ($n = 1$) compared with **46c** ($n = 0$) are ascribed to the squeezing of the cavity by the shorter bridge in the latter.



99

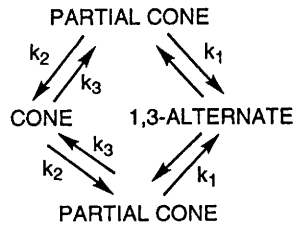
p-tert-Butylcalix[5]arenes bridged between the A,C-hydroxyl groups with polyoxyethylene chains[264] or a phthaloyl moiety[265] have been reported. Replacement of the hydrogens of the three remaining OH groups of the polyoxyethylene-bridged compound with Me or CH_2CO_2Et groups yields cone conformers. Since it is not certain whether ArOMe moieties are capable of conformational inversion in the bridged calix[5]arenes, the trimethyl ether might be the product of either thermodynamic or kinetic control. The tris(ethoxycarbonylmethyl) ether, however, is clearly the product of kinetic control.

p-tert-Butylcalix[6]arenes with lower rim bridges connecting the A,B rings,[265]

[263] van Loon, J.-D.; Groenen, L. C.; Wijmenga, S. S.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, 113, 2378.

[264] Kraft, D.; Arnecke, R.; Böhmer, V.; Vogt, W. *Tetrahedron* **1993**, 49, 6019.

[265] (a) Kraft, D.; Böhmer, V.; Vogt, W.; Ferguson, G; Gallagher, J. F. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1221; (b) Arnecke, R.; Böhmer, V.; Ferguson, G.; Pappalardo, S. *Tetrahedron Lett.* **1996**, 37, 1497.



	46c (n = 2)	**46c** (n = 3)
	temp = 25 °C	temp = -20 °C
k_1	0.58 sec^{-1}	5.4 sec^{-1}
k_2	0.054 sec^{-1}	0.07 sec^{-1}
k_3	0.27 sec^{-1}	0.18 sec^{-1}

Figure 4.16 *Interconversion of cone, partial cone, and* 1,3*-alternate conformers in* **46c** (n = 2 *and* 3)

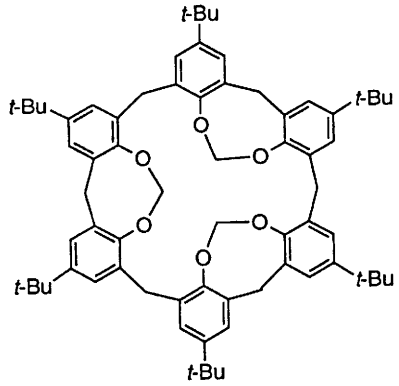
the A,C rings,[266] the A,D rings,[124,266] the A,C,E rings,[182b,228,267,268] and the A,B/C,D/E,F rings[141] have been prepared, as discussed in Chapter 5. Although temperature dependent NMR studies have not been carried out on all of these compounds, it appears likely that most of them cannot undergo complete conformational inversion. One of the few exceptions is the triply-bridged **100**, which exists only in a cone and a partial cone conformation and is completely flexible above − 23 °C.[141] Interconversion of one or more aryl units between 'up' and 'down' orientations, of course, is possible. One of the most surprising of these is the conversion, upon methylation, of the A,D-benzylene-bridged *p-tert*-butylcalix[6]arene **101a** in the flatttened cone conformation to a 1,2,3-alternate conformer in which the benzylene moiety is threaded through the annulus to give the 'self-anchored rotaxane' **102a**.[124] Similarly, **101b**, characterized by X-ray crystallography, can convert to **102b**, characterized by its ^{1}H NMR spectral characteristics.[269] A calix[6]arene bridged on the upper rim by attachment of a 1,3,5-tris(thiomethyl)phenyl group at the A,C,E rings has been reported.[270] It exists as a conformationally non-inverting cone conformer which engages in conformational 'wobble' between a pinched cone and a regular cone.

4.6 Factors Governing Conformational Outcome of Derivatization

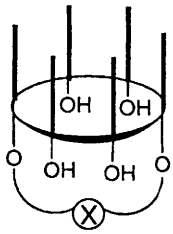
4.6.1 *O*-Tetrasubstitution of Calix[4]arenes

Replacement of all four of the hydrogens of the OH groups of a calix[4]arene with alkyl, acyl, or aroyl groups generally results in conformational immobilization, with the result that non-interconverting cone, partial cone, 1,2-alternate, and 1,3-alternate conformers can be formed. Although approximate guidelines

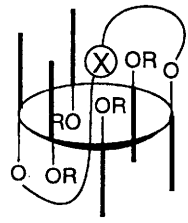
[266] Ross, H.; Lüning, U. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 2555.
[267] Araki, K.; Akao, K.; Otsuka, H.; Nakashima, K.; Inokuchi, F.; Shinkai, S. *Chem. Lett.* **1994**, 1251; Otsuka, H.; Araki, K.; Matsumoto, H.; Harada, T.; Shinkai, S. *J. Org. Chem.* **1995**, 60, 4862.
[268] Janssen, R. G.; Verboom, W.; van Duynhoven, J. P. M.; van Velzen, E. J. J.; Reinhoudt, D. N. *Tetrahedron Lett.* **1994**, 35, 6555.
[269] Saiki, T.; Goto, K.; Okazaki, R. *Chem. Lett.* **1996**, 993.
[270] Takeshita, M.; Nishio, S.; Shinkai, S. *J. Org. Chem.* **1994**, 59, 4032.



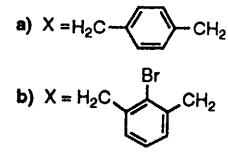
100



101



102



for predicting the conformational outcome under certain conditions have emerged, many puzzling results remain to be explained. The ratio of conformers in the products depends, *inter alia*, on the reaction conditions (temperature, solvent, base), the *p*-substituent of the calix[4]arene, and the steric demands and reactivity of the derivatizing reagent. The base in particular can play a pivotal role in the alkylation process. For example, treatment of $\mathbf{4}^{t\text{-Bu}}$ with *n*-PrBr and NaH yields a mixture containing 42% cone, 55% partial cone, and 3% 1,3-alternate conformers.[189a] With Cs_2CO_3 as the base, however, the product mixture contains no cone, 34% partial cone, 9% 1,2-alternate, and 57% 1,3-alternate conformer.[189a] Starting with the tripropyl ether of $\mathbf{4}^{t\text{-Bu}}$ (u,u,u,d conformation), the tetrapropyl ether of $\mathbf{4}^{t\text{-Bu}}$ was obtained in the 1,2-alternate and partial cone conformations.[198] Similarly, treatment of $\mathbf{4}^{1,1,3,3\text{-tetramethylbutyl}}$ with an excess of $CH_3OCH_2CH_2OTs$ and NaH produces the cone conformer of the tetraether in 81% yield, while with *t*-BuOK as the base the partial cone conformer is formed in 64% yield.[271] Treatment of $\mathbf{4}^{CH_2CN}$ with *p*-bromobenzenesulfonyl chloride, on the other hand, yields the cone conformer with NaH but the 1,3-alternate conformer with 1-methylimidazole.[272]

Alkylating agents of the structure $RCOCH_2X$ generally provide high yields of cone conformer with NaH as base, *e.g.* $\mathbf{4}^{t\text{-Bu}}$ reacts with Et_2NCOCH_2Cl to give a

[271] Araki, K.; Yanagi, A.; Shinkai, S. *Tetrahedron* **1993**, 49, 6763.
[272] Sharma, S. K.; Gutsche, C. D. unpublished results.

95% yield of the cone conformer of the tetraalkylated product.[273] Similarly, **4**$^{t\text{-Bu}}$ undergoes tetra-*O*-substitution with $BrCH_2CO_2Et$ to give the cone conformer with Na_2CO_3 and the partial cone conformer with Cs_2CO_3.[274] However, **4**^{H} gives a significant amount of 1,3-alternate (56%) in addition to partial cone (38%) with Cs_2CO_3.[275] Alkylation with 2-pyridylmethyl chloride and NaH gives cone conformers exclusively, but with K_2CO_3 or Cs_2CO_3 a mixture is produced that contains only a small amount of cone conformer (9%) along with larger amounts of partial cone and 1,3-alternate conformers (54% and 18%, respectively, with **4**$^{t\text{-Bu}}$; 36% and 55%, respectively, with **4**^{H}).[142] The greater tendency for **4**^{H} to form the 1,3-alternate conformer has also been observed with *n*-PrBr as the alkylating agent and Cs_2CO_3 as the base.[189a] Also with Cs_2CO_3 as the base (7.5 equiv/OH group) both **4**^{H} and **4**$^{t\text{-Bu}}$ react with $MeOCH_2CH_2OTs$ to give the 1,3-alternate conformers as the major product (76%) or the exclusive product (100%), respectively.[276] The leaving group of the alkylating agent sometimes exerts an effect on the conformational outcome. For example, one study found a product ratio of 1,3-alternate to partial cone conformer of 80:20 with *n*-propyl tosylate and 60:40 with *n*-propyl bromide starting with the A,C-dipropyl ether of **4**^{H}.[276] Another study found a cone to partial cone ratio of 42:55 with *n*-propyl bromide and 81:15 with *n*-propyl iodide with only a small amount (3–4%) of 1,3-alternate conformer in either case.[189]

Acylation of **4**$^{t\text{-Bu}}$ gives (a) with acetyl chloride/NaH an 89% yield of the cone conformer;[277,278] (b) with acetic anhydride/H_2SO_4 a 42% yield of the partial cone conformer along with 19% 1,3-alternate and 6% 1,2-alternate conformer;[279] (c) with acetic anhydride/*p*-toluenesulfonic acid a mixture containing 1,3-alternate (36%), 1,2-alternate (15%), and partial cone (3%) conformers.[111] Acylation of **4**^{H},[277] on the other hand, gives (a) with acetyl chloride/NaH a 2:1 mixture of partial cone and cone conformers; (b) with acetic anhydride/H_2SO_4 a 6:5 mixture of 1,3-alternate and partial cone conformers; (c) with isobutyryl chloride/NaH a 74% yield of cone conformer; (d) with isobutyryl anhydride a 55:13 mixture of partial cone and 1,3-alternate conformers, leading to the conclusion[277] that the *p-tert*-butyl group favors the cone conformation in the acylation reaction. While acetylation of **4**$^{t\text{-Bu}}$ (*vide supra*) and *n*-butyrylation of **4**^{H} both yield mixtures containing relatively small amounts of the 1,2-alternate conformer,[277] it is the major conformer (43% yield) from **4**$^{t\text{-Bu}}$ and *N,N*-dimethylthiocarbamoyl chloride/NaH.[203] *p*-Allylcalix[4]arene generally yields the 1,3-alternate conformer upon acylation, in contrast to **4**$^{t\text{-Bu}}$ which is more prone to produce the cone conformer (see ref. 1, p. 129). Acetylation of the calix[4]arenecrown-5 **130a** (R = *t*-Bu; $n = 3$) with AcCl gives the cone con-

[273] Arduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R.; Andreetti, G. D.; Calestani, G.; Ugozzoli, F. *J. Inclusion Phenom.* **1988**, 6, 119.

[274] Iwamoto, K.; Fujimoto, K.; Matsuda, T.; Shinkai, S. *Tetrahedron Lett.* **1990**, 31, 7169.

[275] Iwamoto, K.; Shinkai, S. *J. Org. Chem.* **1992**, 57, 7066.

[276] Verboom, W.; Datta, S.; Asfari, Z.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1992**, 57, 5394.

[277] No, K.; Koo, H. J. *Bull. Korean Chem. Soc.* **1994**, 15, 483.

[278] It is also reported[279] that under presumably the same conditions the product is 35% tetraacetate in the cone conformation accompanied by 13% of the triacetate and 4% of the monoacetate.

[279] Akabori, S.; Sannohe, H.; Habata, Y.; Mukoyama, Y; Ishii, T. *J. Chem. Soc., Chem. Commun.* **1996**, 1467.

former with NaH as the base but the partial cone conformer with EtOTl as the base.[280] A study of the effect of *p*-substituents in the aroylating agents on the conformational outcome[281] from **4**^{H} and **4**$^{t\text{-Bu}}$ shows that electron releasing groups (*i.e.* OMe) increase the amount of 1,3-alternate conformer, while electron withdrawing groups (*i.e.* NO_2) increase the amount of cone conformer, as discussed in the previous volume (see ref. 1, pp. 128–130). With **4**^{CH_2CN}, the 1,3 alternate conformer is the major product of aroylation in almost all cases, the one exception being with 3,5-dinitrobenzoyl chloride which also produces a mixture of 1,3-alternate and partial cone conformers.[282] Surprisingly, however, reaction with *p*-bromobenzenesulfonyl chloride yields the cone conformer.[283]

Like the tetraethyl ethers of calix[4]arenes, the tetraacetates are conformationally stable in solution at room temperature but slowly equilibrate in DMSO-d_6 at 150 °C. The conversion of cone to partial cone conformation occurs rapidly (30 min) at this temperature. The overall equilibrium mixture requires a much longer time (384 h) to be established and consists of partial cone (18%), 1,2-alternate (43%), and 1,3-alternate (33%) conformations.[279] The authors postulate that the decreasing order of conformer stability is 1,3-alternate > 1,2-alternate > partial cone > cone, which is quite different from that of the tetraalkyl ethers (see Section 4.2) and is attributed to the greater bulk of an acetyl group compared with an ethyl group.

4.6.2 Mono-, Di-, and Tri-*O*-substitution of Calix[4]arenes

Replacement of one, two, or three of the hydrogens of the OH groups of calix[4]arenes with alkyl, acyl, or aroyl groups (see Chapter 5 for a discussion of method of synthesis) gives products that are generally most stable in the cone conformation but in which the ArOH moieties have the potential for assuming either the 'up' or 'down' orientation. For example, the possible conformations for the monobenzyl ether of **4**$^{t\text{-Bu}}$ include a cone, three partial cones, a 1,2-alternate, and a 1,3-alternate. In solution, however, the cone conformer is much the most stable, so conformational inversion is not detectable on the ^{1}H NMR time scale. Further alkylation, acylation, or aroylation of a partially *O*-substituted calix[4]arene ultimately yields a tetra-*O*-substituted product in which the conformational outcome reflects the flexibility of the ArOH moieties of the intermediates. These pathways have been studied with several alkylating agents, including *n*-propyl bromide,[189] pyridylmethyl chloride,[142] and benzyl halides.[284,285] Figure 4.17 depicts all of the possible pathways for forming tetra-*O*-alkylated calix[4]arenes, reflecting the complexity of the problem. Alkylation of the monoalkyl calixarene **104** produces the *syn*-A,B-diether **106** (pathway C) when NaH is used but the *syn*-A,C-diether **105** (pathway B) when a weak base

[280] Casnati, A.; Pochini, A.; Ungaro, R.; Cacciapaglia, R.; Mandolini, L. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2052.
[281] Iqbal, M.; Mangiafico, T.; Gutsche, C. D. *Tetrahedron* **1987**, 43, 4917.
[282] Sharma, S. K.; Gutsche, C. D. *Synthesis* **1994**, 813.
[283] Sharma, S. K.; Alam, I.; Gutsche, C. D. *Synthesis* **1995**, 1089.
[284] Gutsche, C. D.; Reddy, P. A. *J. Org. Chem.* **1991**, 56, 4783.
[285] Sharma, S. K.; Gutsche, C. D. *Tetrahedron* **1994**, 50, 4087.

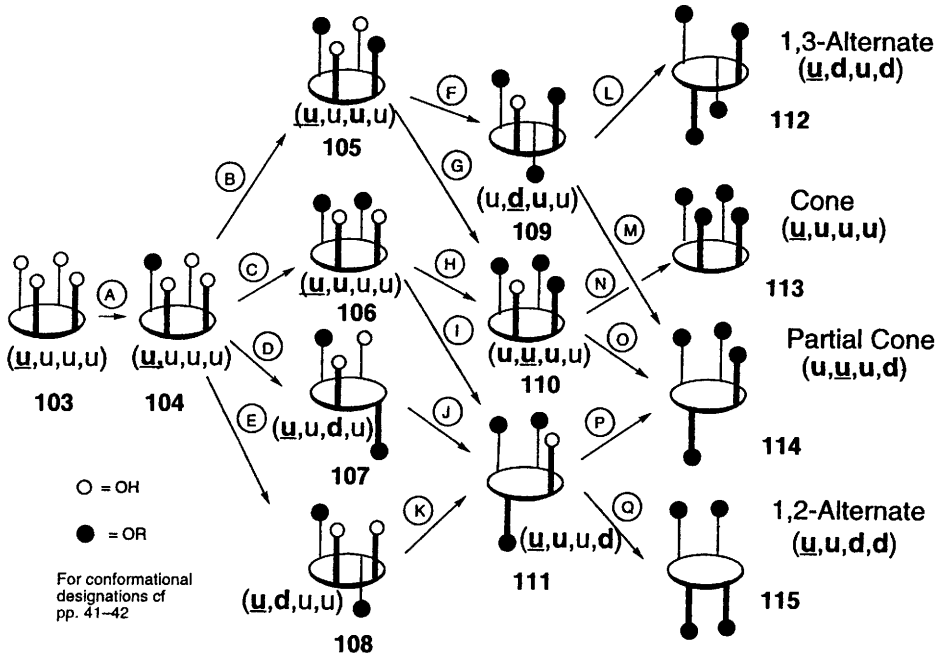


Figure 4.17 *Pathways for stepwise O-alkylation of calix*[4]*arenes. The open circles represent OH groups, and the solid circles represent OR groups. The conformational notation employs the group at the left of the cyclic array as the reference group and proceeds around the system in a clockwise direction* (*see pp.* 41–42)

such as K_2CO_3 is used,[142] both regioisomers being most stable in the cone conformation. Direct conversions of **103** or **104** to the *anti*-A,B and *anti*-A,C diethers **108** and **107** have not been accomplished, but these conformers have been prepared by indirect means.[138]

Conversion to a triether with Cs_2CO_3 as the base gives the partial cone **109** (pathway F) as the major conformer from the *syn*-A,C-diether **106** or the cone conformer **110** (pathway H) from the *syn*-A,B-diether. Conversion of the triether **109** to the tetraether using Cs_2CO_3 as the base then yields the partial cone conformer **114** (pathway M) as the major conformer when the *p*-substituent in the calixarene is *t*-Bu. When the *p*-substituent is hydrogen,[142] however, the 1,3-alternate conformer **112** (pathway L) is formed, the amount of **114** depending on the amount of Cs_2CO_3 used.[189] Another example of the combined effects of the base employed and the *p*-substituent of the calixarene is seen with $\mathbf{4}^{CH_2CN}$.[285] Benzylation in the presence of K_2CO_3 yields the 1,3-alternate conformer of the tetrabenzyl ether **112**, in contrast to $\mathbf{4}^{t\text{-Bu}}$ which yields the A,C-diether **105** in the pinched cone conformation. Benzylation of $\mathbf{4}^{CH_2CN}$ in the presence of NaH, however, yields the cone conformer **113** of a tetrabenzyl ether in which the *p*-cyanomethyl groups have also become α,α-dibenzylated and are much more

bulky. Conversion of the *anti*-A,C-ether **107** with *t*-BuOK as the base yields the 1,2-alternate conformer **115** (pathways J and Q).[138]

The triether **110** (pathway N) yields the cone conformer **113** as the major product with either NaH or Cs_2CO_3 as the base. Formation of the tetraether directly from the A,C-diether **105** with NaH as the base in one case yielded a mixture of almost equal amounts of cone conformer **113** (pathways G and N) and partial cone conformer **114** (pathways F and M and/or pathways G and O)[189] but only the partial cone conformer **114** in another case.[138] The corresponding *anti*-A,C and *anti*-A,B diethers **107** and **108** have been made by indirect methods involving protection and deprotection of OH groups.[138] Conversion of the *anti*-A,C-diether **107** (pathways J and Q) to the tetraether gives preferentially the 1,2-alternate conformer **115** *via* the triether **111** intermediate.

Although it is difficult to draw hard and fast conclusions from these data, the following generalizations appear to apply: (a) the tetraalkylation process proceeds in a stepwise fashion, and the products generally are the result of kinetic control; (b) the conformation of the tetraether is mainly, but not completely, fixed at the trialkylation stage, more so with NaH than with Cs_2CO_3; (c) the 'up/down' interconversion of the ArOH moieties occurs less readily with Na^+ as the cation than with Cs^+; thus, in the conversion of **110** to the tetraether the cone conformation is completely retained with Na^+, partially retained with K^+, and completely inverted to partial cone with Cs^+;[142] (d) strong bases such as NaH favor the formation of tetraethers in the cone conformation; (e) small *p*-substituents in the calixarene favor 1,3-alternate conformers (e.g. H *vs.* *t*-Bu;[142] CH_2CN *vs.* $C(CH_2Ph)_2CN$[285]).

4.6.3 *O*-Substitution of Calix[5]arenes and Calix[6]arenes

No systematic studies have been made to determine the factors governing the conformational outcome in the alkylation, acylation, and aroylation of calixarenes with rings larger than four aryl residues.

CHAPTER 5

Embroidering the Baskets: Modifying the Upper and Lower Rims of Calixarenes

'We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time'
T. S. Eliot, *Little Gidding*, *Collected Poems* 1909–1962

Considerable attention was devoted in the 1980s to functionalizing the upper and lower rims of calixarenes (see ref. 1, pp. 127–148), and this has continued unabated in the 1990s, as witness the relative lengths of the Chapters 5 in the two volumes. This comes as no surprise, because the utility of the calixarenes for the majority of potential applications depends upon suitable modification of the parent compounds. Organic synthesis in its many guises remains essential for a large fraction of chemical research.

5.1 Modifying the Lower Rim of Calixarenes

5.1.1 Esterification

The esters were the earliest of the lower rim-modified calixarenes to be prepared (see ref. 1, pp. 128–130). Although more recent studies have concentrated heavily on the ethers, the esters continue to command considerable attention. With acid halides and NaH, acid halides and $AlCl_3$, or acid anhydrides and H_2SO_4 the acylation or aroylation generally involves all of the OH groups if the derivatizing agent is used in excess. Several exceptions have been reported, however. One is the acylation and aroylation of $\mathbf{4}^{CH_2CN}$ in the presence of $AlCl_3$;[282] another is the benzoylation of $\mathbf{4}^{H}$ with benzoyl chloride/NaH,[286] both reactions giving the A,C-diesters. The reactions leading to complete esterification have been studied in some detail in the calix[4]arenes, and it has been shown,[277] for example, that

[286] Shu, C-m.; Liu, W-c.; Ku, M-c.; Tan, F-s.; Yeh, M-l.; Lin, L-g. *J. Org. Chem.* **1994**, 59, 3730.

acetylation, propionylation, butyrylation, and isobutyrylation of **4**$^{t\text{-Bu}}$ and **4**^{H} all yield the tetraacylates, although with varied and somewhat unpredictable conformational outcomes. Similarly, the penta-acetate, -propionate, -*n*-butanoate, -isobutanoate, -cyclopropylcarbanoate, -pivaloate, -benzoate, and -tosylate of **5**$^{t\text{-Bu}}$ have been prepared *via* either the acid halide/NaH or the anhydride/H_2SO_4 procedure, again with varied and uncertain conformational outcomes.[112] While acetylation of the calix[6]arenes goes to completion to form the hexaacetates, aroylation is less likely to do so. Thus, **6**$^{t\text{-Bu}}$ reacts with *p*-nitrobenzoyl chloride/NaH to give a mixture of the tetra- and pentaesters;[287] **6**^{H} reacts with benzoyl chloride/pyridine to give a tetraester[287] rather than a hexaester;[288] **6**^{allyl} under the same conditions yields the hexaester.[287] The difference is probably due to the greater solubility of the *p*-allylcalixarenes which forestalls the precipitation of the product as the esterification proceeds. Calix[7]arenes remain largely unstudied, but **8**$^{t\text{-Bu}}$ readily forms the octaacetate (see ref. 1, pp. 49–70, 130, 153).[289]

Esterification studies carried out in the 1990s have focused primarily on partial substitution because of the potential utility of the products for selective upper rim functionalization. By using acid halides in the presence of bases weaker than NaH, by using limiting amounts of the esterifying reagent, and/or by using bulky esterifying reagents it is often possible to obtain partially-substituted calixarenes in quite selective fashion. The early example of **4**$^{t\text{-Bu}}$ reacting with benzoyl chloride in the presence of pyridine to give the tribenzoate[288] has been followed by several other studies,[250,289–292] one of which[250] involves the rather complex situation encountered with 3,5-dinitrobenzoyl chloride as the esterifying reagent. The scheme shown in Figure 5.1 illustrates the effect that seemingly small changes in reaction conditions can have on the outcome of the reaction. Thus, **4**$^{t\text{-Bu}}$ can be converted directly and/or indirectly to the monoester **119**, the *syn*-A,C-diester **116**, the *syn*-A,B-diester **120**, the *anti*-A,B-diester **121**, the *syn-anti-syn*-triester **117**, or the *syn-syn-syn*-triester **118** simply by changing the relative number of equivalents of reactants, the base (*i.e.* imidazole, 1-methylimidazole, or 1-butylimidazole) and the solvent (*i.e.* $CHCl_3$ or MeCN). The rearragement of the *syn*-A,C-diester **116** to the *anti*-A,B-diester **121** is attributed to a cleavage/reassembly process in which the imidazole may play a cooperative role as nucleophile and proton acceptor/donor.[250]

The reactions of calix[4]arenes with acyl or aroyl halides in the presence of $AlCl_3$ yields either the tetraester (*i.e.* with **4**^{H})[288] or the A,C-diester (*i.e.* with mono-*p*-(cyanomethyl)calix[4]arene,[283] the difference being attributable either to the *p*-substituent and/or the solvent (CH_2Cl_2 in the first case; CH_2Cl_2/DMF in the second case). With mono-*p*-(cyanomethyl)calix[4]arene **122** the diben-

[287] Rogers, J. S.; Gutsche, C. D. *J. Org. Chem.* **1992**, 57, 3152.
[288] Gutsche, C. D.; Lin, L-G. *Tetrahedron* **1986**, 42, 1633.
[289] Huang, Z.-T.; Wang, G.-Q. *Synth. Commun.* **1994**, 24, 11.
[290] Consoli, G. M. L.; Cunsolo, F.; Piattelli, M.; Neri, P. *J. Org. Chem.* **1996**, 61, 2195.
[291] Beer, P. D.; Keefe, A. D.; Drew, M. G. B. *J. Organomet. Chem.* **1989**, 378, 437; Beer, P. D.; Keefe, A. D.; Böhmer, V.; Goldmann, H.; Vogt, W.; Lecocq, S.; Perrin, M. *J. Organomet. Chem.* **1991**, 421, 265.
[292] Nam, K. C.; Yang, Y. S.; Chun, J. C.; Choi, Y. K. *Bull. Korean Chem. Soc.* **1996**, 17, 502.

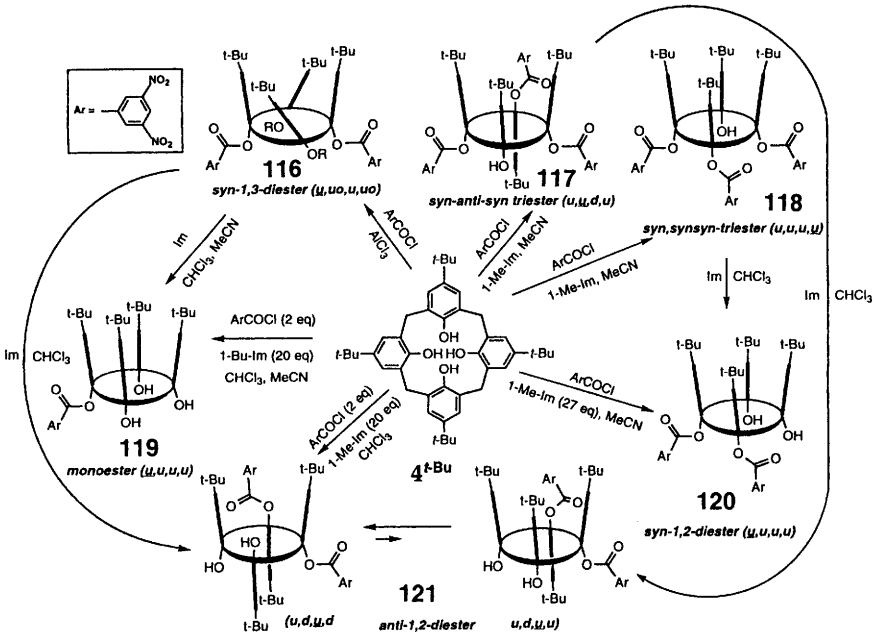


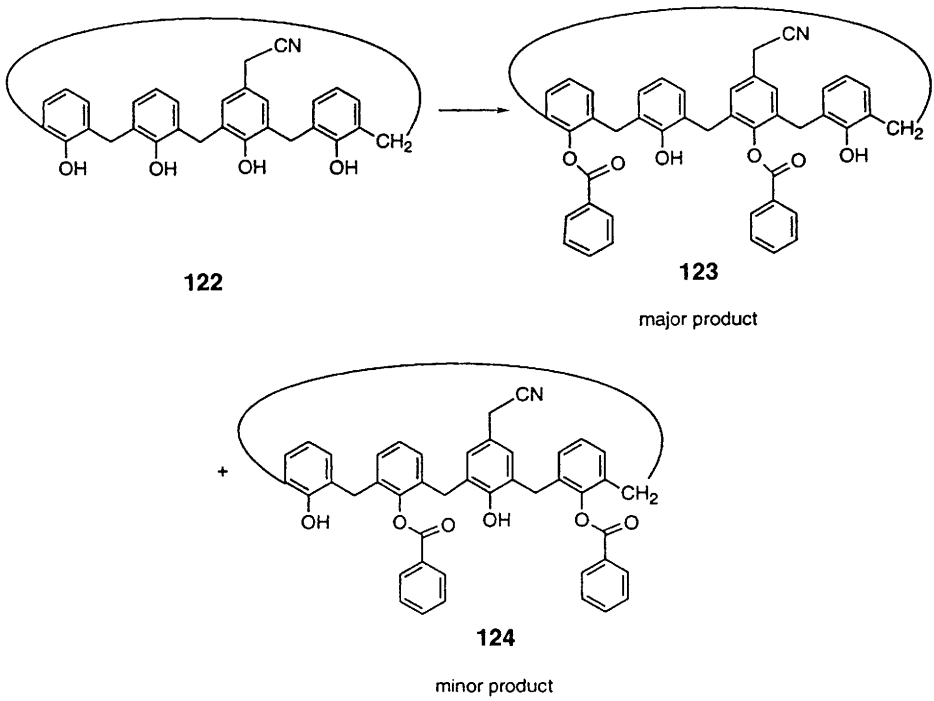
Figure 5.1 *Esterification of* p-tert-*butylcalix*[4]*arene* (**4**$^{t\text{-Bu}}$) *with* 3,5-*dinitrobenzoyl chloride. For viewing convenience the conformational designations start with the left-hand residue and proceed in clockwise fashion around the ring, with the reference residue specified with an underlined 'u' or 'd' (see Section* 4.1)

zoylation occurs preferentially at the *p*-cyanomethyl-ArOH and its distal ArOH residue to give **123** as the major product along with **124** as the minor product.[283]

In the calix[5]arenes the only reported partial ester is the tetrapivaloate (probably the cone conformer), prepared from **5**$^{t\text{-Bu}}$ and pivaloyl chloride/NaH.[112] In the calix[6]arenes, A,B,D,E-tetraesters can be obtained in good yield with aroyl chlorides and 1-methylimidazole[287] or NaH.[293] Several hepta-aroylates of **8**$^{t\text{-Bu}}$ have been prepared in 45–80% yields by using a slight excess of aroylating agent in the presence of pyridine.[290]

A number of other types of calixarene esters are known, including the aryl-sulfonates (often used to establish the calix[4]arenes in the cone conformation[293,294]), phosphates (often used as intermediates in the replacement of the OH groups with H[137,295]) and phosphonates.[296]

[293] Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1992**, 57, 3160.
[294] Gutsche, C. D.; Nam, K. C. *J. Am. Chem. Soc.* **1988**, 110, 6153.
[295] Regnouf de Vains, J.-B.; Pellet-Rostaing, S.; Lamartine, R. *Tetrahedron Lett.* **1994**, 35, 8147.
[296] Floriani, C.; Jacoby, D.; Chiesi-Villa, A.; Guastini, C. *Angew. Chem., Int. Ed. Engl.* **1989**, 28, 1376.



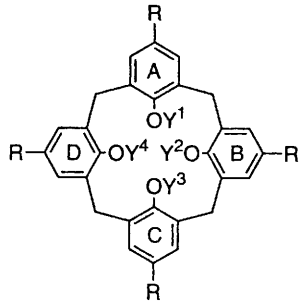
5.1.2 Etherification

5.1.2.1 *With Simple Alkyl Halides*

Alkylation has been studied in considerable detail in the calix[4]arene series, and methods have been devised for preparing the mono-, A,B-di-, A,C-di-, tri-, and tetraethers. Monoethers **125a** can be prepared in moderate to good yields by direct alkylation using (a) an alkylating agent with NaH as the base in toluene solution,[297] (b) $Ba(OH)_2$ as the base in DMF solution,[297] or (c) 1.2 equiv of a weak base (*i.e.* K_2CO_3 in MeCN or CsF in DMF) and an excess of alkylating agent RX where R includes methyl, ethyl, allyl, or ethoxycarbonylmethyl.[298] The surprising difficulty in avoiding polyalkylation in spite of the large gap in pK_1 and pK_2 of the calix[4]arenes (see Section 3.4) is attributed to the comparable pK_1 values for the parent calix[4]arene and its monoalkylated counterpart: the proton that is abstracted from the OH group distal to the OR moiety of the monoether leads to a monoanion stabilized by hydrogen bonding to the two flanking OH groups.[298] An alternative to direct alkylation for generating partially alkylated calixarenes involves selective dealkylation of the readily available A,C-diethers **125c** or tetraethers **125e** by means of stoichiometric amounts of Me_3SiI. By this procedure, 60–90% yields of monomethyl, monoethyl, mono-

[297] Iwamoto, K.; Araki, K.; Shinkai, S. *Tetrahedron* **1991**, 47, 4325.
[298] Groenen, L. C.; Ruël, B. H. M.; Casnati, A.; Verboom, W.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron* **1991**, 47, 8379.

isopropyl, mono-*n*-butyl, and monobenzyl ethers of $\mathbf{4}^{t\text{-Bu}}$ have been obtained.[299] Another alternative takes advantage of the accessibility of the mono-3,5-dinitrobenzoyl ester of calix[4]arene and involves alkylation at the distal ArOH followed by hydrolytic removal of the ester function.[300] Monobenzylation of A,C-*p*-dinitrocalix[4]arene has been achieved with benzyl bromide and Me_3SiOK, which gives an 82% yield of **125f**; the alkylation occurs preferentially on one of the *p*-nitrophenyl moieties.[301] On the other hand, benzoylation of this same calixarene with $AlCl_3$ as the catalyst yields **125g**, the aroylation occurring preferentially on the aryl residues not containing the *p*-NO_2 groups.[301]



125

a) $Y^1 = G; Y^{2-4} = H$

b) $Y^{1,2} = G; Y^{3,4} = H$

c) $Y^{1,3} = G; Y^{2,4} = H$

d) $Y^{1-3} = G, Y^4 = H$

e) $Y^{1-4} = G$

G = alkyl, CH_2Ar, CH_2Py, etc

f) $Y^{1,3,4} = H; Y^2 = CH_2Ph; R^{A,C} = H; R^{B,D} = NO_2$

g) $Y^{1,3} = COPh; Y^{2,4} = H; R^{A,C} = H; R^{B,D} = NO_2$

Distal dialkylation leading to A,C-diethers **125c** is generally much more easily achieved than proximal dialkylation leading to A,B-diethers **125b**. Under conditions similar to those leading to monoethers, but with an excess of the alkylating agent, A,C-diethers are produced, often in very high yields.[302,303] For example, $\mathbf{4}^{t\text{-Bu}}$ treated with an excess of benzyl bromide in acetone with K_2CO_3 as the base gives a 98% yield of the A,C-dibenzyl ether **125c** (R = *t*-Bu; G = CH_2Ph).[297] With weak bases the reaction generally stops at this point, because the remaining OH groups are no longer flanked by other OH groups to provide an H-bond-stabilized anion. However, the reaction does not stop at dialkylation in all cases; for example, $\mathbf{4}^{CH_2CN}$ forms the tetrabenzyl ether **125e** (R = CH_2CN; G = CH_2Ph) under conditions that give only the A,C-diether[283] with other calix[4]arenes carrying *p*-substituents, apparently due to the increased phenolic acidity promoted by the *p*-cyanomethyl groups. Conversely, the A,C-dimethyl ether **125c** (R = *t*-Bu; G = Me) is reported to form by the treatment of $\mathbf{4}^{t\text{-Bu}}$ with methyl tosylate and the weak base K_2CO_3 in acetone.[302] Surprisingly, treatment of the tetramethyl ether **125e** (R = *t*-Bu; G = Me) with potassium metal in various solvents[304] yields the A,C-dimethyl ether **125c** (R = *t*-Bu; G = Me).

[299] Casnati, A.; Arduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R. *Tetrahedron* **1991**, 47, 2221.
[300] Nam, K. C.; Kim, J. M.; Kim, D. S. *Bull. Korean Chem. Soc.* **1995**, 16, 186; Park, Y. J.; Shin, J. M.; Nam, K. C.; Kim, J. M.; Kook, S.-K. *Bull. Korean Chem. Soc.* **1996**, 17, 643.
[301] Sharma, S. K.; Gutsche, C. D. *J. Org. Chem.* **1996**, 61, 2564.
[302] Dijkstra, P. J.; Brunink, J. A. J.; Bugge, K.-E.; Reinhoudt, D. N.; Harkema, S.; Ungaro, R.; Ugozzoli, F.; Ghidini, E. *J. Am. Chem. Soc.* **1989**, 111, 7567.
[303] No, K.; Hong, M. *J. Chem. Soc., Chem. Commun.* **1990**, 572.
[304] Grynszpan, F.; Dinoor, N.; Biali, S. E. *Tetrahedron Lett.* **1991**, 32, 1909.

Proximal dialkylation leading to A,B-diethers **125b** can be carried out by direct alkylation or by selective dealkylation. In the former case, a strong base (*e.g.* NaH) is used with a limiting amount of alkylating agent.[305] For example, **4**$^{t\text{-Bu}}$ treated with 4 equiv of pyridylmethyl chloride and NaH in DMF gives a 70% yield of the A,B-diether **125b** (R = *t*-Bu; G = CH_2Py) accompanied by only small amounts of the mono- and triethers.[142,174] Proximal substitution is the result, to some extent, of a statistical advantage, but more particularly it is attributed to the formation of the trianion of the monoalkyl precursor in which the anion *proximal* to the ArOR moiety (introduced in the first step) is a stronger nucleophile (*i.e.* conjugate base of a weaker acid) than the oxyanion *distal* to this moiety.[142,174,306] Thus, A,C-dialkylation is due to *selective anion formation* at the distal ArOH, while A,B-dialkylation is due to the *selective reactivity* of the proximal ArO^-. A selective dealkylation route to A,B-dialkyl ethers has been applied in the methyl ether series where treatment of the tetramethyl ether **125e** (G = Me) with 2 equiv of $TiBr_4$ in $CHCl_3$ gives the A,B-dimethyl ether **125b** (G = Me) in good yield.[307]

Trimethylation of **4**$^{t\text{-Bu}}$ to give **125d** (R = *t*-Bu; G = Me) can be accomplished in fair yield with Me_2SO_4 in DMF in the presence of $BaO.Ba(OH)_2$.[251] Higher yields of triether, however, are obtained when the starting material is already partially alkylated. The *syn*-A,B-dipyridylmethyl ether of **4**$^{t\text{-Bu}}$, for example, produces a high yield of the triether **125d** (R = *t*-Bu; G = CH_2Py) in the cone conformation when treated with pyridylmethyl chloride and K_2CO_3 in DMF; the *syn*-1,3 analog produces a considerably lower yield of the same triether in the partial cone conformation accompanied by other products.[142] Another approach to the triether as well as the mono- and diethers involves protection/deprotection sequences. For example, as part of a program to prepare all of the possible conformational isomers of *O*-alkyl-*p*-*tert*-butylcalix[4]arenes the (u,u,u,d) conformer of the tri-*n*-propyl ether **125d** (G = Me) was obtained by monobenzylation of **4**$^{t\text{-Bu}}$ followed by tri-*n*-propylation and debenzylation.[297] In similar fashion, the *anti*-A,C-diethyl ether **125c** (R = *t*-Bu; G = Et) was made by first preparing the A,C-dibenzyl ether and then subjecting it to ethylation with EtI and *t*-BuOK followed by removal of the benzyl groups with 2 equiv of Me_3SiBr.[138]

Tetraalkylation of calix[4]arenes to give **125e** is generally carried out with an excess of the alkylating agent in the presence of the strong base NaH, although in some instances the much weaker base K_2CO_3 suffices (*vide supra*). A wide variety of alkyl and aralkyl groups have been introduced in this fashion, ranging in size from Me to naphthylmethyl.[285] An unusual example of disproportionation upon methylation occurs when **146e** is treated with BuLi and CF_3SO_3Me to give a product consisting of a 1:1 mixture of the tetramethyl ether of the calixarene **125e** (G = Me) and the doubly-bridged **147e**.[308]

[305] Brunink, J. A. J.; Verboom, W.; Engbersen, J. F. J.; Harkema, S.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas*, **1992**, 111, 511.

[306] Araki, K.; Iwamoto, K.; Shigematsu, S.; Shinkai, S. *Chem. Lett.* **1992**, 1095.

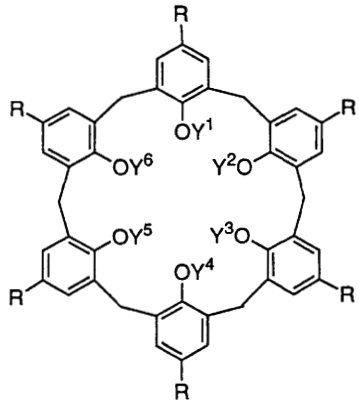
[307] Arduini, A.; Casnati, A.; Dodi, L.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1990**, 1597.

[308] Fan, M.; Zhang, H.; Lattman, M. *Organometallics* **1996**, 15, 5216.

Only a few examples of pentaalkyl ethers of calix[5]arenes have been published, including the methyl,[112] ethyl,[112] *n*-propyl,[112] isopropyl,[112] *n*-octyl,[309] benzyl,[112,259] and pyridylmethyl[215] compounds. The mono-*O*-alkylated **5**$^{t\text{-Bu}}$ include the methyl, ethyl, *n*-propyl, benzyl[112] and pyridylmethyl compounds.[215] In addition, the 1,2-, 1,3-, 1,2,3-, 1,2,4-, and tetramethyl and pyridylmethyl ethers of **5**$^{t\text{-Bu}}$ have been prepared.[112,215] Considerable attention has been devoted to ethers of calix[6]arenes. By using a combination of direct alkylation methods and by taking advantage of the knowledge gained from the calix[4]arene series, all of the methyl ethers **126** (R = *t*-Bu; Y = Me) of **6**$^{t\text{-Bu}}$ [225,310] and ten of the twelve pyridylmethyl ethers **126** (R = *t*-Bu; Y = CH_2Py)[311] have been synthesized. The critical effect that small changes in reaction conditions can have on the product composition is well illustrated by a study[225] in which a series of methylations were carried out with **6**$^{t\text{-Bu}}$ under essentially identical conditions (Me_2CO solvent, MeI, 70 °C in an autoclave at 2 atm for 20 h) but with different bases in different amounts. With Cs_2CO_3 in four-fold excess the product is a mixture of the A,B,C-triether **126c** (R = *t*-Bu) (38%) and the pentaether **126f** (R = *t*-Bu) (15%); with K_2CO_3 in three-fold excess the product is a mixture of the A,B-diether **126b** (R = *t*-Bu) (5%), A,C,E-triether **126d** (R = *t*-Bu) (72%), and A,B,D,E-tetraether **126e** (R = *t*-Bu) (15%); with K_2CO_3 in four-fold excess the yield of the A,B,D,E-tetraether **126e** climbs to 35%. The surprising increase in the yield of the A,C,E-triether **126d** (R = *t*-Bu) from the previously reported[312] 30% to 72% is inferred to be due to the increase in pressure from 1 atm to 2 atm; it remains to be determined whether this is, in fact, the case and whether this is a general phenomenon in calixarene derivatization. The formation of the A,C,E-triether is not limited to methylation but also proceeds in 25–35% yield using other alkyl halides (including *p*-substituted arylmethyl halides), with CsF as the base in MeCN.[313] The formation of the A,C,E-triethers supports the assertion that in the presence of weak bases the alkylation proceeds through the monoanions which are stabilized by two flanking hydrogen-bonded OH groups. The hexamethyl ether **126g** (R = *t*-Bu) is produced in almost quantitative yield using NaH as the base and Me_2SO_4 as the methylating agent.[225] Another subtlety that can affect the outcome of the methylation is the change of the *p*-substituent from *tert*-butyl to hydrogen. The reaction of **6**^{H} with MeI and K_2CO_3 gives a mixture of monoether **126a** (R = H) (8%), A,B-diether **126b** (R = H) (16%), and A,B,C-triether **126c** (R = H) (32%).[225] A similar result has also been reported from another laboratory[314] in which the same conditions were used that produces the A,C,E-trimethyl ether **126d** (R = *t*-Bu) from **6**$^{t\text{-Bu}}$.

Larger alkyl groups, including butyl, octyl,[315] and arylmethyl,[293] have also

[309] Dedek, P.; Janout, V.; Regen, S. L. *J. Org. Chem.* **1993**, 58, 6553.
[310] (a) Otsuka, H.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1994**, 59, 1542; (b) Otsuka, H.; Araki, K.; Shinkai, S. *Tetrahedron* **1995**, 51, 8757.
[311] Neri, P.; Pappalardo, S. *J. Org. Chem.* **1993**, 58, 1048.
[312] Casnati, A.; Minari, P.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1991**, 1413.
[313] Neri, P.; Consoli, G. M. L.; Cunsolo, C.; Piattelli, M. *Tetrahedron Lett.* **1994**, 35, 2795.
[314] Moran, J. K.; Roundhill, D. M. *Inorg. Chem.* **1992**, 31, 4213.
[315] (a) Conner, M. D.; Janout, V.; Regen, S. L. *J. Am. Chem. Soc.* **1993**, 115, 1178; (b) Conner, M. D.; Janout, V.; Kudelka, I.; Dedek, P.; Zhu, J.; Regen, S. L. *Langmuir* **1993**, 9, 2389.



126

a) Y^1=Me; Y^{2-6} = H

b) $Y^{1,2}$ = Me; Y^{3-6} = H

c) $Y^{1,2,3}$ = Me; $Y^{4,5,6}$ = H

d) $Y^{1,3,5}$ = Me; $Y^{2,4,6}$ = H

e) $Y^{1,2,4,5}$ = Me; $Y^{3,6}$ = H

f) Y^{1-5} = Me; Y^6 = H

g) Y^{1-6} = Me

been introduced, in which case it was found that NaH as the base gives mainly the A,B,D,E-tetraether while Me_3SiOK as the base gives mainly the A,D-diether. A,D-Dialkylation has been accomplished in similar fashion with various other alkyl halides, including allyl bromide.[316] The change from tetra- to dialkylation is attributed to the formation of a complex of K^+ with the OH groups at the B, C, E, F rings, leaving the OH groups at the A and D rings more accessible to reaction with the arylmethyl halide. The monobenzyl ether of $\mathbf{6^H}$ has been reported in 78% yield using K_2CO_3 and $PhCH_2Cl$ in limiting amounts.[225]

The calix[8]arenes present an even more complicated case (for a review, see ref. 13d). In addition to the fully *O*-substituted calix[8]arenes, which can be obtained by treatment with strong bases and a large excess of derivatizing agent,[317] 28 partially alkylated calix[8]arenes are possible. In spite of this daunting prospect, Neri and coworkers have made considerable headway in unraveling the intricacies of these processes. Their first success in selective lower rim substitution provided details for the preparation of the A,C,E,G-tetra-*O*-arylmethyl ether of $\mathbf{8^{t\text{-}Bu}}$, obtainable in yields of 20–41% using K_2CO_3 as the base.[318] Tetramethylation of the A,C,E,G-tetrabenzyl derivative followed by Me_3SiBr-induced debenzylation yields the B,D,F,H- (*i.e.* A,C,E,G)-tetramethyl ether,[319] one of the several components in mixtures obtained by direct methyla-

[316] Nam, K. C.; Park, K. S. *Bull. Korean Chem. Soc.* **1995**, 16, 153.
[317] Neri, P.; Battocolo, E.; Cunsolo, F.; Geraci, C.; Piatelli, M. *J. Org. Chem.* **1994**, 59, 3880.
[318] Neri, P.; Geraci, C.; Piattelli, M. *Tetrahedron Lett.* **1993**, 34, 3319.
[319] Cunsolo, F.; Consoli, G. M. L.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1995**, 36, 3751.

tion of $\mathbf{8}^{t\text{-Bu}}$. The direct methylation has been studied in considerable detail, and procedures have been worked out for generating some of the partially methylated compounds in isolable yield, including the monomethyl ether (33%), A,C-dimethyl ether (52%), A,B,D-trimethyl ether (26%), A,B,C,D-tetramethyl ether (12%), and heptamethyl ether (23%).[320] The course of *O*-benzylation with CsF as the base has been monitored by analyzing aliquots removed at various times during the course of reactions using $\mathbf{8}^{t\text{-Bu}}$ or various of its partially-benzylated derivatives as starting materials.[321] The major route that is followed is called the 'alternate pathway' in which the sequence of alkylation is A → A,C → A,C,E → A,C,E,G → A,B,C,E,G → A,B,C,E,F,G → A,B,C,D,E,F,G. Concurrently, a minor route is followed in which the sequence is uncertain but which may be A → A,D → A,B,D → *etc.* The 'alternate pathway' is commensurate with the concept of a reaction driven by preferential formation of monoanions that are stabilized by hydrogen bonds to two flanking OH groups. It has been suggested,[320] however, that due to the conformational flexibility of the calix[8]arene ring system, stabilization from a non-flanking OH group might also be possible, accounting for the minor pathways of alkylation.

5.1.2.2 *With Functionalized Alkylating Agents*

Alkylating agents of the structure XCH_2Y (X is a leaving group, generally Br or tosyl; Y is a functional group) have frequently been used for introducing functionality onto the lower rim of calixarenes. Considering C=C and C≡C as functional groups, the simplest examples employ $BrCH_2CH{=}CH_2$ to give allyl ethers **127a**,[174,322] and $BrCH_2C{\equiv}CH$ to give propargyl ethers **127b**.[112,323,324] In the majority of cases, however, the Y of XCH_2Y contains a heteroatom, the most often used reagents being generated from compounds of the general structure XCH_2COZ to give structures **128**, including: (a) ester **128a**[214,260,275,325-328] (with R′ ranging from groups as small as Me to as large as pyrenylmethyl,[329] cholesteryl,[260] and α-sialoside[330]), (b) amides **128b**,[325,326b,331-334] and (c)

[320] Consoli, G. M. L.; Cunsolo, F.; Neri, P. *Gazz. Chim. Ital.* **1996**, 126, 791; Neri, P.; Consoli, G. M. L.; Cunsulo, F.; Rocco, C.; Piattelli, M. *J. Org. Chem.* **1997**, 62, 4236.

[321] Neri, P.; Geraci, C.; Piatelli, M. *J. Org. Chem.* **1995**, 60, 4126.

[322] Gutsche, C. D.; Levine, J. A.; Sujeeth, P. K. *J. Org. Chem.* **1985**, 50, 5802.

[323] Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1995**, 60, 6070.

[324] Xu, W.; Vittal, J. J.; Puddephatt, R. J. *Can. J. Chem.* **1996**, 74, 766.

[325] Arnaud-Neu, F.; Collins, E. M.; Deasy, M.; Ferguson, G.; Harris, S. J.; Kaitner, B.; Lough, A. J.; McKervey, M. A.; Marques, E.; Ruhl, B. L.; Schwing-Weill, M.-J.; Seward, E. M. *J. Am. Chem. Soc.* **1989**, 111, 8681.

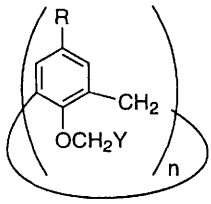
[326] (a) Arnaud-Neu, F.; Collins, E. M.; Deasy, M.; Ferguson, G.; Harris, S. J.; Kaitner, B.; Lough, A. J.; McKervey, M. A.; Marques, E.; Ruhl, B. L.; Schwing-Weill, M.-J.; Seward, E. M. *J. Am. Chem. Soc.* **1989**, 111, 868; (b) Arnaud-Neu, F.; Schwing-Weill, M.-J.; Ziat, K.; Cremin, S.; Harris, S. J.; McKervey, M. A. *New J. Chem*, **1991**, 15, 33.

[327] Ungaro, R.; Pochini, A.; Andreetti, G. D. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1984**, 2, 199; Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R. *Tetrahedron* **1986**, 42, 2089.

[328] Arnaud-Neu, F.; Barrett, G.; Cremin, S.; Deasy, M.; Ferguson, G.; Harris, S. J.; Lough, A. J.; Guerra, L.; McKervey, M. A.; Schwing-Weill, M. J.; Schwinte, P. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1119.

[329] Takeshita, M.; Shinkai, S. *Chem. Lett.* **1994**, 125.

[330] Meunier, S. J.; Roy, R. *Tetrahedron Lett.* **1996**, 37, 5469.



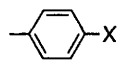
127

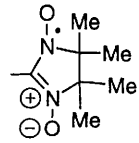
a) Y = $CH{=}CH_2$

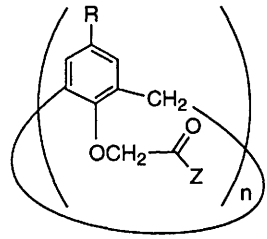
b) Y = $C{\equiv}CH$

c) Y = CH_2CH_2OH

d) Y = 2-Pyridyl

e) Y = 

f) Y = 



128

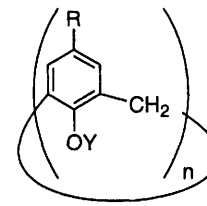
a) Z = OR'

b) $Z = NR'_2$

c) Z = R'

d) Z = OH

e) Z = Cl



129

a) $Y = CH_2CH_2OH$

b) $Y = CH_2CH_2OR$

c) $Y = CH_2CH_2SR$

d) $Y = CH_2CH_2SC(S)NEt_2$

e) $Y = CH_2CH_2OCH_2C(S)NMe_2$

f) $Y = CH_2C(S)NR'_2$

g) $Y = CH_2(CH_2OCH_2)_nCH_2OMe$

ketones **128c** (Z = alkyl[325,335]). A variety of transformation products from **127a,b** and **128a–c** have been reported. For example, hydroboration of **127a** (n = 4, 6, 8) followed by oxidative work-up yields **127c**.[147] Calixarene esters **128a** have been converted (a) by hydrolysis to the acids **128d**[214,328] from which acid chlorides **128e**,[336] esters **128a**, amides **128b**, *etc.* can be prepared, (b) to **129a**,[147,333] **129b** and **129c** and products derived therefrom such as **129d** and **129e**,[333] and (c) by sulfuration with Lawesson's reagent to **129f**.[333] Polyoxyalkyl ethers **129g** can be made *via* the appropriate XCH_2CH_2OR reagent[271,337-339] or *via* direct oxyethylation with ethylene oxide.[340] With $Cl(CH_2CH_2O)_3Ts$ as the

[331] (a) Chang, C.-K.; Cho, I. *Chem. Lett.* **1984**, 477; (b) Chang, S.-K.; Cho, I. *J. Chem. Soc., Perkin Trans. 1* **1986**, 211; (c) Chang, S.-K.; Kwon, S.-K.; Cho, I. *Chem. Lett.* **1987**, 947.

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[333] Cobben, P. L. H. M.; Egberink, R. J. M.; Bomer, J. G.; Bergveld, P.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1992**, 114, 10573.

[334] Casnati, A.; Minari, P.; Pochini, A.; Ungaro, R.; Nijenhuis, W. F.; de Jong, F.; Reinhoudt, D. N. *Isr. J. Chem.* **1992**, 32, 79.

[335] Ferguson, G.; Kaitner, B.; McKervey, M. A.; Seward, E. M. *J. Chem. Soc., Chem. Commun.* **1987**, 584.

[336] Ostaszewski, R.; Stevens, T. W.; Verboom, W.; Reinhoudt, D. N.; Kaspersen, F. M. *Recl. Trav. Chim. Pays-Bas*, **1991**, 110, 294.

[337] Bocchi, V.; Foina, D.; Pochini, A.; Ungaro, R.; Andreetti, G. D. *Tetrahedron* **1982**, 38, 373.

[338] Nomura, E.; Taniguchi, H.; Kawaguchi, K.; Otsuji, Y. *J. Org. Chem.* **1993**, 58, 4709.

[339] Conner, M.; Kudelka, I.; Regen, S. *Langmuir* **1991**, 7, 982.

[340] (a) Shi, Y. H.; Zhang, Z. H. *Chin. Chem. Lett.* **1993**, 4, 953; (b) Shi, Y.; Zhang, Z. *J. Chem. Soc., Chem. Commun.* **1994**, 375; (c) Shi, Y.; Zhang, Z. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 18, 137.

O-alkylating agent and subsequent conversion of Cl to N_3 followed by treatment with C_{60}, a fullerene attached to $\mathbf{8}^{t\text{-Bu}}$ has been prepared.[341]

Alkylation with arylmethyl halides containing heteroatoms provides still another route for the introduction of functional groups onto the lower rim. Examples include (a) pyridylmethyl ethers **127d**, extensively studied by Pappalardo and coworkers[142] (for a review, see ref. 13g), (b) nitrobenzyl ethers **127e** (X = NO_2),[250,293,342] (c) halobenzyl ethers **127e** (X = halogen),[342] and (d) cyanobenzyl ethers **127e** (X = CN).[113,293] Of special note is the introduction of nitroxo groups by this route to give spin-labelled calixarenes **127f**. Using the Mitsunobu reaction (diethyl azodicarboxylate and PPh_3), *O*-glycosyl groups have been introduced onto the lower rim of $\mathbf{4}^{H}$.[343] Phosphorus-containing moieties have been introduced by treatment of calixarenes, *inter alia*, with Ph_2PCl.[314,345]

5.1.3 Lower Rim-bridged Calixarenes

(for short reviews see refs. 12b,f,k and 13f)

5.1.3.1 *Intramolecular Bridges*

The prototype of the lower rim A,C ring-bridged calixarene is the calix[4]arenecrown **130a**, first synthesized,[327,346] in the early 1980s and now represented by dozens of examples with various chain lengths (*n*) and Y groups including H, acyl,[347,348] alkyl,[349,350] allyl,[351] ethoxycarbonylmethyl,[352] ω-hydroxyalkyl,[353] and aryloxyalkyl,[354,355] as well as a second crown bridge which gives the double-bridged 1,3-alternate compound **131a**.[196,356] The parent calix-

[341] Takeshita, M.; Susuki, T.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* **1994**, 2587.
[342] Sharma, S. K.; Gutsche, C. D. *J. Org. Chem.* **1994**, 59, 6030.
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[344] Marra, A.; Scherrmann, M.-C.; Dondoni, A.; Casnati, A.; Minari, P.; Ungaro, R. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 2479. Also see Li, Z. J.; Huang, Z. T. *Chin. Chem. Lett.* **1997**, 8, 369.
[345] Matt, D.; Loeber, C.; Vicens, J.; Asfari, Z. *J. Chem. Soc., Chem. Commun.* **1993**, 604.
[346] Loeber, C.; Matt, D.; De Cian, A.; Fischer, J. *J. Organomet. Chem.* **1994**, 475, 297; Wieser, C.; Matt, D.; Fischer, J.; Harriman, A. *J. Chem. Soc., Dalton Trans.* **1997**, 2391.
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[349] Cacciapaglia, R.; Casnati, A.; Mandolini, L.; Schiavone, S.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1993**, 369.
[350] Ungaro, R.; Casnati, A.; Ugozzoli, F.; Pochini, A.; Dozol, J.-F.; Hill, C.; Rouquette, H. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 1506.
[351] Ghidini, E.; Ugozzoli F.; Ungaro, R.; Harkema, S.; El-Fadl, A. A.; Reinhoudt, D.N. *J. Am. Chem. Soc.* **1990**, 112, 6979.
[352] King, A. M.; Moore, C. P.; Sandanayake, K. R. A. S.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1992**, 582.
[353] Zhong, Z.-L.; Chen, Y.-Y.; Lu, X.-R. *Synth. Commun.* **1996**, 26, 307.
[354] Nechifor, A. M.; Philipse, A. P.; de Jong, F.; van Duynhoven, J. P.; Reinhoudt, D.N. *Langmuir* **1996**, 12, 3844.
[355] Rudkevich, D. M.; Mercer-Chalmers, J. D.; Verboom, W.; Ungaro, R.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, 117, 6124.
[356] Casnati, A.; Pochini, A.; Ungaro, R.; Ugozzoli, F.; Arnaud, F.; Fanni, S.; Schwing, M.-J.; Egberink, R. J. M.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, 117, 2767.

crowns **130a** ($Y^{1,2}$ = H) as well as their dimethyl ethers **130a** ($Y^{1,2}$ = Me) retain some conformational flexibility and can exist in cone, partial cone, and 1,3-alternate conformations, but ethers with larger groups such as isopropyl and benzyl have fixed conformations. Thus, alkylation with sufficiently large alkyl groups yields the 1,3-alternate conformer as the major product with Cs_2CO_3 as the base,[350] while alkylation with NaH as the base yields a mixture from which the cone and partial cone conformers have been isolated.[351]

Taking advantage of the alkylation techniques described above (see Section 5.1.2.1), A,B ring-bridged calix[4]arenecrowns such as **132**[307,357-360] have also been made. Other crown ether-type bridges include those in compounds such as the calixsalophen crown **130b**,[361] the calix-binaphthyl crown ether **130c**,[362] the azacrowns **130e**[363] and **130f**,[364] the anisylmethylene compounds **130g** (n = 1-3),[365] the bipyridyls **130h**,[366] and a variety of azacrown-type structures.[367] Another type of A,C-bridged calix[4]arene includes those with a double bond in the bridge[368] such as **130d** prepared by the ruthenium-catalyzed coupling of the A,C-bisbutenyl ether.[369]

Only a few examples of calixcrowns of the larger calixarenes have been reported. The spanning of $\mathbf{5}^{t\text{-Bu}}$ has been accomplished with tetraethyleneoxy and pentaethyleneoxy chains joining the A,C rings and with hexaethyleneoxy chains joining the A,C rings (major product) or the A,B rings (minor product).[216,264] Both $\mathbf{6}^{t\text{-Bu}}$ and $\mathbf{6}^{H}$ have been spanned between the A,D rings by tetraethyleneoxy chains.[370] Two doubly-bridged *p-tert*-butylcalix[8]arenes have been made by treatment of the A,C,D,E-tetra-*p-tert*-butylbenzyl ether of $\mathbf{8}^{t\text{-Bu}}$ with $TsOCH_2(CH_2OCH_2)_nCH_2OTs$ and base,[371] one with bridging between the A,C and E,G rings (**136**) and the other with bridging between the A,E, and

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[363] Pulpoka, B.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **1996**, 37, 6315.

[364] Beer, P. D.; Martin, J. P.; Drew, M. G. B. *Tetrahedron* **1992**, 48, 9917.

[365] Zhong, Z.-L.; Chen, Y.-Y.; Lu, X.-R. *Tetrahedron Lett.* **1995**, 36, 6735.

[366] Szemes, F.; Hesek, D.; Chen, Z.; Dent, S. W.; Drew, M. G. B.; Goulden, A. J.; Graydon, A. R.; Grieve, A.; Mortimer, R. J.; Wear, T.; Weightman, J. S.; Beer, P. D. *Inorg. Chem.* **1996**, 35, 5868.

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[368] Wang, J.-S.; Gutsche, C. D. unpublished results.

[369] McKervey, M. A.; Pitarch, M. *J. Chem. Soc., Chem. Commun.* **1996**, 1689.

[370] Casnati, A.; Jacopozzi, P.; Pochini, A.; Ugozzoli, F.; Cacciapaglia, R.; Mandolini, L.; Ungaro, R. *Tetrahedron* **1995**, 51, 591.

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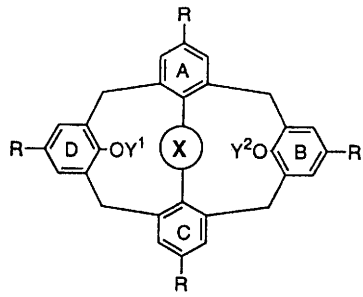
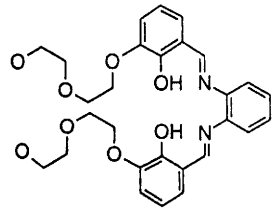


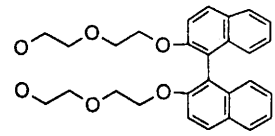
130

a) X = $OCH_2(CH_2OCH_2)_nCH_2O$

b) X =

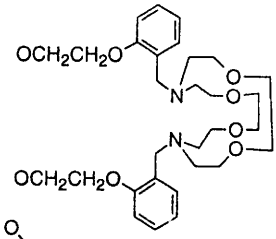


c) X =

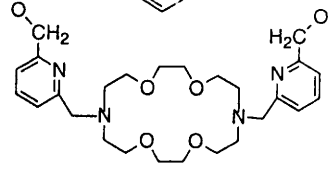


d) X = $O(CH_2)_2CH{=}CH(CH_2)_2O$

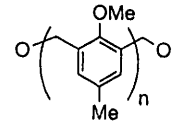
e) X =



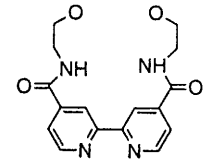
f) X =



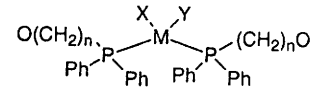
g) X =



h) X =

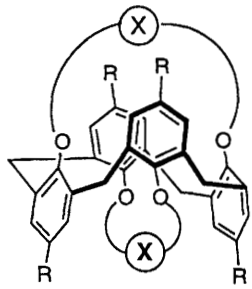


i) X =

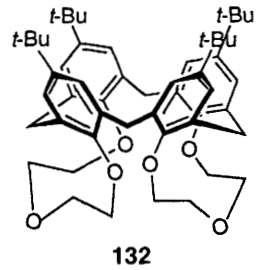


C,G rings (**137**).[372] The singly-bridged compounds can be made by similar treatment of the parent calixarene, the position of the bridging depending on the base employed.[373] With NaH or KH as the base, modest yields of the A,D-bridged calixarene **134** are obtained, while with K_2CO_3 or Cs_2CO_3 the A,C-bridged **133** or A,E-bridged **135** are formed in low yield. The A,D bridging induced by strong bases is attributed to the formation of a tetraanion **141** of the

[372] Geraci, C.; Chessari, G.; Piattelli, M.; Neri, P. *J. Chem. Soc., Chem. Commun.* **1997**, 921.
[373] Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1996**, 37, 3899.



131

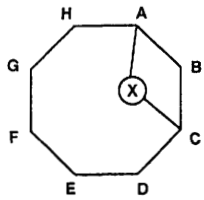


132

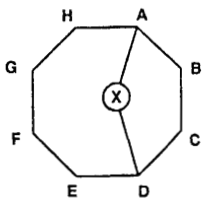
a) X = $CH_2(CH_2OCH_2)_nCH_2$

b) X = $[CH_2(CH_2OCH_2)_2CH_2O]_2Ar$

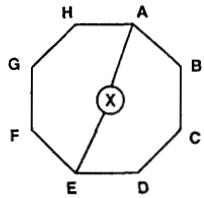
initially formed monosubstituted intermediate, intramolecular alkylation then proceeding at one or the other of the oxyanions three residues away.[373] With weaker bases, however, the reaction proceeds *via* a monoanion of the monoether in which the charge is localized at the oxygen on the C-ring,[373] thereby leading prefererentially to A,C bridging. From the A,D-bridged compound, two more doubly-bridged calix[8]arenes have been made, **138** with A,D and E,H bridging and **139** with A,D and B,E bridging.[374]



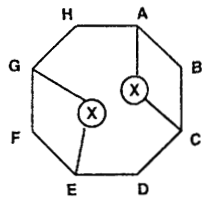
133



134



135



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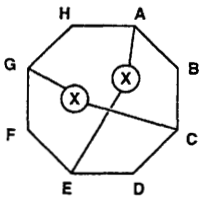

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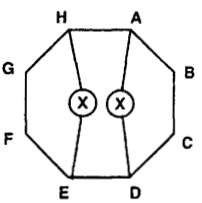

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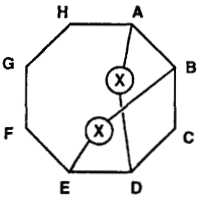


139

a) X = $OCH_2(CH_2OCH_2)_nCH_2O$

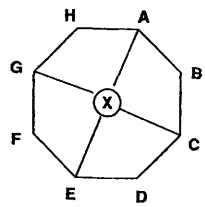
b) X = OCH_2ArCH_2O

A variety of other types of bridges have also been employed to span the lower rim of calix[4]arenes. Included among these are hemispherand moieties to give **142a,b**[302,375] metallocene moieties to give **143**,[376] and a variety of spanners of the general structure Ar–Ar or X–Ar–Y–Ar–X (X = SO_2, CO, or CH_2; Y = CO,

[374] Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1996**, 37, 7627.

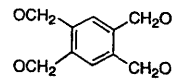
[375] Reinhoudt, D. N.; Dijkstra, P. J.; in't Veld, P. J. A.; Bugge, K.-E.; Harkema, S.; Ungaro, R.; Ghidini, E. *J. Am. Chem. Soc.* **1987**, 109, 4761.

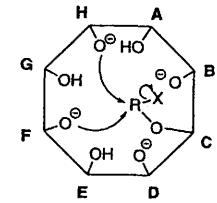
[376] Beer, P.D.; Keefe, A. D. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1987**, 5, 499.



140

X =



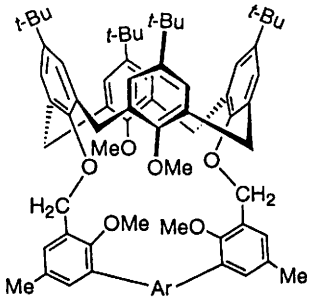


141

SO_2) to give **144**.[377] In most cases the major product from these reactions is the A,C distally-bridged calix[4]arene, although small amounts of the intermolecularly bridged compound (see p. 98) are obtained with the O_2SAr–Y–$ArSO_2$ spanner. With phthaloyl as the spanner the A,B-bridged **146a** and A,B/C,D doubly-bridged **147a** compounds are obtained,[265,377] and a similar compound **147b** is formed with methylene as the spanner.[141] With sebacoyl as the spanner only the A,C-bridged compound is formed in high yield.[377] It is interesting to note that treatment of **146a** with $BrCH_2CO_2Et$ under various reaction conditions yields either the monoether **146a** ($Y^1 = CH_2CO_2Et$) or the diether **146a** ($Y^{1,2} = CH_2CO_2Et$), the latter in both the *syn* and *anti* forms. The doubly-spanned double-cavity calix[4]arene **148a** and singly-spanned double-cavity calix[4]arene **148b** have been prepared by spanning the amino moieties of the A,C-diether containing the appropriate aminobenzyl moieties.[378,379] Triple attachment to the lower rim has been achieved by Vicens and coworkers through the reaction of tris(aminoethyl)amine with a calix[4]arene functionalized on the lower rim with three aldehyde-containing moieties to give, after reduction of the tris-imine, **149**.[380] Several examples of porphyrins quadruply attached to the lower rim of a calixarene have been reported, including **145a**,[381] **145b**,[382] and **145c**.[383]

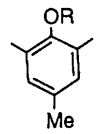
One of the few lower rim-spanned calix[5]arenes that has been reported is the A,C-diester obtained in low yield from $\mathbf{5}^{t\text{-Bu}}$ and *o*-phthaloyl chloride,[265] but considerable attention has been devoted to bridging the lower rim of calix[6]arenes with spanners other than polyethyleneoxy. For example, a variety of CH_2ArCH_2 spanners have been introduced to give generally good yields of A,D-bridged compounds: (a) **150a–c** (from 1,4-CH_2ArCH_2 where Ar is phenylene,[124] durylene,[124] anthrylene,[124] or 1,10-phenanthroline[384a]); (b) **150d** (from 1,3-CH_2ArCH_2 where Ar is phenylene substituted at the 2-position with H,[227,310,384] Br,[227a] NO_2,[384b] SBu,[227b] SOBu,[227b] SOH,[227b] or N_3[385]); and (c)

[377] van Loon, J.-D.; Kraft, D.; Ankoné, M. J. K.; Verboom, W.; Harkema, S.; Vogt, W.; Böhmer, V.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, 55, 5176.
[378] Gutsche, C. D.; See, K. A. *J. Org. Chem.* **1992**, 57, 4527.
[379] See, K. A.; Liemann, U. S. unpublished observations.
[380] Tuntulani, T.; Ruangpornvisuti, V.; Tantikunwatthana, N.; Ngammpaiboonsombut, O.; Seangprasertkij-Magee, R.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **1997**, 38, 3985.
[381] Gale, P. A.; Sessler, J. L.; Lynch, V.; Sansom, P. I. *Tetrahedron Lett.* **1996**, 37, 7881.
[382] Kobayashi, N.; Mizuno, K.; Osa, T. *Inorg. Chim. Acta* **1994**, 224, 1.
[383] Nagasaki, T.; Fijishima, H.; Shinkai, S. *Chem. Lett.* **1994**, 989; Nagasaki, T.; Fijishima, H; Takeuchi, M.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1883.
[384] (a) Ross, H.; Lüning, U. *Tetrahedron* **1996**, 52, 10879; (b) *idem. Tetrahedron Lett.* **1997**, 38, 4539.
[385] Tokitoh, N.; Saiki, T.; Okazaki, R. *J. Chem. Soc., Chem. Commun.* **1995**, 1899.



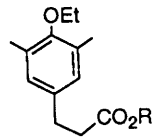
142

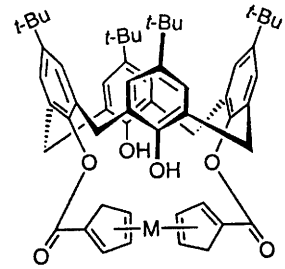
a) Ar=



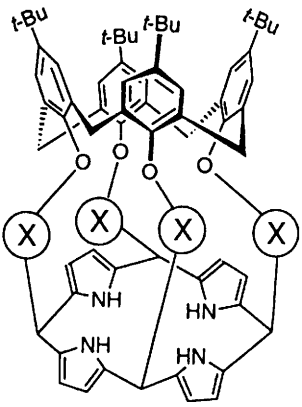
b) Ar =

c) Ar =





143

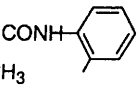


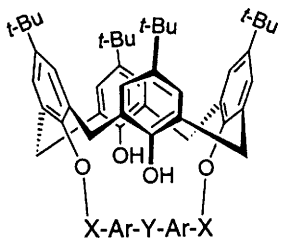
145

a) X = $-OCH_2-$

b) X = $-CH_2CH_2O-$

c) X = $-OCH_2CONHCHCONH-$

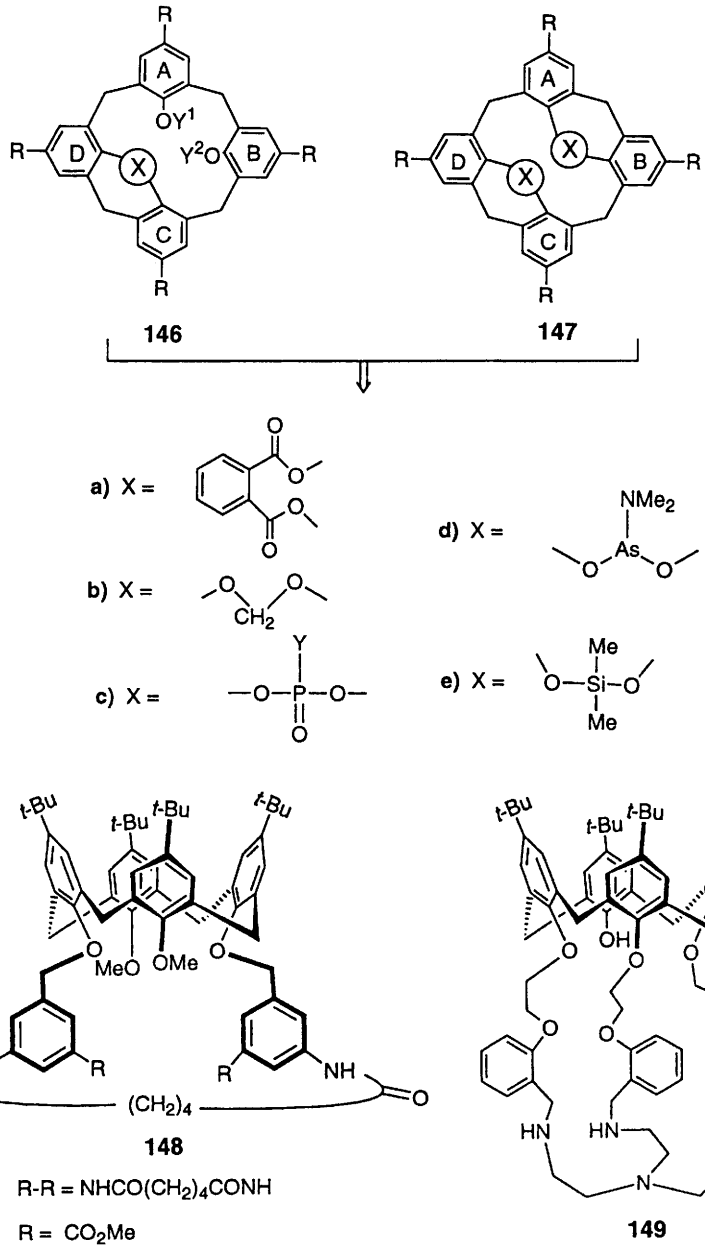




144

X = CH_2, CO, SO_2

Y = CO, SO_2, direct attachment of Ar rings



150e (from 2,6-CH_2PyCH_2,[266,386] Y = H, Me, Et, CH_2CO_2Et, or CH_2Ph). Similarly, $(CH_2)_n(CO)_2$-bridged diesters **150i** are readily synthesized.[124] The reaction of $\mathbf{6}^{t\text{-Bu}}$ with pyridine-2,6-dicarbonyl chloride yields the A,C-bridged compound **151f** (Y = H),[266] while the reaction with α,α′-dibromo-*o*-xylene yields

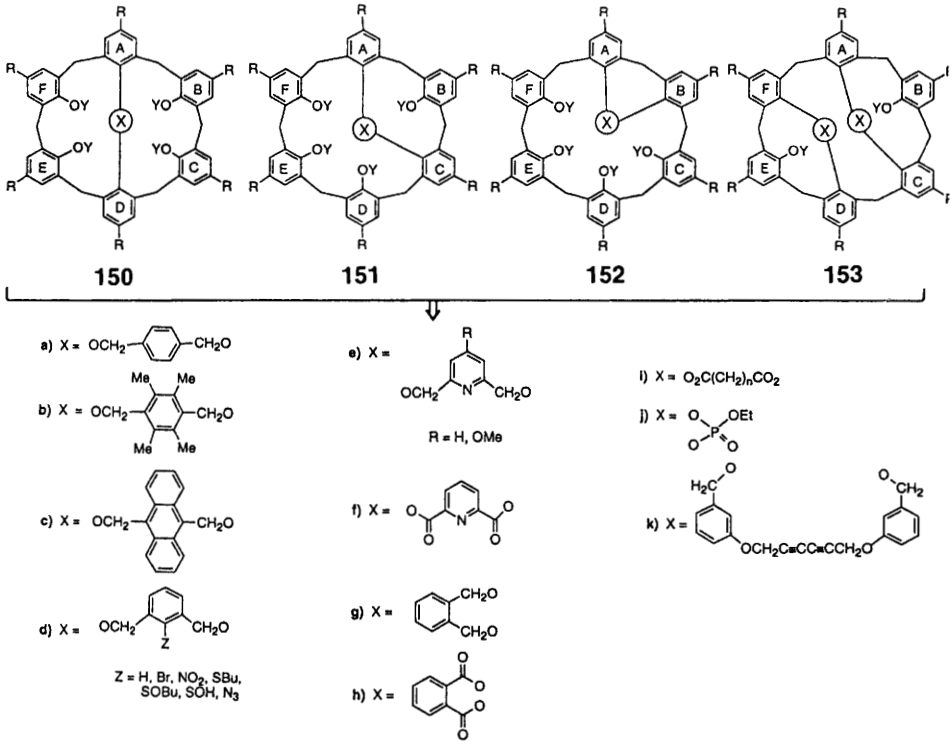
[386] Ross, H.; Lüning, U. *Liebigs Ann. Chem.* **1996**, 1367.

the A,B-bridged compound **152g** (Y = H).[310] With *o*-phthaloyl dichloride the A,B-bridged compound **152h** (Y = H) is obtained.[265] Treatment of the B,D,E,F-tetramethyl ether of **6**$^{t\text{-Bu}}$ with α,α′-dibromo-*o*-xylene yields the A,C-bridged compound **151h** (Y = Me).[310a] If the A,D bridge is sufficiently bulky, as in the case of the anthrylene-bridged **150c**,[124] or sufficiently stiff, as in the case of the diacetylene-bridged **150k**,[387] the calix[6]arene is conformationally inflexible and retains a cone structure. However, with less bulky spanners, conformational flexibility is retained, especially when the OH groups are converted to OMe groups. For example, **150a** (Y = H) exists primarily in the cone conformation (**u**,u,u,u,u,u) under ordinary conditions, but the corresponding tetramethyl ether **150a** (Y = Me) exists in the 1,2,3-alternate conformation (**u**,u,d,d,d,u),[124] as also do the tetramethyl ether **150d** (Y = Me, Z = Br)[227a] and the tetraethyleneoxy-spanned calix[6]arene **150** (X = $OCH_2(CH_2OCH_2O)_2CH_2O$).[370] The conformational behavior of the various **150e** compounds has been analyzed in some detail.[386] Conformationally more rigid calix[6]arenes are produced by triple attachment of the lower rim spanner, as exemplified by **154a** (Y = Pr),[267a] **154b** (Y = Me),[267b] and **154c** (Y = Me).[268] In **154a** and **154b** the spanner moiety was preformed before introduction into the calixarene, whereas with **154c** (called 'cryptocalix[6]arenes') the veratryl units were first introduced and then converted to a cycloveratrylene moiety by treatment with perchloric acid–acetic acid.

Calix[8]arenes have been bridged at the lower rim not only with polyoxyalkyl moieties (*vide supra*) but with a variety of arylene spanners (*p*-phenylene, *m*-phenylene, *o*-phenylene, 2,6-naphthylene) to give A,E-bridged **135**,[148] A,D-bridged **134**,[388] and A,C/E,G-doubly bridged **136**.[148] Calix[8]arenes have been quadruply-spanned by (a) a durylene moiety to give **140**,[389] described as having a 'fixed pseudo pleated loop' conformation with an architecture reminscent of the picket fence porphyrins, and (b) a calix[4]arene moiety to give **155**.[390]

Phosphorus, in a number of guises, has been used to build bridges onto the lower rims of calixarenes. Phosphate can be singly-attached to one or more of the phenolic residues to give simple esters, doubly-attached to give bridged calixarenes such as **147c** (Y = Cl),[182b] **152j** and **156**,[391] or triply-attached to give bridged calixarenes such as **157**.[182b,228,392] The reaction of **4**$^{t\text{-Bu}}$ with $(Me_2N)_3P$ yields **158** in which all four of the phenolic oxygens are involved in binding to the phosphorus.[185,393] Dimethylamine is extruded upon heating **158**, resulting in compound **159a** which can be oxidized to the phosphate **159b**.[394] In comparable fashion, treatment of **4**$^{t\text{-Bu}}$ with $(Me_2N)_3As$ yields **159c** or **147d**, depending on the

[387] Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1996**, 61, 2511.
[388] Ikeda, A.; Akao, K.; Harada, T.; Shinkai, S. *Tetrahedron Lett.* **1996**, 37, 1621; also see Tsantrizos, Y. S.; Chew, W.; Colebrook, L. D. *Tetrahedron Lett.* **1997**, 38, 5411.
[389] Cunsolo, F.; Consoli, G. M. L.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1996**, 37, 715.
[390] Arduini, A.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1995**, 879.
[391] Moran, J. K.; Roundhill, D. M. *Phosphorus, Sulfur, Silicon* **1992**, 71, 7.
[392] Parlevliet, F. J.; Olivier, A.; de Lange, W. G. J.; Kamer, P. C. J.; Kooijman, H.; Spek, A. L.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Chem. Commun.* **1996**, 583.
[393] Khasnis, D. V.; Lattman, M.; Gutsche, C. D. *J. Am. Chem. Soc.* **1990**, 112, 9422; Khasnis, D. V.; Burton, J. M.; Lattman, M.; Zhang, H. C. *J. Chem. Soc., Chem. Commun.* **1991**, 562.
[394] Shevchenko, I.; Zhang, H.; Lattman M. *Inorg. Chem.* **1995**, 34, 5405.



ratio of reactants,[395] and treatment with $(Me_2N)_3SiMe$ yields **159d**.[396] Incorporation of phosphorus in the lower rim bridge in still another fashion is illustrated by the compound **130i** (M = Cu or Pt).[397]

A number of metals have been employed for attachment to the lower rim oxygen atoms (in most instances with calix[4]arenes), including aluminum,[398] tungsten,[399,400] molybdenum,[240,400-402] zirconium,[403] niobium,[404] and tantalum.[404]

[395] Shang, S.; Khasnis, D. V.; Zhang, H.; Small, A. C.; Fan, M.; Lattman, M. *Inorg. Chem.* **1995**, 34, 3610.

[396] Shang, S.; Khasnis, D. V.; Burton, J. M.; Santini, C. J.; Fan, M.; Small, A. C.; Lattman, M. *Organometallics* **1994**, 13, 5157.

[397] Cameron, B. R.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *J. Org. Chem.* **1995**, 60, 2802.

[398] Gardiner, M. G.; Koutsantonis, G. A.; Lawrence, S. M.; Nichols, P. J.; Raston, C. L. *J. Chem. Soc., Chem. Commun.* **1996**, 2035.

[399] Corazza, F.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Inorg. Chem.* **1991**, 30, 4465; Zanotti-Gerosa, A.; Solari, E.; Giannini, L.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *J. Chem. Soc., Chem. Commun.* **1996**, 119.

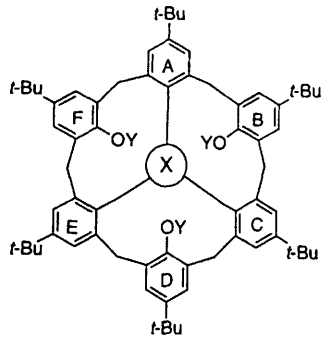
[400] Xu, B.; Carroll, P. J.; Swager, T. M. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 2094; Harvey, P. D.; Gagnon, J.; Provencher, R.; Zu, B.; Swager, T. M. *Can. J. Chem.* **1996**, 74, 2279.

[401] Corazza, F.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *J. Chem. Soc., Chem. Commun.* **1990**, 640.

[402] Acho, J. A.; Ren, T.; Yun, J. W.; Lippard, S. *J. Inorg. Chem.* **1995**, 34, 5226.

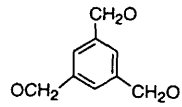
[403] Giannini, L.; Solari, E.; Zanotti-Gerosa, A.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 85.

[404] Acho, J. A.; Doerrer, L. H.; Lippard, S. *J. Inorg. Chem.* **1995**, 34, 2542.

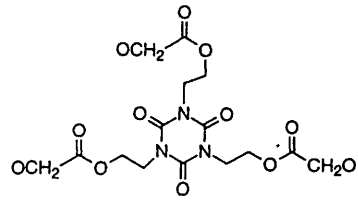


154

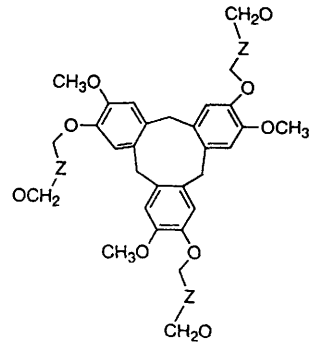
a) X =



b) X =



c) X =

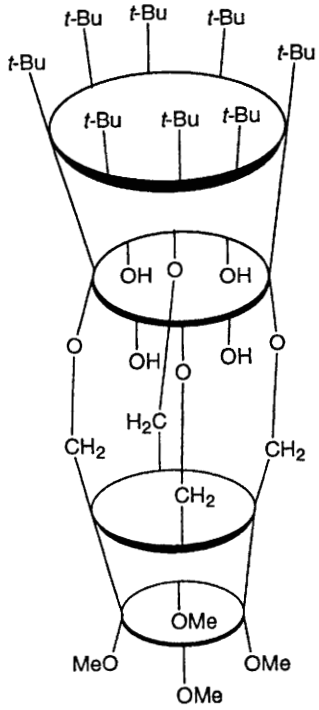


Z = $(CH_2)_n$ and $(CH_2OCH_2)_n$

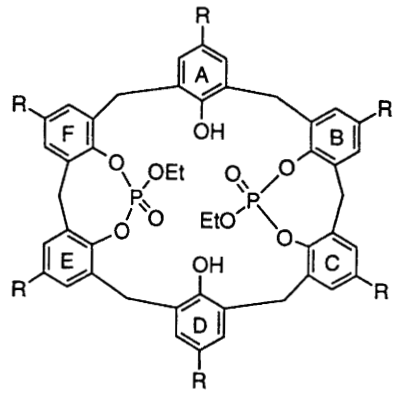
5.1.3.2 *Intermolecular Bridges*

Calixarene units have been joined one to another at their lower rims with a variety of spanners. In the majority of cases the bis-calixarenes that are formed are doubly-spanned, although some examples of singly-spanned and quadruply-spanned bis-calixarenes have been reported. Among the bis-calixarenes connected by a single bridge are **160a** (n = 3, 4, 5),[368] **160b** (n = 3, 4, 5),[368] **160c** (n = 3[369] and 5[369]), **160d** (n = 5),[113] **160e** (n = 5),[113] **160f** (n = 3),[405] and **160g** (n = 3).[406] An investigation of intra- *vs.* intermolecular spanning using a variety of spanners showed that in all of the cases studied the intermolecular product is favored; only with the planar 'bent' disulfonyl chlorides are compounds **161a** formed in low yield.[377] However, other spanners (for a short review, see ref. 12m) often provide quite reasonable yields of bis-calixarenes such as the doubly-spanned **161b** from a planar 'straight' spanner,[407] the polyethyleneoxy com-

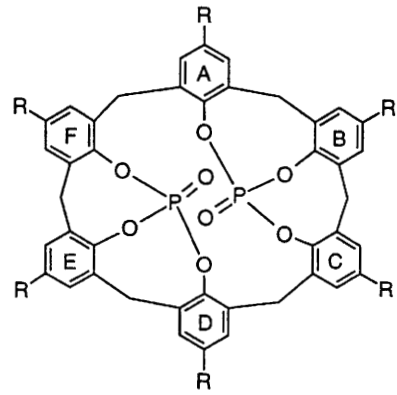
[405] Arimura, T.; Brown, C. T.; Springs, S. L.; Sessler, J. L. *J. Chem. Soc., Chem. Commun.* **1996**, 2293.
[406] McKervey, A. M.; Owens, M.; Schulten, H.-R.; Vogt, W.; Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1990**, 28, 280.
[407] Kraft, D.; van Loon, J.-D.; Owens, M.; Verboom, W.; Vogt, W.; McKervey, M. A.; Böhmer, V.; Reinhoudt, D. N. *Tetrahedron Lett.* **1990**, 31, 4941.



155



156



157

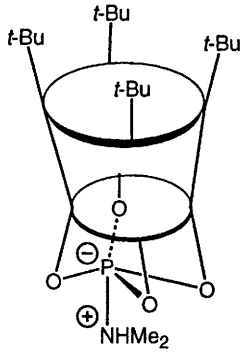
pounds **161c**,[408] the alkene-bridged compounds **161c**,[368,369] the anisyl compound **161e**,[365] the pyridyl compound **161f**,[266] the bipyridyl compound **161g**,[409] and the metallocenyl compounds **161h**.[410a] With 1,2,4,5-tetrakis(chlorocarbonyl)benzene a bis-calixarene **162** joined at the A,B rings of each unit is produced in 29% yield.[265] Bis-calixarenes connected by four bipyridyl or four ethylene bridging moieties have been reported.[409,410b] The nano-sized tetracalixarene **164** comprises four $\mathbf{4}^{t\text{-Bu}}$ moieties attached, *via* lower rim bridges containing Pt atoms, to four 4,4′-bipyridyl residues.[411] Examples among the

[408] (a) Asfari, Z.; Abidi, R.; Arnaud, F.; Vicens, J. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, 13, 163; (b) Asfari, Z.; Weiss, J.; Pappalardo, S.; Vicens, J. *Pure Appl. Chem.* **1993**, 65, 585.

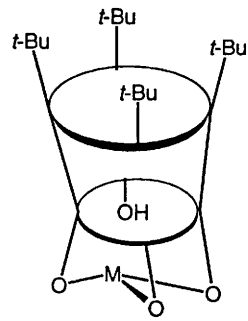
[409] Ulrich, G.; Ziessel, R. *Tetrahedron Lett.* **1994**, 35, 6299.

[410] (a) Beer, P. D.; Keefe, A. D.; Slawin, A, M. Z.; Williams, D. J. *J. Chem. Soc., Dalton Trans.* **1990**, 3675; (b) Schmitt, P.; Beer, P. D.; Drew, M. G. B.; Sheen, P. D. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 1840.

[411] Stang, P. J.; Cao, D. H.; Chen, K.; Gray, G. M.; Muddiman, D. C.; Smith R. D. *J. Am. Chem. Soc.* **1997**, 119, 5163.



158



159

a) M = P
b) M = P=O
c) M = As
d) M = Si-Me

calix[6]arenes include **166a** and **166b**.[368] A few tris-calixarenes such as **163a** (R = *t*-Bu),[407] **163a** (R = *t*-Bu, Y,Y = tetrakis(oxyethylene) bridges),[408b] and **163b** (R, Y = H)[410] have been synthesized in unstated yield and 34% yield, respectively. Even larger cyclic arrays of the general structure **165** have been reported,[412] with the octacalixarene **165** (n = 8) obtained in yields as high as 10%.

5.1.4 Replacement of OH with H, N, and S

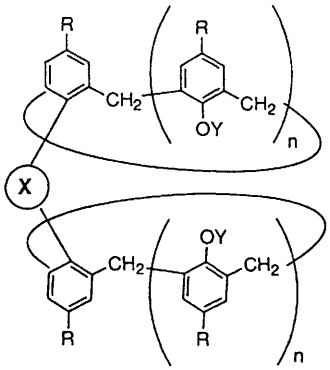
(for a review, see ref. 413a)

Calixarenes in which one or more of the OH groups are replaced by hydrogen have been of interest for conformational studies (see Section 4.3.1). One approach for obtaining such molecules makes use of stepwise synthesis routes (see Section 2.2). A '3 + 1' method is represented by the preparation of 5-*tert*-butyl-11,17,23-trimethylcalix[4]arene-25,26,27-triol by condensation of **34** (R^1 = *t*-Bu; X = OH) with **35** ($R^{1,2}$ = Me, but middle aryl moiety lacks the OH group).[108] A '2 + 2' approach using organolithium methodology has been employed to generate **90** (R^{1-4} = Br, CHO, or D; Y^{1-4} = H).[413b] The more often used approach, however, makes use of the reduction of phosphate esters such as **90** (R^{1-4} = *t*-Bu; Y^{1-4} = $OPO(OEt)_2$) and **90** (R^{1-4} = H; Y^{1-4} = $OPO(OEt)_2$) prepared by reaction of the calixarene with $ClP(O)(OEt)_2$. Using this procedure,[414] the completely dehydroxylated *p-tert*-butylcalix[4]arene **167** (R = *t*-Bu; Y = H; n = 4),[201b] calix[4]arene **167** (R = H; Y = H; n = 4),[139] *p-tert*-butylcalix[6]arene **167** (R = *t*-Bu; Y = H; n = 6),[295] and *p-tert*-butylcalix[8]arene **167** (R = *t*-Bu; Y = H; n = 8)[201b] have been prepared, as well as the partially-dehydroxylated trihydroxy compound **95a**[248] and the A,C-

[412] Lhoták, P.; Kawaguchi, M.; Ikeda, A.; Shinkai, S. *Tetrahedron* **1996**, 52, 12399.

[413] (a) Biali, S. *Isr. J. Chem.* **1997**, 37, 131; (b) Rajca, A.; Padmakumar, R.; Smithhisler, D. J.; Desai, S. R.; Ross, C. R. II,; Stezowski, J. J. *J. Org. Chem.* **1994**, 59, 7701; Rajca, A.; Rajca, S.; Desai, S. R. *J. Am. Chem. Soc.* **1995**, 117, 806.

[414] For a commentary on the mechanism of this reaction, in particular the source of the hydrogen that replaces the OH group, see Grynszpan, F.; Biali, S. E. *J. Phys. Org. Chem.* **1992**, 5, 155.



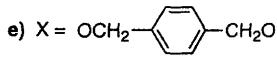
160

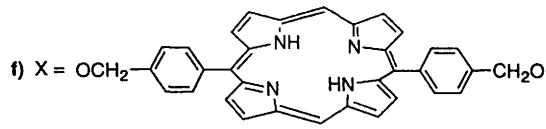
a) X = $OCH_2C(=CH_2)CH_2O$

b) X = $OCH_2CH{=}CHCH_2O$

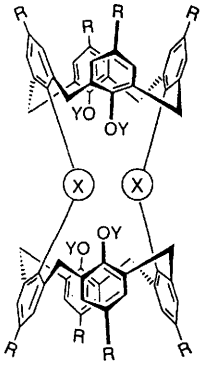
c) X = $O_2C(CH_2)_nCO_2$

d) X = $OCH_2C{\equiv}C\text{-}C{\equiv}CCH_2O$

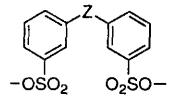
e) X = 

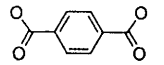
f) X = 

g) X = $OCH_2C(=O)\text{-}Z\text{-}CH_2CH_2\text{-}Z\text{-}C(=O)CH_2O$ (Z = NH or O)



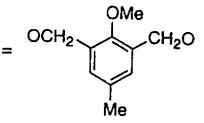
161

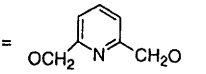
a) X =  Z = CO, SO_2

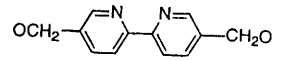
b) X = 

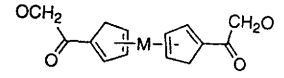
c) X = $OCH_2CH{=}CHCH_2O$ or $OCH_2C(=CH_2)CH_2O$

d) X = $OCH_2(CH_2OCH_2)_nCH_2O$

e) X = 

f) X = 

g) X = 

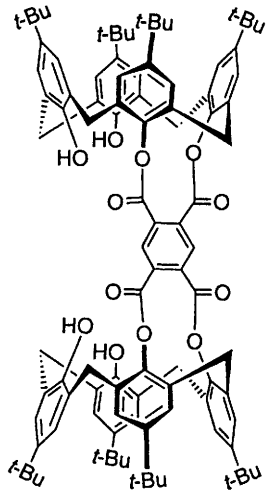
h) X = 

dihydroxy compound **95c**.[248,199] However, **95a** is only a minor product from the reduction of the monophosphate and is more effectively prepared from a *p-tert*-butylcalix[4]arene spirodienone precursor[248] (see Section 5.3.3). Similarly, the A,B-dihydroxy compound **168a** has been prepared *via* a spirodienone and phosphate cleavage route.[247]

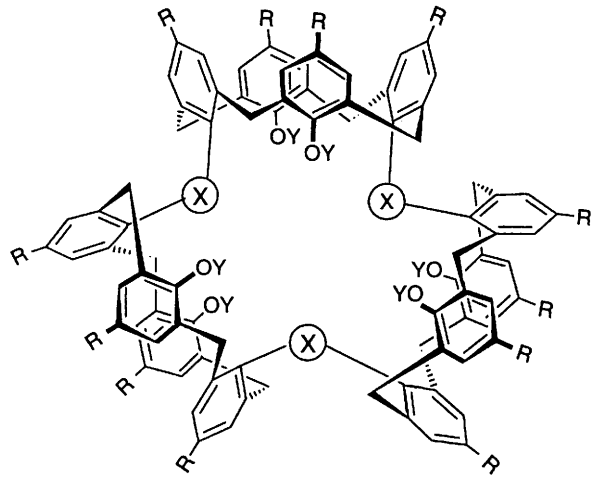
Replacement of OH with NH_2 has been attempted in a stepwise fashion *via* the A,C-dihydroxy compound **95b**, but treatment with NO_2BF_4 results in oxidation (see Section 5.3.2) rather than nitration.[304] A more successful approach involves treatment of the diphosphate ester **168** ($Y^{1,3}$ = $OPO(OEt)_2$; $Y^{2,4}$ = OH) with KNH_2 in NH_3, which gives a mixture from which the monoamine **168b** and diamine **168c** can be isolated in 44% and 8% yield, respectively.[415,416] Still

[415] Ohseto, F.; Murakami, H.; Araki, K.; Shinkai, S. *Tetrahedron Lett.* **1992**, 33, 1217.

[416] One group of workers initially reported[201a] the monoamine **168b** as the trihydroxy compound **95c** but later revised this assignment.[248]

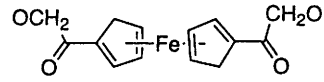


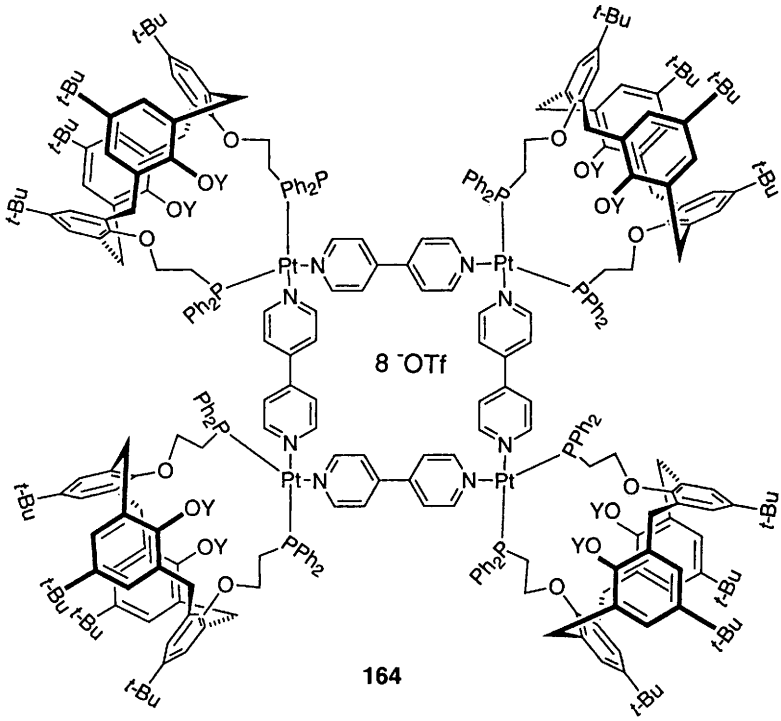
162



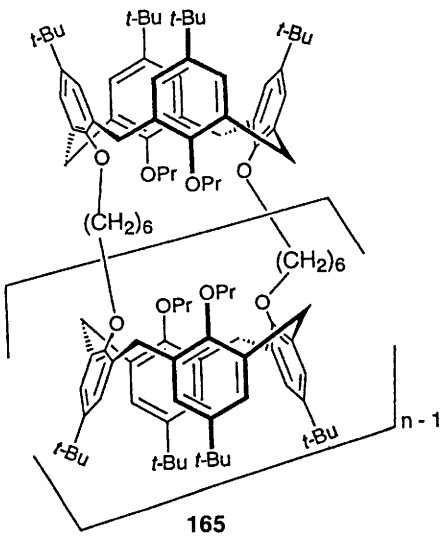
163

a) X = $OCH_2CH_2(OCH_2CH_2)_nO$

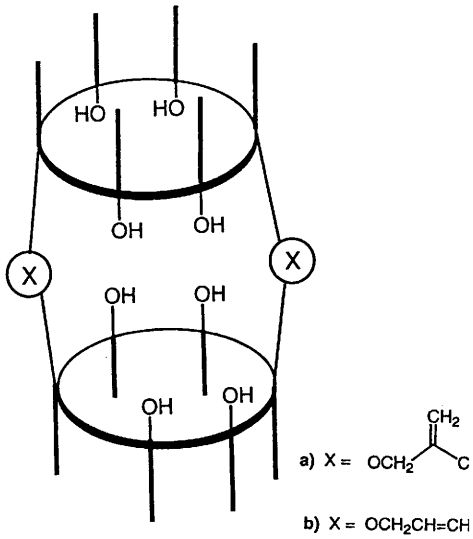
b) X = 



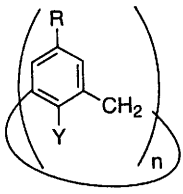
164



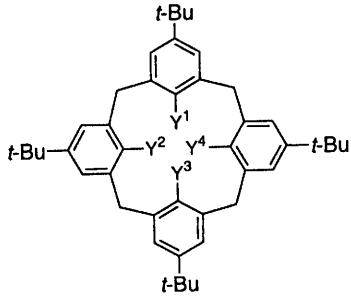
165



166



167



a) $Y^{1,2}$ = H; $Y^{3,4}$ = OH

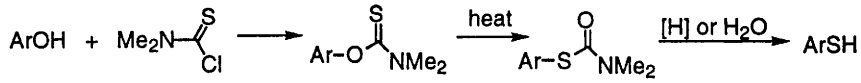
b) Y^{1} = NH_2; Y^{2-4} = OH

c) $Y^{1,3}$ = NH_2; $Y^{2,4}$ = OH

168

another route to **168c** involves the hydrazinolysis of a spirodienone from $\mathbf{4}^{t\text{-Bu}}$ (see Section 5.3.3) followed by reduction/aromatization with Pd/C.[247a] Using similar methodology and starting with a spirodienone from $\mathbf{5}^{t\text{-Bu}}$, a monoamino-*p-tert*-butylcalix[5]arenetetrol has been made in 54% yield.[417,418]

Replacement of OH with SH has been accomplished by means of the Newman–Kwart procedure which involves the reaction sequence:



In this fashion, $\mathbf{4}^{t\text{-Bu}}$ has been converted to the monothio compound **95g**,[203]

[417] Aleksiuk, O.; Grynszpan, F.; Biali, S. E. *J. Org. Chem.* **1993**, 58, 1994.
[418] Aleksiuk, O.; Cohen, S.; Biali, S. E. *J. Am. Chem. Soc.* **1995**, 117, 9645.

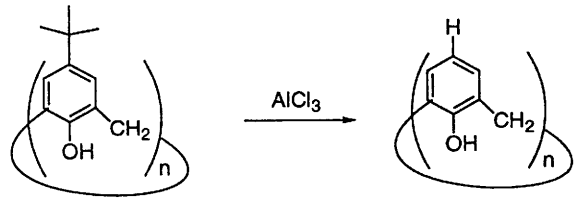
A,C-dithio compound **95h**,[203,205] trithio compound **95i**,[203] and tetrathio compound **95j**.[203,204] In similar fashion the tetrathiol analog of **40**[419] as well as the *O*-dimethyl ether of **95h**[199] have been prepared.

5.2 Modifying the Upper Rim of Calixarenes

5.2.1 General Overview

The fragment condensation method for the synthesis of calixarenes (see Section 2.2 and ref. 1, pp. 36–47) is well adapted to functionalizing the upper rim, and a variety of groups have been incorporated in this fashion including halogen,[41,47] CO_2R,[47] and NO_2.[47] The method is useful primarily for the synthesis of calix[4]arenes of the general structure **36**, but there is at least one example of a calix[6]arene synthesized in this fashion, *viz.* the chlorine-containing **37**.[47] Although the procedures for the fragment condensation have been nicely optimized and are exceedingly useful in a variety of applications, they are not readily amenable to the large scale production of calixarenes.

Because $\mathbf{4}^{t\text{-Bu}}$, $\mathbf{6}^{t\text{-Bu}}$, and $\mathbf{8}^{t\text{-Bu}}$ are so easily available on any scale of operation, from milligrams to kilograms, the major attention to the introduction of functional groups onto their upper rims has been devoted to these starting materials. For this purpose it is a fortunate circumstance that the *tert*-butyl groups are easily removed by $AlCl_3$-catalyzed transfer[420,421] to toluene (Figure 5.2), which is generally used as the solvent.



$\mathbf{4}^{t\text{-Bu}}$, $\mathbf{5}^{t\text{-Bu}}$,$\mathbf{6}^{t\text{-Bu}}$, etc $\mathbf{4}^{H}$, $\mathbf{5}^{H}$, $\mathbf{6}^{H}$, etc

Figure 5.2 *De-*tert*-butylation of calix[n]arenes*

Small amounts of phenol are often added to the de-*tert*-butylating mixture to increase the rate of reaction, possibly because phenol is a good acceptor molecule but also because, for steric reasons, it may be more effective than the calixarene in generating the H^+ necessary to initiate the reaction.[422] Thus, $\mathbf{4}^{t\text{-Bu}}$ affords $\mathbf{4}^{H}$ in

[419] Delaigue, X.; Hosseini, M. W. *Tetrahedron Lett.* **1993**, 34, 8111.

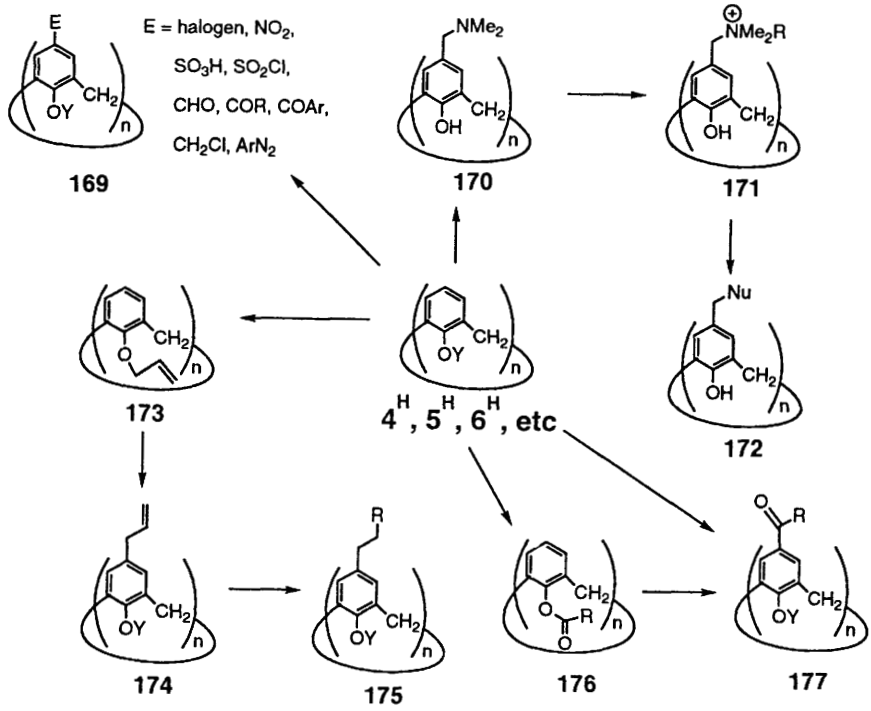
[420] Kämmerer, H.; Happel, G.; Böhmer, V.; Rathay, D. *Monatsh. Chem.* **1978**, 109, 767.

[421] Gutsche, C. D.; Levine, J. A. *J. Am. Chem. Soc.* **1982**, 104, 2652. A pair of unexpected compounds isolated from de-*tert*-butylations carried out in toluene are 2,6- and 2,7-dimethylanthracene: Yao, B.; Bassus, J.; Lamartine, R. *An. Quim.* **1997**, 93, 165.

[422] This suggestion is supported by the fact that the de-*tert*-butylation of the more weakly intramolecularly hydrogen-bonded *p-tert*-butylcalix[5]arene is very rapid even in the absence of phenol, while that of the more strongly intramolecularly hydrogen-bonded *p-tert*-butylcalix[4]arene is very sluggish: Gibbs, C. G.; Gutsche, C. D. unpublished observation.

reasonably good yield,[322] and the other *p-tert*-butylcalixarenes behave in like fashion.[288] Another fortunate circumstance is the sensitivity of the de-*tert*-butylation reaction to the substituents attached to the phenolic oxygens. For example, the A,C-dimethyl ether of $\mathbf{4}^{t\text{-Bu}}$ undergoes selective de-*tert*-butylation at the B,D rings,[423,424] to give **180** ($Y^{1,3}$ = Me; $Y^{2,4}$ = H; $R^{1,3}$ = *t*-Bu; $R^{2,4}$ = H),[425] and the tribenzoate of $\mathbf{4}^{t\text{-Bu}}$ loses a single *tert*-butyl group to give **180** (Y^{1-3} = COPh; Y^4 = H; R^{1-3} = *t*-Bu; R^4 = H),[426] illustrative of the general phenomenon that *p-tert*-butylphenols are more easily dealkylated than their corresponding ethers or esters. Similar selectivity has been achieved in the calix[6]arene series where, for example, the A,C,E-trimethyl ether **126d** (R = *t*-Bu)[270] and the pentamethyl ether **126f** (R = t-Bu)[427] undergo selective de-*tert*-butylation only at the phenolic rings, leaving the other *tert*-butyl groups in place.

With the *p*-positions of the calixarenes made available by de-*tert*-butylation, a wide variety of *p*-functionalization procedures have been explored. A number of these were developed in the 1980s (see ref. 1, pp. 135–144), including the electrophilic substitution route $\mathbf{4}^{H}$, $\mathbf{5}^{H}$, $\mathbf{6}^{H}$, *etc.* → **169** (E = NO_2, SO_3H, COR, COAr, CH_2Cl), the *p*-Claisen rearrangement route $\mathbf{4}^{H}$, $\mathbf{5}^{H}$, $\mathbf{6}^{H}$, *etc.* → **173** → **174**, and the



[423] van Loon, J.-D.; Arduini, A.; Verboom, W.; Ungaro, R.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *Tetrahedron Lett.* **1989**, 30, 2681.

[424] van Loon, J.-D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, 55, 5639.

[425] Tashiro, M.; Koya, K.; Yamato, T. *J. Am. Chem. Soc.* **1982**, 104, 3707.

[426] Berthalon, S.; Regnouf de Vains, J.-B.; Lamartine, R. *Synth. Commun.* **1996**, 26, 3103.

[427] de Mendoza, J.; Carramolino, M.; Cuevas, F.; Nieto, P. M.; Prados, P.; Reinhoudt, D. N.; Verboom, W.; Ungaro, R.; Casnati, A. *Synthesis* **1994**, 47.

p-quinonemethide route **4**^{H}, **5**^{H}, **6**^{H}, *etc.* → **170** → **171** → **172**. These procedures continue to be exploited and improved in the 1990s, and several additional procedures have also been introduced.

5.2.2 Halogenation Routes

Tetrabromination to give **169** (E = Br) can be effected in high yield by treating the tetraalkyl ethers of **4**^{H} with *N*-bromosuccinimide,[23,187,428] while B,D-dibromination of the A,C-dialkyl ether **180** ($Y^{1,3}$ = Me; $Y^{2,4}$ = H; $R^{1,3}$ = *t*-Bu; $R^{2,4}$ = H) has been accomplished with Br_2.[423,429] A monobromo calix[6]arene **182d** and an A,C,E-tribromo compound **182e**[430] have been reported. *p*-Iodination to give **169** (E = I) has been effected indirectly by the action of I_2 on the *p*-trifluoroacetoxymercury calixarene,[424,431] or KI on the *p*-trifluoroacetoxythallium calixarene.[431] Direct iodination has been accomplished in quantitative yield through the use of silver trifluoroacetate and I_2 in $CHCl_3$ and can be carried out selectively by controlling the amount of reagent used.[432,433]

Halocalixarenes are useful intermediates for the introduction of other moieties onto the *p*-positions. Cyanation can be effected with $Cu(CN)_2$ to give **178c**, which reacts with dicyanodiamide to generate **178d** containing *p*-diaminotriazine moieties.[434] Amination has been achieved by treatment with phthalimide and Cu_2O followed by hydrolysis.[435a] Tetralithiation of the conformationally inflexible alkyl ethers of *p*-tetrabromocalix[4]arene **178a** (X = Br; Y = hexyl) to yield **178h** (Y = hexyl) can be effected with *tert*-butyllithium.[428,436] *n*-Butyllithium, however, yields only the A,C-dilithio compound **178g** (X^2 = Br; Y = hexyl) or, if only 1 equiv is used, the monolithio compound **178f** (Y = Pr).[437] On the other hand, lithiation with *n*-butyllithium of the conformationally flexible methyl ether of *p*-tetrabromocalix[4]arene **178a** (X = Br; Y = Me) appears to go almost to completion.[23] The lithio compounds have been converted (a) to *p*-carboxylic acids **179a** by carbonation,[23] (b) to *p*-hydroxy compounds **179b** and **179c** by treatment with $B(OMe)_3$ followed by oxidation with $NaOH–H_2O_2$[428b] or to boronic acids **179d** by hydrolysis,[438] (c) to *p*-methyl compounds **179e** ($R^{1,2}$ = Me) by treatment with MeI,[436] and (d) to *p*-formyl compounds **179f** by

[428] (a) Paek, K.; Ihm, H; No, K. *Bull. Korean Chem. Soc.* **1994**, 15, 422; (b) Paek, K.-S.; Kim, H.-J.; Chang, S.-K. *Supramol. Chem.* **1995**, 5, 83; (c) Paek, K.; Ihm, H. *Chem. Lett.* **1996**, 311.

[429] Linnane, P.; James, T. D.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* **1995**, 1997.

[430] Casnati, A.; Domiano, L.; Pochini, A.; Ungaro, R.; Carramolino, M.; Magrans, J. O.; Nieto, P. M.; López-Prados, J.; Prados, P.; de Mendoza, J.; Janssen, R. G.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1995**, 51, 12699.

[431] Arduini, A.; Pochini, A.; Rizzi, A.; Sicuri, A. R.; Ungaro, R. *Tetrahedron Lett.* **1990**, 31, 4653.

[432] Timmerman, P.; Verboom, W.; Reinhoudt, D. N.; Arduini, A.; Grandi, S.; Sicuri, A. R.; Pochini, A.; Ungaro, R. *Synthesis* **1994**, 185.

[433] Arduini, A.; Pochini, A.; Sicuri, A. R.; Secchi, A.; Ungaro, R. *Gazz. Chim. Ital.* **1994**, 124, 129.

[434] Vreekamp, R. H.; Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1996**, 115, 363.

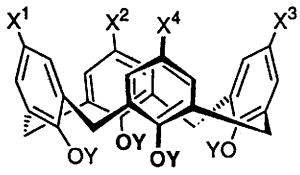
[435] Timmerman, P., Ph.D. Thesis, Universiteit Twente, Enschede, The Netherlands, **1994**: (a) p. 78 (b) p. 73.

[436] Ihm, H.; Paek, K. *Bull. Korean Chem. Soc.* **1995**, 16, 71.

[437] Larsen, M; Jørgensen, M. *J. Org. Chem.* **1996**, 61, 6651.

[438] Ohseto, F.; Yamamoto, H.; Matsumoto, H; Shinkai, S. *Tetrahedron Lett.* **1995**, 36, 6911.

treatment with 4-formylmorpholine[436] or dimethylformamide[439] followed by HCl. Vinyl moieties have been introduced into the hexakis(methoxyethoxyethyl) ether of $\mathbf{6}^{H}$ by treatment with $CH_2=CHSnBu_3$ and $Pd(PPh_3)_4$.[315] The acetylenic moieties C≡CH and C≡CHCH$_2$OH have been introduced into **178a** (X = I) and **178b** (X^1 = I; X^2 = *t*-Bu) by treating with HC≡CSiMe$_3$ followed by desilylation or with HC≡CCH$_2$OH in the presence of $Pd(PPh_3)_4$ to yield **179g** and **179h**, respectively.[433] Ethylthio groups replace the bromines upon treatment of the methyl ether of the calixarene with CuSEt to give **179i**.[187]

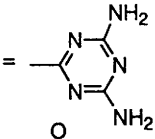


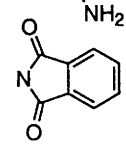
178

a) X^{1-4} = Br or I

b) $X^{1,3}$ = Br or I; $X^{2,4}$ = H or *t*-Bu

c) $X^{1,3}$ = CN; $X^{2,4}$=H

d) $X^{1,3}$ =  $X^{2,4}$ = H

e) $X^{1,3}$ =  ; $X^{2,4}$ = NO_2

f) X^1 = Li; $X^{2,3,4}$ = Br

g) $X^{1,3}$ = Li; $X^{2,4}$ = Br or I

h) X^{1-4} = Li

Bromination at the *m*-position has been achieved by taking advantage of the activating influence of acetylamino or alkoxy groups in the *p*-position. For example, treatment of **90j** with *N*-bromosuccinimide results in bromination of the two rings carrying acetylamino groups but not at the available *p*-positions of the other two rings.[180] Treatment of the pentyl ether of *p*-hydroxycalix[4]arene ($\mathbf{4}^{OH}$) with Br_2–$AgNO_3$ in $CHCl_3$–HNO_3 gives a 67% yield of the octabromocalix[4]arene (1,3-alternate conformer), and similar treatment of the pentyl ether of $\mathbf{8}^{OH}$ gives a 55% yield of the hexadecabromocalix[8]arene.[440]

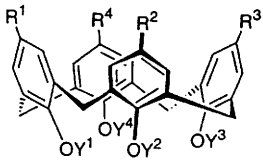
5.2.3 Nitration Routes

The nitration procedures described in the 1980s, using $\mathbf{4}^{t\text{-Bu}}$ as the starting material and leading to *p*-tetranitrocalix[4]arene **180a** (Y^{1-4} = H),[441] have more recently been employed in selective fashion. Using the ethoxyethyl ether of $\mathbf{4}^{t\text{-Bu}}$,

[439] Lhoták, P.; Shinkai, S. *Tetrahedron Lett.* **1996**, 37, 645.

[440] Mascal, M.; Naven, R. T.; Warmuth, R. *Tetrahedron Lett.* **1995**, 36, 9361.

[441] Shang, W.-C.; Zheng, Y.-S.; Huang, Z.-T.; *Synth. Commun.* **1997**, 3763 describe a nitrating procedure using KNO_3 and $AlCl_3$ in MeCN at 0°C. Attempts to reproduce their results under the conditions described as well as a number of variations on these conditions have failed.[272]



179

a) $R^{1-4} = CO_2H$

b) $R^{1,3} = OH$; $R^{2,4} = Br$

c) $R^{1-4} = OH$

d) $R^{1-4} = B(OH)_2$

e) R^{1-4} = Alkyl or Aryl

f) $R^{1-4} = CHO$

g) $R^{1,3} = C{\equiv}CH$ or $C{\equiv}CCH_2OH$; $R^{2,4}$ = *t*-Bu

h) R^{1-4} = $C{\equiv}CH$ or $C{\equiv}CH_2OH$

i) R^{1-4} = SEt

j) $R^{1,3}$ = *t*-Bu; $R^{2,4}$ = H; $Y^{1-4} = CH_2CO_2Et$

k) $R^1R^2 = B(OH)_2$; $R^{3,4}$ =H; $Y^{1,2}$ = Me; $Y^3Y^4 = CH_2(CH_2OCH_2)_nCH_2$

l) $R^{1,3}$ = *t*-Bu; $R^{2,4}$ = H; $Y^{1,3}$ = Pr; $Y^{2,4}$ = H

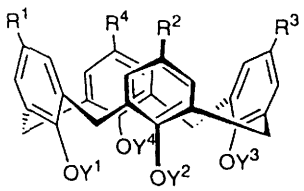
which is less reactive than the parent calixarene, a mixture containing 30–40% of the A,C-dinitro compound and 20% of the mononitro compound is produced.[140] Cleaner reaction is observed, however, with the A,C-dipropyl ether **179l**, which reacts with 65% HNO_3 at room temperature to afford 61% of **180d**, the nitration occurring preferentially on the ArOH rings. In similar fashion the A,C-bis-benzoyl and A,B,C-tris-benzoyl esters of calix[4]arene are selectively nitrated to B,D-*p*-dinitro- and *p*-mononitrocalix[4]arenes,[442] respectively. Of particular note is the recent application of *ipso* nitration[443] whereby the *tert*-butyl groups of the calixarenes are directly replaced with nitro groups, obviating the necessity for their prior removal in a separate step. Although the procedure fails with $\mathbf{4}^{t\text{-Bu}}$, its ethers generally undergo the reaction to give nitrocalix[4]arenes in reasonably good yield. Thus, the tetramethyl ether of $\mathbf{4}^{t\text{-Bu}}$ treated with 20 equiv of 100% HNO_3 gives a 75% yield of the tetranitro compound **180a** (Y^{1-4} = Me). Under less strenuous conditions the tetrapropyl ether of $\mathbf{4}^{t\text{-Bu}}$ reacts with 50 equiv of 65% HNO_3 in CH_2Cl_2–HOAc solution to produce a mixture of trinitro- (**180b**), A,B-dinitro- (**180c**), and A,C-dinitrocalix[4]arenes (**180d**), while with 200 equiv of the same nitrating mixture the trinitro compound **180b** is the only product, formed in 58% yield.[443] The tetrakis(ethoxyethyl)ether of $\mathbf{4}^{t\text{-Bu}}$ is somewhat less reactive than the propyl ether and with 50 equiv of the nitrating mixture gives the mononitro compound **180e** in 73% yield. A particularly interesting case is the *ipso* nitration of the A,C-di-*tert*-butyl compound **179j**, which gives the A,C-dintro compound **180g** rather than the B,D-dinitro compound, *ipso* nitration proceeding more rapidly than direct nitration. Related to this is the selective *ipso* nitration that occurs with partially etherified calixarenes, the *tert*-butyl groups *para* to OH being replaced more rapidly than those *para* to OR.[444] Thus, A,C-diethers of $\mathbf{4}^{t\text{-Bu}}$ give **180h**, accompanied by a small amount (8–12%) of the cyclohexadienone derivative **181**.[444,445]

[442] Nam, K. C.; Kim, D. S. *Bull. Korean Chem. Soc.* **1994**, 15, 284.

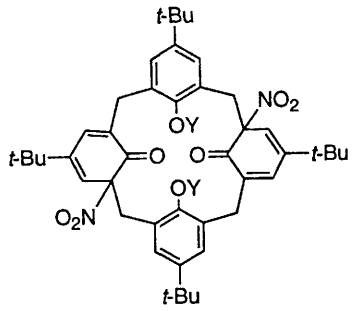
[443] Verboom, W.; Durie, A.; Egberink, R. J. M.; Asfari, Z.; Reinhoudt, D. N. *J. Org. Chem.* **1992**, 57, 1313.

[444] Mogck, O.; Böhmer, V.; Ferguson, G.; Vogt, W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1711.

[445] Cyclohexadienone structures have also been assigned to the incompletely characterized products from the action of Cl_2 on calixarenes in the solid state: Lamartine, R.; Perrin, R.; Perrin, M.; Lecocq, S.; Duchamp, C. *Mol. Cryst. Liq. Cryst.* **1994**, 248, 61.



180



181

a) $R^{1-4} = NO_2$

b) $R^{1,2,3} = NO_2$; R^4 = *t*-Bu, Y^{1-4}= Pr

c) $R^{1,2}$= NO_2; $R^{3,4}$ = *t*-Bu; Y^{1-4} = Pr

d) $R^{1,3} = NO_2$; $R^{2,4}$ = *t*-Bu; $Y^{1,3}$ = H; $Y^{2,4}$ = Pr

e) $R^1 = NO_2$, $R^{2,3,4}$ = *t*-Bu; $Y^{1-4} = EtOCH_2CH_2$

f) $R^{1,3} = NO_2$; $R^{2,4}$ = H ; $Y^{1,3}$ = Pr; $Y^{2,4}$ = H

g) $R^{1,3,} = NO_2$; $R^{2,4,}$ = H; $Y^{1-4} = CH_2CO_2Et$

h) $R^{1,3} = NO_2$; $R^{2,4}$ = H ; $Y^{1,3}$ = H; $Y^{2,4}$ = alkyl

i) $R^{1,3} = NO_2$; $R^2 = CH_2OH$; R^4 = H; Y^{1-4} = Pr

A number of nitrations of the larger calixarenes have been reported. For example, treatment of $\mathbf{6}^{SO_3H}$ and $\mathbf{8}^{SO_3H}$ with HNO_3 affords $\mathbf{6}^{NO_2}$ [446a] and $\mathbf{8}^{NO_2}$,[104,446b] respectively. The hexamethyl ether of $\mathbf{6}^{H}$ has been converted to the corresponding hexanitro compound,[447] and *ipso* nitration takes place selectively on the phenolic rings of **126f**, **126e** and **126d** to give the mononitro compound **182a**, the A,D-dinitro compound **182b**, and the B,D,F-trinitro compound **182c**, respectively.[427,430]

The nitrocalixarenes provide extremely useful intermediates for the introduction of other functional groups, generally *via* the amino calixarenes obtained by reduction with H_2 and Raney Ni,[448] NH_2NH_2 and Raney Ni,[180] NH_2NH_2 and $FeCl_3$,[449] or $SnCl_2$.[450,451] In the calix[4]arene series, mononitro, A,C-dinitro, and tetranitro compounds have been converted to a variety of *N*-substituted products, including the simple monoamide **183a**,[180] the tetraamides **183b**

[446] (a) Shinkai, S.; Tsubaki, T.; Sone, T.; Manabe, O. *Tetrahedron Lett.* **1985**, 26, 3343; (b) Shinkai, S.; Araki, K.; Tsubaki, T.; Arimura, T.; Manabe, O. *J.Chem. Soc., Perkin Trans. 1* **1987**, 2297.

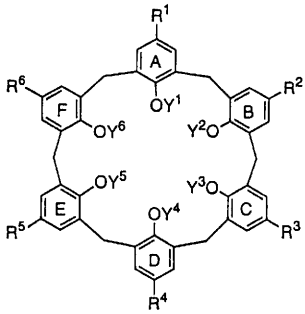
[447] Yilmaz, M.; Deligöz, H. *Synth. React. Inorg. Met.-Org. Chem.* **1993**, 23, 67; Deligöz, H.; Yilmaz, M. *Synth. React. Inorg. Met.-Org. Chem.* **1996**, 26, 943.

[448] Jakobi, R. A.; Böhmer, V.; Grüttner, C.; Kraft, D.; Vogt, W. *New J. Chem.* **1996**, 20, 493.

[449] Shinkai, S.; Arimura, T.; Araki, K.; Kawabata, H.; Satoh, H.; Tsubaki, T.; Manabe, O.; Sunamoto, J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2039.

[450] Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, 59, 3683.

[451] Mislin, G.; Graf, E.; Hosseini, M. W. *Tetrahedron Lett.* **1996**, 37, 4503.



182

a) Y^{1-5} =Me; Y^6 = H; R^{1-5} = t-Bu; $R^6 = NO_2$

b) $Y^{1,2,4,5}$ = Me; $Y^{3,6}$ = H; $R^{1,2,4,5}$ = *t*-Bu; $R^{3,6} = NO_2$

c) $Y^{1,3,5}$ = Me; $Y^{2,4,6}$ = H; $R^{1,3,5}$ = *t*-Bu; $R^{2,4,6} = NO_2$

d) Y^{1-5} =Me; Y^6 = H; R^{1-5} = *t*-Bu; R^6 = Br

e) $Y^{1,3,5}$ = H; $Y^{2,4,6}$ = Me; $R^{1,3,5}$ = Br; $R^{2,4,6}$ = *t*-Bu

(R′ = $ClCH_2$, $MeO_2CCH_2CH_2$, *etc.*),[448] the tetraaroylamide **183c**,[448] the A,C-diamides **183d**,[452] **183e**,[453b] and **183g**,[454,455] the tetraamide **183f**,[451] the tetraurea **183h**,[448,456] the A,C-bis-triazine **183i** (where R′ and/or R″ can be converted to amino functions),[140] and the tetrabenzalamine **183j**.[448,457] Functionalization routes involving nitration have been used only rarely with the larger calixarenes. One of the few examples involves the reduction of the hexamethyl ether of $\mathbf{6}^{NO_2}$ to $\mathbf{6}^{NH_2}$ followed by treatment with chloroglyoxime to yield a calix[6]arene carrying NHC(=NOH)CH=NOH groups in all six *p*-positions.[447]

5.2.4 Sulfonation Routes

One of the earliest of the water soluble calixarenes was made by sulfonation of the upper rim, and this remains a frequently used procedure. Experimental details have been reported for the sulfonation of $\mathbf{4}^{H}$,[446b,458] $\mathbf{5}^{H}$,[459c] $\mathbf{6}^{H}$,[459c] and $\mathbf{8}^{H}$[446b,460] to yield **184a** (Y = H; n = 4, 5, 6, 8). *Ipso* sulfonation can also be effected; for example, $\mathbf{6}^{t\text{-Bu}}$ is directly converted to $\mathbf{6}^{SO_3H}$[461] in 50% yield.

The sulfonatocalixarenes are important in their own right as water soluble compounds but can also serve as intermediates for additional functionalization, generally by conversion to a sulfonamide. Treatment of *p*-sulfonatocalixarenes

[452] van Loon, J.-D.; Janssen, R. G.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron Lett.* **1992**, 33, 5125.

[453] (a) Beer, P. D.; Chen, Z.; Goulden, A. J.; Graydon, A.; Stokes, S. E.; Tear, T. *J. Chem. Soc., Chem. Commun.* **1993**, 1834; (b) Beer, P. D.; Chen, Z.; Goulden, A. J.; Grieve, A.; Hesek, D.; Szemes, F.; Wear, T. *J. Chem. Soc., Chem. Commun.* **1994**, 1269.

[454] Beer, P. D.; Drew, M. G. B.; Hazlewood, C.; Hesek, D.; Hodacova, J.; Stokes, S. E. *J. Chem. Soc., Chem. Commun.* **1993**, 229.

[455] Beer, P. D.; Hesek, D.; Kingston, J. E.; Smith, D. K.; Stokes, S. E. *Organometallics* **1995**, 14, 3288.

[456] Mogck, O.; Böhmer, V.; Vogt, W. *Tetrahedron* **1996**, 52, 8489; Mogck, D.; Pons, M.; Böhmer, V.; Vogt, W. *J. Am. Chem. Soc.* **1997**, 119, 5706.

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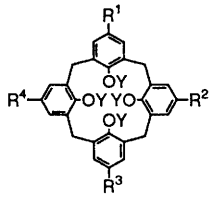
[458] Chawla, H. M.; Hooda, U.; Singh, V. *Synth. React. Inorg. Met.-Org. Chem.* **1996**, 26, 775.

[459] (a) Shinkai, S.; Mori, S.; Tsubaki, T.; Sone, T.; Manabe, O. *Tetrahedron Lett.* **1984**, 25, 5315; (b) Shinkai, S.; Mori, S.; Koreishi, H.; Tsubaki, T.; Manabe, O. *J. Am. Chem. Soc.* **1986**, 108, 2409; (c) Shinkai, S.; Koreishi, H.; Ueda, K.; Arimura, T.; Manabe, O. *J. Am. Chem. Soc.* **1987**, 109, 6371.

[460] Shinkai, S.; Araki, K.; Manabe, O. *J. Chem. Soc., Chem. Commun.* **1988**, 187.

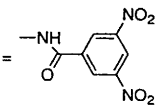
[461] Shinkai, S.; Kawaguchi, H.; Manabe, O. *J. Polym. Sci.* **1988**, 26, 391.

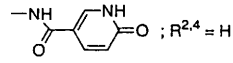


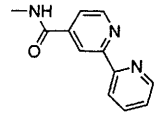
183

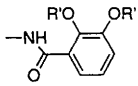
a) R^1 = NHCOR^1; R^{2-4} = *t*-Bu or H

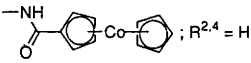
b) R^{1-4} = NHCOR'

c) R^{1-4} = 

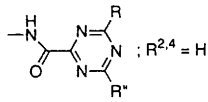
d) $R^{1,3}$ =  ; $R^{2,4}$ = H

e) $R^{1,3}$ =  ; $R^{2,4}$ = H

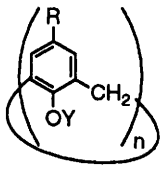
f) R^{1-4} = 

g) $R^{1,3}$ =  ; $R^{2,4}$ = H

h) R^{1-4} = NHCONHR

i) $R^{1,3}$ =  ; $R^{2,4}$ = H

j) R^{1-4} = N=CHAr



184

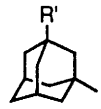
a) R = SO_3H

b) R = SO_2Cl

c) R = SO_2Cl; Y = CH_2COCl

d) R = SO_3H; Y = CH_2CO_2Me

e) R = $SO_2NR'R''$

f) R =  n = 4

g) R =  n = 4

h) R = CH_2Cl n = 4,6,8

i) R = CH_3

j) R = CH_2CH_3

k) R = CH_2Ar

l) R = CH_2OR

m) R = CH_2SCOCH_3

n) R = CH_2SH

o) R = CH_2NR_2 or $CH_2\overset{\oplus}{N}R'_3$

p) R = $CH_2PO(OEt)_2$

q) R = $CH_2PO_3H_2$

r) R = 

with $SOCl_2$ yields the chlorosulfonyl compounds **184b**, an interesting example being **184b** (Y = CH_2CO_2H; $n = 4$) which produces acid chloride functions not only on the sulfonato groups but also on the carboxyl groups to give **184c** ($n = 4$).[462] Owing to the greater reactivity of the carbonyl chloride groups, **184c** ($n = 4$) can be easily converted to **184d** ($n = 4$). *p*-Chlorosulfonatocalixarenes can also be obtained directly by treatment of a *p*-H-calixarene with HSO_3Cl. For example, with the calix[4]arene **184** (R = H; Y = CH_2CONEt_2; $n = 4$), chlorosulfonation yields either the A,C-bis(chlorosulfonyl) compound or the tetra(chlorosulfonyl) compound **184b** (Y = CH_2CONEt_2; $n = 4$), depending on the reaction conditions.[463] *p*-Chlorosulfonyl calixarenes react (a) with NH_3 to

[462] Casnati, A.; Ting, Y.; Berti, D.; Fabbi, M.; Pochini, A.; Ungaro, R.; Sciotto, D.; Lombardo, G. G. *Tetrahedron* **1993**, 49, 9815.

[463] Morzherin, Y.; Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1993**, 58, 7602.

give the simple sulfonamides **184e** (R = R′ = H; Y = CH_2CH_2OMe; $n = 4$)[463] and **184e** (R = R′ = H; Y = H; $n = 6$),[461] (b) with simple amines like propylamine and *tert*-butylamine to give *N*-alkylsulfonamides, and (c) with various ethanolamines[464] to yield the water soluble sulfonamides[463] such as **184e** (R′ and R′ = CH_2CH_2OH; Y = H; $n = 4, 6, 8$).[465]

5.2.5 Diazo Coupling Route

The first reported calixarene diazo coupling involved the reaction of *p*-nitrobenzenediazonium tetrafluoroborate with $\mathbf{4}^{H}$.[466] Unexpectedly, it proceeded in an autocatalytic fashion to give **185e** as the almost exclusive product with only small amounts of **185a–d**. Benzenediazonium, *p*-methylbenzenediazonium, *p*-methoxybenzenediazonium, and *p*-carboxybenzenediazonium chlorides react in comparable fashion to give the corresponding tetrasubstituted compounds **185e**.[206b] However, by limiting the amount of the diazonium salt prepared from 6-amino-1,3-benzodioxin and by adding the calixarene to the diazonium solution, the monosubstituted **185a**, A,B-disubstituted **185b**, A,C-disubstituted **185c**, and trisubstituted **185d** have been isolated and characterized.[467a] Calix[4]arenes carrying fewer than four arylazo groups have also been prepared from calix[4]arenes substituted with other groups (*e.g.* allyl[467b]) at one or more of the *p*-positions.

5.2.6 Alkylation (including Chloromethylation) Route

Friedel–Crafts alkylation of $\mathbf{4}^{H}$ has been carried out with *i*-PrBr and $FeCl_3$ to yield 63% of $\mathbf{4}^{i\text{-Pr}}$,[468] with 1-hydroxyadamantane in F_3CCO_2H[469] to yield **184f** (Y = H), with methoxycycloheptatriene[470] to yield **184r**, and with other alkyl chlorides in the presence of $AlCl_3$ in $CHCl_3$ solution.[471] With a 1-hydroxyadamantane carrying a *p*-methylsulfonylphenyl group at the 3-position the reaction can be controlled to yield mainly the A,B-diadamantyl compound at 20–50 °C, the triadamantyl compound at 60–70 °C, or the tetraadamantyl compound at 80–90 °C,[472] in which R′ = $MeC_6H_4SO_2$. With cyclohexene and HBF_4, $\mathbf{4}^{H}$ affords a 42% yield of *p*-cyclohexylcalix[4]arene **184g** (Y = H).[473]

[464] Grote Gansey, M. H. B.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron Lett.* **1994**, 35, 7127.
[465] Shinkai, S.; Kawabata, H.; Matsuda, T.; Kawaguchi, H.; Manabe, O. *Bull. Chem. Soc. Jpn.* **1990**, 63, 1272.
[466] Shinkai, S.; Araki, K.; Shibata, J.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* **1989**, 195.
[467] (a) Yeh, M.-l.; Tang, F.-s.; Chen, S.-l.; Liu, W.-c.; Lin, L.-g. *J. Org. Chem.* **1994**, 59, 754; (b) Shu, C.-m; Yuan, T.-s.; Ku, M.-c.; Ho, Z.-c.; Liu, W.-c.; Tang, F.-s.; Lin, L.-g. *Tetrahedron* **1996**, 52, 9805.
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[470] Wendel, V.; Abraham, W. *Tetrahedron Lett.* **1997**, 38, 1177.
[471] Zheng, Y.-S.; Huang, Z.-T. *Synth. Commun.* **1997**, 27, 1237.
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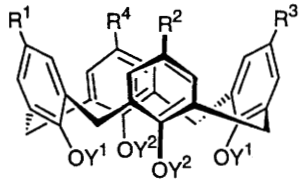
[473] Arduini, A.; Pochini, A.; Rizzi, A.; Sicuri, A. R.; Ugozzoli, F.; Ungaro, R. *Tetrahedron* **1992**, 48, 905.

With propylene and a $NiSO_4/Al_2O_3$ catalyst in a solid state reaction, $\mathbf{4}^{H}$ gives 51% of $\mathbf{4}^{i\text{-}Pr}$.[474]



185

a) R^1 = N=NAr; $R^{2,3,4}$ = H

b) $R^{1,2}$ = N=NAr; $R^{3,4}$ = H

c) $R^{1,3}$ = N=NAr; $R^{2,4}$ = H

d) $R^{1,2,3}$ = N=NAr; R^4 = H

e) $R^{1\text{-}4}$ = N=NAr

f) $R^{1,3}$ = COMe; $R^{2,4}$ = H; Y^1 = Me; Y^2 = H

g) $R^{1,3}$ = COMe; $R^{2,4}$ = H; Y^1 = H; Y^2 =Me

Chloromethylation is the most useful of the Friedel–Crafts alkylation procedures. It was first introduced in the late 1980s by Ungaro and coworkers,[475] who used a chloromethyl alkyl ether in the presence of a Lewis acid such as $SnCl_4$ to place a CH_2Cl group on the *p*-position of the calixarene ring. Thus, **184h** (Y = H or alkyl; n = 4, 6, 8) are produced from $\mathbf{4}^{H}$, $\mathbf{6}^{H}$, and $\mathbf{8}^{H}$ or their *O*-alkyl ethers. An alternative procedure uses paraformaldehyde along with a mixture of acetic acid, phosphoric acid, and conc HCl to give, for example, *p*-tetrakis(chloromethyl)calix[4]arene **184h** (Y = Pr)[476] from the tetrapropyl ether of $\mathbf{4}^{H}$. Another procedure uses paraformaldehyde and trimethylchlorosilane with $SnCl_4$ to accomplish the same reaction starting with the tetraethyl ether.[358,430] Selective chloromethylation can, of course, be carried out on partially *O*-alkylated calixarenes as, for instance, with the A,C-dimethyl ether of $\mathbf{4}^{H}$ which gives an 81% yield of the bis-chloromethyl compound.[477]

The particular virtue of the chloromethyl group is the facility with which it can be converted to various other moieties. Reduction with $LiAlH_4$ produces the *p*-methylcalixarene **184i**;[473,475] reaction with MeLi gives the next higher homolog **184j**;[473] treatment with aromatic compounds in the presence of BF_3 gives *p*-arylmethylcalixarenes **184k**,[473] where Ar can be phenyl, 2,4,6-trimethylphenyl, or 1-hydroxy-2,6-dimelthylphenyl (reaction occurs *para* to the phenolic group); displacement with RONa yields ethers **184l**;[315b] displacement with KSCOMe produces the acetylthio compound **184m**,[315b] which can be reduced to the corresponding thiol **184n** with $LiAlH_4$; treatment with thiourea yields **184n** directly;[478] treatment with amines yields **184o** (including water soluble quaternary amines); and treatment with $P(OEt)_3$ gives **184p** which can be hydrolyzed to the corresponding phosphonic acid **184q**.[475]

[474] Yao, B.; Bassus, J.; Lamartine, R. *New J. Chem.* **1996**, 20, 913.
[475] Almi, M.; Arduini, A.; Casnati, A.; Pochini, A.; Ungaro, R. *Tetrahedron* **1989**, 45, 2177.
[476] Ikeda, A.; Shinkai, S. *J. Am. Chem. Soc.* **1994**, 116, 3102.
[477] Huang, Z.-T.; Wang, G.-Q.; Yang, L.-M.; Lou, Y.-X. *Synth. Commun.* **1995**, 25, 1109.
[478] (a) Blanda, M. T.; Griswald, K. E. *J. Org. Chem.* **1994**, 59, 4313; (b) *idem, ibid.* **1994**, 59, 8315.

5.2.7 Acylation and Aroylation Routes

Treatment of calixarenes with acetyl chloride or benzoyl chloride in the presence of $AlCl_3$ at or below room temperature generally results in esterification to give **176**.[288] To achieve *p*-substitution the calixarene ethers have been used[23,315] to give **177** (Y = alkyl; $n = 4, 6$). The esters **176**, however, can be converted to **177** (Y = H) by the Fries rearrangement,[171,479,480] carried out with $AlCl_3$ at higher temperatures. By carrying out the $AlCl_3$-catalyzed acylation of $\mathbf{4}^{H}$ at 70 °C, *p*-substitution can be directly effected, presumably the result of initial *O*-acylation followed by a Fries rearrangement.[165] By using nitrobenzene or a 1:4 mixture of nitromethane and 1,1,2,2-tetrachloroethane as solvent and a 2:1 molar ratio of $AlCl_3$ to calixarene, the direct acylation can even be effected at room temperature.[481] Acylation with ethyl oxalyl chloride is also reported to yield the *p*-acyl product directly.[292] An $AlCl_3$-catalyzed acetylation of the A,C-dimethyl ether of $\mathbf{4}^{H}$ has been reported to occur on the anisole rings to yield the diacetyl compound **185f**,[303] but X-ray crystallographic data indicate that the product is actually **185g**.[482]

A particularly useful acylation involves the introduction of formyl groups onto the upper rim of calixarenes. In most cases the reaction has been carried out by the Gross method[483] using Cl_2CHOMe and a Lewis acid ($SnCl_4$ or $TiCl_4$), but occasionally the Duff method[484] using hexamethylenetetramine and CF_3CO_2H has been employed. First depicted[485a] in 1991 and followed later with experimental details,[485b,486] the selective conversion of the tetraalkyl ethers of calix[4]arene (**186a**) to the monoformyl, A,C-diformyl, triformyl, and tetraformyl compounds **186b**, **186c**, **186d**, and **186e** is described, the selectivities accomplished by careful control of the temperature (− 10 to 40 °C), amount of reagents (14 equiv to 50 equiv) and catalyst ($SnCl_4$ and $TiCl_4$). Special attention is drawn to the product of diformylation, which is almost exclusively the A,C regioisomer **186c** with only a small amount of the A,B-diformyl isomer when the reaction is carried out on the tetra-CH_2CH_2OEt or -CH_2CO_2Et ethers of $\mathbf{4}^{H}$. With the tetraoctyl ether the product is a 45:55 mixture of A,C and A,B products in 25% yield. This is attributed[485b] to the preferential coordination of the catalyst to the two more basic ether chains on the bottom rim, producing a specific deactivation of these aromatic rings and forcing the second formyl group to enter on the remaining site to establish the A,C regiochemistry. Selective formylation is also

[479] (a) No, K. H.; Noh, Y.; Kim, Y. *Bull. Koren Chem. Soc.* **1986**, 7, 442; (b) No, K.; Hong, M. S. *Bull. Korean Chem. Soc.* **1990**, 11, 58; (c) Hwang, K. L.; Ham, S-H.; No, K. *Bull. Korean Chem. Soc.* **1992**, 13, 689; (d) Hwang, K. L.; Ham, S-H.; No, K. H. *Bull. Korean Chem. Soc.* **1993**, 14, 79.

[480] Arimura, T.; Shinkai, S.; Matsuda, T.; Hirata, Y.; Satoh, H.; Manabe, O. *Bull. Chem. Soc. Jpn.* **1988**, 61, 3733.

[481] Huang, Z.-T.; Wang, G.-Q. *Chem. Ber.* **1994**, 127, 519.

[482] Huang, Z.-T.; Wang, G.-Q. *J. Chem. Soc., Perkin Trans. 1* **1993**, 167.

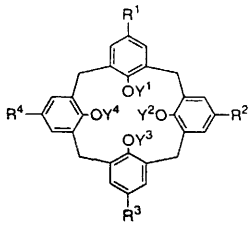
[483] Rieche, A.; Gross. H.; Holt, E. *Chem. Ber.* **1960**, 93, 88.

[484] Smith, W. E. *J. Org. Chem.* **1972**, 37, 3972.

[485] (a) Arduini, A.; Manfredi, G.; Pochini, A.; Sicuri, A. R.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1991**, 936; (b) Arduini, A.; Fanni, S.; Manfredi, G.; Pochini, A.; Ungaro, R.; Sicuri, A. R.; Ugozzoli, F. *J. Org. Chem.* **1995**, 60, 1448.

[486] Kelderman, E.; Derhaeg, L.; Verboom, W.; Engbersen, J. F. J.; Harkerma, S.; Persoons, A.; Reinhoudt, D. N. *Supramol. Chem.* **1993**, 2, 183.

accomplished *via* selective etherification on the lower rim. Thus, treatment of the tetrakis(methoxyethyl) ether or the tetrapropyl ether of $\mathbf{4}^{H}$ with Cl_2CHOMe and $TiCl_4$ yields the A,C-diformyl compounds **186f**.[276] A comparable reaction yielding an A,C-diformylcalix[4]arene has also been effected with hexamethylenetetraamine and F_3CCO_2H.[429] Using the Gross formylation the pentaoctyl ether of $\mathbf{5}^{H}$ has been converted to the *p*-pentaformyl compound.[309] In an extensive paper dealing with selective functionalization of the upper rim of calix[6]arenes,[430] conversions are described of **187a** to the B,D,F-triformyl compound **187c** and of **187b** to the C,F-diformyl compound **187d**. The transformation of **187a** to **187c** proceeds in higher yield (albeit only 18%) using the Duff reaction, but that of **187b** to **187d** gives better yields (94%) using the Gross reaction.



186

a) R^{1-4} = H; Y^{1-4} = Pr or CH_2CH_2OEt

b) R^1 = CHO; $R^{2,3,4}$ = H; Y^{1-4} = Pr or CH_2CH_2OEt

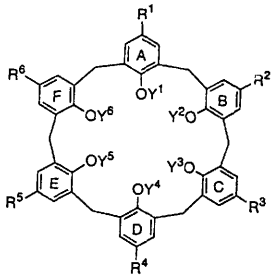
c) $R^{1,3}$ = CHO; $R^{2,4}$ = H; Y^{1-4} = Pr or CH_2CH_2OEt

d) $R^{1,2,3}$ = CHO; R^4 = H; Y^{1-4} = Pr or CH_2CH_2OEt

e) R^{1-4} = CHO; Y^{1-4} = Pr or CH_2CH_2OEt

f) $R^{1,3}$ = CHO; $R^{2,4}$ = H; $Y^{1,3}$ = H; $Y^{2,4}$ = Pr or CH_2CH_2OMe

g) R^{1-4} = Aryl



187

a) $R^{1,3,5}$ = t-Bu; $R^{2,4,6}$ = H; $Y^{1,3,5}$ = Me; $Y^{2,4,6}$ = H

b) $R^{1,2,4,5}$ = t-Bu; $R^{3,6}$ = H; $Y^{1,2,4,5}$ = $CH_2CH_2OCH_2CH_2OMe$; $Y^{3,6}$ = H

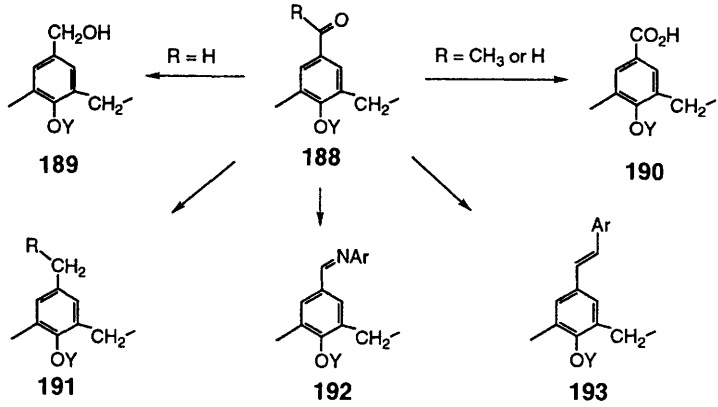
c) $R^{1,3,5}$ = t-Bu; $R^{2,4,6}$ = CHO; $Y^{1,3,5}$ = Me; $Y^{2,4,6}$ = H

d) $R^{1,2,4,5}$ = t-Bu; $R^{3,6}$ = CHO; $Y^{1,2,4,5}$ = $CH_2CH_2OCH_2CH_2OMe$; $Y^{3,6}$ = H

Acyl groups in calixarenes (**188**), especially formyl groups, are useful for conversion to various other functionalities. *p*-Acetylcalix[4]- and -[6]arenes **188** (R = Me) have been oxidized with NaOBr or $NaClO_2$ to the corresponding carboxylic acids **190**;[23,315b] *p*-tetrahexanoylcalix[4]arene (**188**, R = C_5H_{11}) has been reduced to *p*-tetrahexylcalix[4]arene (**191**, R = C_5H_{11}) with Et_3SiH;[165] formylcalixarenes **188** (R = H) have been reduced to *p*-hydroxymethylcalixarenes **189**[424] (and converted, for example, to CH_2O-glycosyl moieties[487]), oxidized to *p*-carboxycalixarenes **190**,[424] condensed with amines to

[487] Marra, A.; Dondoni, A.; Sansone, F. *J. Org. Chem.* **1996**, 61, 5155.

give azomethinecalixarenes **192**,[488] and subjected to Wittig-type reactions to yield *p*-stilbenecalixarenes **193** (Ar = *p*-nitrophenyl,[486] *p*-cyanophenyl,[486] 2-pyridyl,[489] 2-bipyridyl[489]).



Still another route for selective formylation makes use of the tricarbonylchromium complexes of calix[4]arenes. Reaction of the tetrapropyl ether of $\mathbf{4}^{H}$ with $Cr(CO)_3$ produces a complex in which a $Cr(CO)_3$ moiety is associated with a single aromatic residue of the calixarene. Treatment of the complex with BuLi and then D_2O, MeI, or DMF followed by decomplexation with I_2 yields monosubstituted calix[4]arenes carrying D at a *p*- or *m*-position, Me at a *p*-position, and CHO at a *p*-position, respectively.[490]

5.2.8 Arylation Reactions

p-Arylcalix[4]arenes are not readily accessible by the one-step synthesis, so particular interest attends methods for attachment of *p*-aryl groups to preformed calixarenes. One useful route involves the *p*-bromo compounds **178a** (X = Br; Y ≠ H) as starting materials which when treated with BuLi followed by $ArB(OH)_2$ and $Pd(PPh_3)$[181b,428,491] afford *p*-aryl compounds **186g**. A splendid example of the application of this Suzuki-type arylation involves the introduction of four 3-benzyloxyphenyl moieties onto the *p*-positions of the tetrabenzyl ether of $\mathbf{4}^{H}$ to give **186g** (R^{1-4} = 3-benzyloxyphenyl; $Y^{1-4} = CH_2Ph$).[492a] Another *p*-arylation route starts with the *p*-iodo compound **178a** (X = I) and entails photolysis in benzene solution[431] or treatment with PhZnCl in the presence of a nickel catalyst.[431,433,492b]

A method for introducing a pyridinium residue into a calixarene involves the

[488] Komori, T.; Shinkai, S. *Chem. Lett.* **1992**, 901.
[489] Regnouf-de-Vains, J.-B.; Lamartine, R. *Tetrahedron Lett.* **1996**, 37, 6311.
[490] Kikuchi, T.; Iki, H.; Tsuzuki, H.; Shinkai, S. *Supramol. Chem.* **1993**, 1, 103.
[491] Wong, M. S.; Nicoud, J.-F. *Tetrahedron Lett.* **1993**, 34, 8237.
[492] (a) Gleave, C. A.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1994**, 1873; also see ref. 49b; (b) Larsen, M.; Jørgensen, M.; *J. Org. Chem.* **1997**, 62, 4177.

treatment of a trialkyl ether of a *p*-aminocalixarene with 2,4,6-triphenylpyridine in CH_2Cl_2 containing a small amount of AcOH.[493]

5.2.9 Aminomethylation: The *p*-Quinonemethide Route

The *p*-quinonemethide route, introduced in the late 1980s,[294] starts with the reaction of a *p*-H-calixarene with HCHO and a dialkylamine to produce a Mannich base, followed by methylation of the Mannich base to give the quaternary salt, and treatment with two equivalents of a nucleophile to produce a *p*-CH_2Nu-calixarene, as illustrated by the conversion of **194** to **196**. The Mannich reaction appears to occur with greater facility with the fully hydroxylated calixarenes than with their partial ethers, perhaps a consequence of the greater acidity of the former. For example, $\mathbf{4^H}$ reacts smoothly at room temperature (24 h) to afford the tetrakis(dimethylaminomethyl)calix[4]arene,[294] whereas its A,C-dimethyl ether fails to react under these conditions and requires 66 h reaction time in refluxing dioxane.[424] The A,C-dibenzoate and the A,C-diallyl ether of $\mathbf{4^H}$ both fail to undergo the Mannich reaction even at 140 °C.[494]

In some instances the Mannich base itself is the synthesis objective, as with a series of piperazinomethylcalix[4]arenes prepared for X-ray crystallographic analysis,[495] a series of calix[4–8]arenes prepared for their water solubility,[496,497] the dimethylamino product from **27** (R^1 = H; R^2 = Me) prepared to test the *p*-reactivity of these compounds,[41] and the bis-dimethylamino product from **186** ($R^{1,3}$ = *t*-Bu; $R^{2,4}$ = H; Y^{1-4} = Et) prepared to test the reactivity of the two unsubstituted *p*-positions on the upper rim.[423]

The cyanomethylcalix[4]arene **196a** (n = 4), obtained by the action of CN^- on the quaternary salt from **195** (n = 4)[294] has proved to be a particularly valuable intermediate for the synthesis of other *p*-substituted calix[4]arenes, yielding (a) the corresponding carboxymethyl compounds **197a** (n = 4) by hydrolysis;[498] (b) the aminoethyl compounds **197b** (n = 4) by reduction;[294] (c) the aldol condensation products **197d** (n = 4) from condensation with aromatic aldehydes;[283,342] and (d) the α,α-disubstitution products **197c** (n = 4) from strong base-induced condensation with alkyl or aralkyl halides (as large as 2-naphthylmethyl[285]). With weaker bases such as K_2CO_3 it is possible to effect only A,C-di-*O*-alkylation of **196a** (n = 4), but with strong bases both *O*- and *C*-alkylation take place.

To the list of nucleophiles used in the *p*-quinonemethide route (see ref. 1, p. 142) has been added $CH(CO_2Et)_3$, from which calix[4]- and -[8]arenes **196b**

[493] Bitter, L.; Grün, A.; Tóth, G.; Szöllösy, A.; Horváth, G.; Agai, B.; Töke, L. *Tetrahedron* **1996**, 52, 639.

[494] Nam, K. C.; Yoon, T. H. *Bull. Korean Chem. Soc.* **1993**, 14, 169.

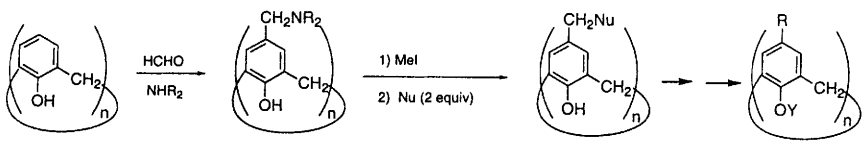
[495] Atwood, J. L.; Orr, G. W.; Bott, S. G.; Robinson, K. D. *Angew. Chem., Int. Ed. Engl.* **1993**, 32, 1093; Atwood, J. L.; Orr, G. W.; Robinson, K. D.; Hamada, F. *Supramol. Chem.* **1993**, 2, 309. The Mannich bases described in these papers should be named as piperazino rather than piperidino compounds.

[496] Gutsche, C. D.; Alam, I. *Tetrahedron* **1988**, 44, 4689; Alam, I.; Gutsche, C. D. *J. Org. Chem.* **1990**, 55, 4487.

[497] Nam, K. C.; Kim. D. *J. Korean Chem. Soc.* **1992**, 36, 933.

[498] Sharma, S. K.; Kanamathareddy, S.; Gutsche, C. D. *Synthesis* **1997**, 1268.

(n = 4 and 8) have been prepared carrying 12 and 24 CO_2Et groups, respectively, on the upper rim.[499] These compounds were transformed to the methyl ethers and treated with tris(hydroxymethyl)methylamine to give the highly water soluble compounds **197e** (n = 4 and 8) called 'silvanols'.



194 **195** **196** **197**

a) Nu = CN
b) Nu = $C(CO_2Et)_3$

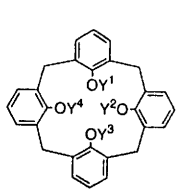
a) R = CH_2CO_2H
b) R = $CH_2CH_2NH_2$
c) R = $-C(R^1)_2-CN$
d) R = $-C(CN)=CH-Ar$
e) R = $CH_2C[CONHC(CH_2OH)_3]_3$

5.2.10 *p*-Claisen Rearrangement Routes

The *p*-Claisen rearrangement, one of the earliest of the methods used for functionalizing the upper rim of calixarenes,[421] has found further application in the 1990s. Recent work of Lin and coworkers has completed the series of *p*-allylcalix[4]arenes by adding the A,B-diallyl, A,C-diallyl, and triallylcalix[4]arenes to the earlier synthesized monoallyl **199a** and tetraallylcalix[4]arenes **199e**.[421] The diallylcalix[4]arenes were prepared by taking advantage of the *O*-alkylation procedures described in Section 5.1.2, wherewith, by proper choice of reaction conditions, the A,B or A,C regiochemistry can be established. Thus, Claisen rearrangements of the A,B and A,C diallyl ethers **198a** and **198b** lead directly to A,B and A,C *p*-diallylcalix[4]arenes **199b** and **199c**, respectively.[467b] However, *p*-triallylcalix[4]arene **199d**, like *p*-monoallylcalix[4]arene **199a**, requires a less direct synthesis route that involves treatment of the A,C-diallyl ether with benzoyl chloride and pyridine followed by allylation to yield the monobenzoate **198c**, removal of the benzoate group by hydrolysis to give the triallyl ether **198d**, and Claisen rearrangement of **198d** to yield *p*-triallylcalix[4]arene **199d**.[500]

The Claisen rearrangements of the hexaallyl ether, the A,C,E-triallyl ether, and the A,D-diallyl ether of calix[6]arene are reported to proceed in 21% yield,[288] 42% yield,[430] and 81%,[316] respectively. It has recently been shown that the rearrangement of the hexaallyl ether can be effected in much higher yield by carrying out the reaction in the presence of a silylating agent followed by hydrolysis of the resulting *O*-silyl ether, a procedure that applies with equal facility to the rearrangement of the pentaallyl ether of $\mathbf{5}^{H}$, the octaallyl ether of $\mathbf{8}^{H}$, and Claisen rearrangements of various other calixarene allyl ethers.[501]

[499] Newkome, G. R.; Hu, Y.; Saunders, M. J.; Fronczek, F. R. *Tetrahedron Lett.* **1991**, 32, 1133.
[500] Ho, Z.-c.; Ku, M.-c.; Shu, C.-m.; Lin, L.-g. *Tetrahedron* **1996**, 52, 13189.



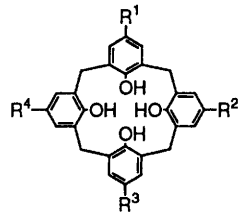
198

a) $Y^{1,2} = CH_2CH{=}CH_2$; $Y^{3,4} = H$

b) $Y^{1,3} = CH_2CH{=}CH_2$; $Y^{2,4} = H$

c) $Y^{1,2,3} = CH_2CH{=}CH_2$; $Y^{4} = COPh$

d) $Y^{1,2,3} = CH_2CH{=}CH_2$; $Y^{4} = H$



199

a) $R^1 = CH_2CH{=}CH_2$; $R^{2,3,4} = H$

b) $R^{1,2} = CH_2CH{=}CH_2$; $R^{3,4} = H$

c) $R^{1,3} = CH_2CH{=}CH_2$; $R^{2,4} = H$

d) $R^{1,2,3} = CH_2CH{=}CH_2$; $R^{4} = H$

e) $R^{1\text{-}4} = CH_2CH{=}CH_2$

The *p*-allyl group is amenable to conversion to a variety of functional groups (see ref. 1, p. 140). Photochemically-mediated addition of HBr produces $CH_2CH_2CH_2Br$;[191b] ozonolysis produces *p*-CH_2CHO from which *p*-CH_2CH_2OH, CH_2CH_2Br, $CH_2CH_2N_3$, and $CH_2CH_2NH_2$ have been generated.[322] Isomerization of $CH_2CH = CH_2$ to $CH = CHCH_3$ by treatment with a rhodium catalyst[322] or with potassium *tert*-butoxide,[423,424] can be followed by ozonolysis to give *p*-CHO.[322,423]

5.2.11 Upper Rim-bridged Calixarenes

5.2.11.1 *Intramolecular Bridges*

Some of the most interesting appendage alterations of calixarenes involve bridge building at the upper rim. Although the earliest success was achieved by fragment condensations, as discussed in Section 2.3, most examples involve the addition of the bridge to the already constructed calixarene framework. A number of these start from the A,C-*p*-diaminocalix[4]arene, obtained by reduction of the *p*-dinitrocalix[4]arene, and proceed to yield compounds of the general structure **200** where the bridge moiety X is the diyne in **200a**,[502] the *p*-phenylene unit in **200b**,[502] the sulfur- and nitrogen-containing spanners in **200c**[503] and **200d**,[450] and a calix[4]arene in **200e**.[504] A particularly striking example is the porphyrin molecule **201** doubly capped on its two faces by a pair of calix[4]arene moieties.[505]

Another group of upper rim-bridged calix[4]arenes employs A,C-*p*-

[501] Gibbs, C. G.; Gutsche, C. D. unpublished results.

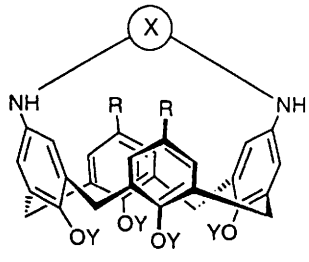
[502] Arduini, A.; McGregor, W. M.; Pochini, A.; Secchi, A.; Ugozzoli, F.; Ungaro, R. *J. Org. Chem.* **1996**, 61, 6881.

[503] Cameron, B. R.; Loeb, S. J. *J. Chem. Soc., Chem. Commun.* **1996**, 2003.

[504] Beer, P. D.; Gale, P. A.; Hesek, D. *Tetrahedron Lett.* **1995**, 36, 767.

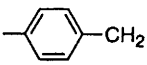
[505] Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron Lett.* **1994**, 35, 7131; *idem. J. Org. Chem.* **1995**, 60, 6585.

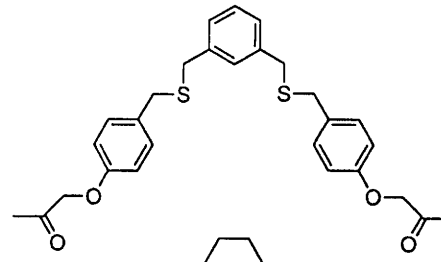
bis(chloromethyl)-, A,C-*p*-bis(hydroxymethyl)-, or A,C-*p*-bis(dialkylaminomethyl) calix[4]arenes as starting materials, which yield compounds of the

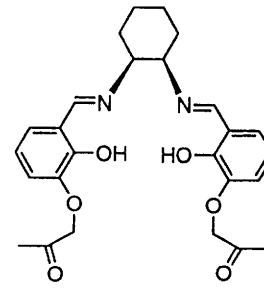


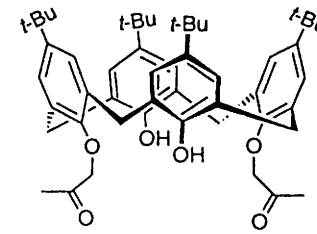
200

a) X = $CH_2C{\equiv}C\text{-}C{\equiv}CCH_2$

b) X = 

c) X = 

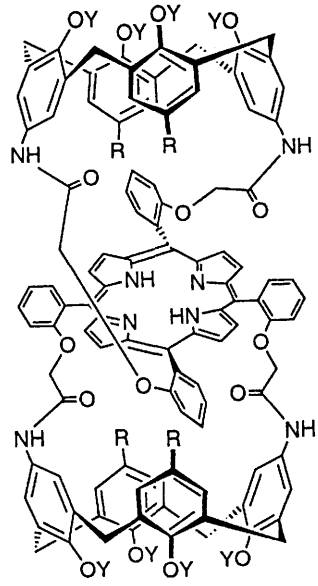
d) X = 

e) X = 

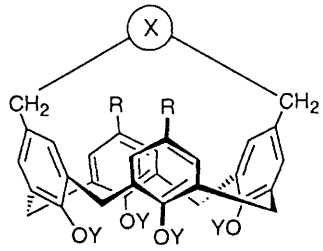
general structure **202** where the bridge moiety is a single oxygen atom in **202a**,[485b,506] an oxyethylene chain in **202b** (n = 0–8),[263] a diyne in **202c**,[323,507] an arylene in **202d** (Ar = *p*-phenyl and 9,10-anthryl)[358,485a] and **202e**,[502] or a bis-Schiff base in **202f**.[508] From the readily available A,C-bis(cyanomethyl)calix[4]arene, hydrolysis of the cyano groups to carboxyl groups followed by cyclization *via* $(COCl)_2$ yields the anhydride **202g**, which provides a useful intermediate for making half esters and half amides by subsequent treatment with alcohols and amines, respectively.[509]

Two-carbon bridges have been constructed by subjecting A,C-diformylcalix[4]arenes **203** to the action of low valent titanium (from $TiCl_4$ and Mg/Hg).[439,506] The product is **204a**, **204b**, or **204c**, depending on the reaction conditions and the identity of R^1/R^2 in **203**.[506] From a 5 h reaction with **203a** the major product is **204a** ($R^{1,2}$ = H), whereas from an 18 h reaction the major

[506] Arduini, A.; Fanni, S.; Pochini, A.; Sicuri, A. R.; Ungaro, R. *Tetrahedron* **1995**, 51, 7951.
[507] Arduini, A.; Cantoni, M.; Graviani, E.; Pochini, A.; Secchi, A. R.; Sicuri, R.; Ungaro, R.; Vicenti, M. *Tetrahedron* **1995**, 51, 599.
[508] Seangprasertkij, R.; Asfari, Z.; Arnaud, F.; Weiss, J.; Vicens, J. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, 14, 141.
[509] Xie, D. J.; Gutsche, C. D. *J. Org. Chem.* **1997**, 62, 2280.



201



202

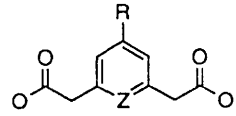
a) X = O

b) X = $OCH_2(CH_2OCH_2)_nCH_2O$

c) X = $OCH_2C{\equiv}C\text{-}C{\equiv}CCH_2O$

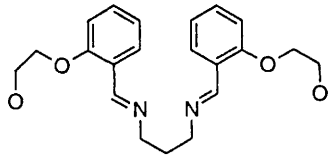
d) X = OCH_2ArCH_2O

e) X =



Z = CH; R = H
Z = N; R = H
Z = N; R = OMe
Z = N; R = NMe_2

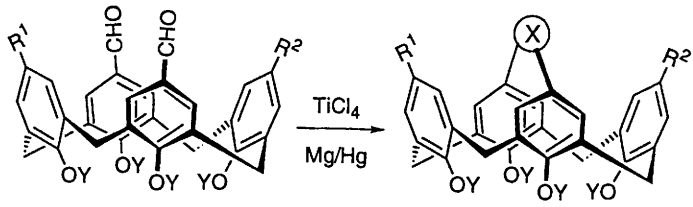
f) X =



g) X = $-C(=O)-O-C(=O)-$

product is **204b** ($R^{1,2}$ = H). Starting with **204b**, however, the alkene **204a** ($R^{1,2}$ = *t*-Bu) and the alkane **204c** ($R^{1,2}$ = *t*-Bu) are produced in a 1:4 ratio. Similarly, **203c** gives a mixture of the alkene **204a** ($R^{1,2}$ = Me) and the alkane **204c** ($R^{1,2}$ = Me), the formyl groups undergoing reduction to methyl groups.

Several examples of upper rim doubly-bridged calix[4]arenes are known. In the case of A,C/B,D bridging the necessary conformation is 1,3-alternate, so the designation 'upper rim' simply specifies that the bridges are attached to the *p*-carbons (*i.e. exo* rim) rather than the phenolic oxygens (*i.e. endo* rim). The



203 **204**

a) $R^{1,2}$ = H

b) $R^{1,2}$ = *t*-Bu

c) $R^{1,2}$ = CHO

a) X = CH=CH

b) X = CHOHCHOH

c) X = CH_2CH_2

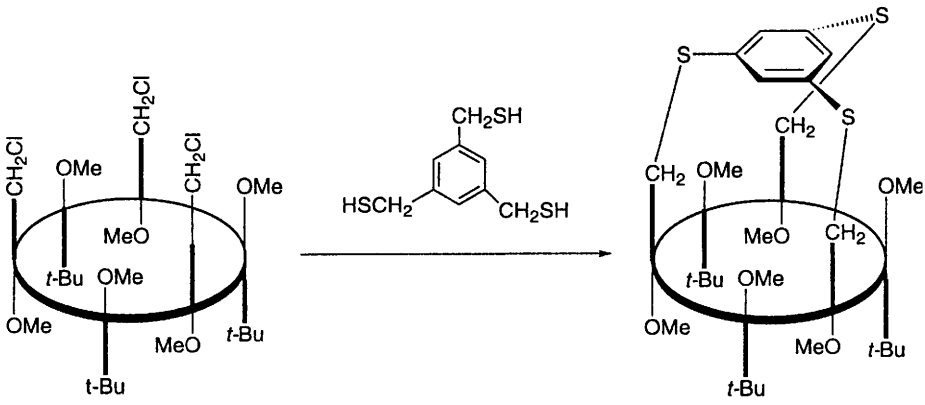
yne-coupling reaction of the 1,3-alternate conformer of *p*-tetrakis(propargyloxymethyl)calix[4]arene **205a** (Y = CH_2Ph) produces the doubly-bridged compound **208a** (Y = CH_2Ph),[323] and treatment of the 1,3-alternate conformer of *p*-tetrakis(chloromethyl)calix[4]arene **205b** (Y = Pr) with catechol gives the A,C/B,D doubly-bridged compound **208b** (Y = Pr).[476] Double anhydride formation of the tetrakis(*p*-bromobenzenesulfonyl) ester of $\mathbf{4}^{CH_2CO_2H}$ in the 1,3-alternate conformation affords good yields of **208d** (Y = $SO_2C_6H_4Br$).[272] Calix[4]arene itself is reported to react with bisdiazonium compounds ($^+N_2ArN_2^+$) to give high yields of the doubly-bridged compounds **208e**.[510] The cone conformer of **205b** (Y = CH_2CH_2OEt) reacts with ethylene glycol to give the A,B/C,D doubly-bridged compound **206a**;[358] the cone conformer of **205c** (Y = $EtOCH_2CH_2$) reacts with 1,2-bis(bromomethyl)benzene to give the doubly-bridged compound **206d**.[478a,b] From the reaction of the cone conformer of **205b** (Y = Pr) with salicylic acid or 3-hydroxymethyl-2-naphthol, the A,B/C,D doubly-bridged compounds **206e**[511] and **206f**[512] are formed. However, treatment of the conformationally mobile **205b** (Y = Me) with catechol or resorcinol yields mixtures containing varying amounts of the cone, 1,2-alternate, and 1,3-alternate conformers of the doubly bridged compounds **206b** and **206c**, **207a** and **207b**, and **208b** and **208c**, the ratio depending on the bridging unit (*i.e.* catechol or resorcinol) and the reaction conditions.[511]

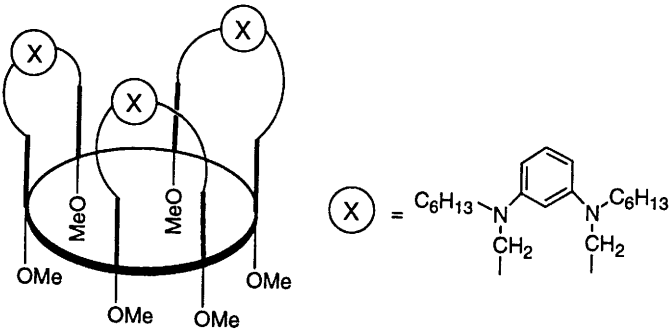
In contrast to the calix[4]arenes, only a few examples have been reported of upper rim bridges in the larger calixarenes. Treatment of the A,C,E-tris(chloromethyl)calix[6]arene **209** with 1,3,5-tris(mercaptomethyl)benzene gives a 28% yield of **210** as a conformationally immobile calix[6]arene.[270] Treatment of the hexamethyl ether of $\mathbf{6}^{CH_2Cl}$ with N,N′-hexyl-1,3-phenylenediamine produces the triply-bridged **211**.[513] The intramolecular upper rim bridging of $\mathbf{8}^{H}$ by treatment with the bis-diazonium salt from 4,4′-diaminobiphenyls has been reported to yield tetra-bridged calix[8]arenes in which the four bridges are specified as

[510] Chawla, H. M.; Srinivas, K. *J. Org. Chem.* **1996**, 61, 8464.
[511] Ikeda, A.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2671.
[512] Ikeda, A.; Yoshimura, M.; Lhotak, P.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1945.
[513] Araki, K.; Akao, K.; Ikeda, A.; Suzuki, T.; Shinkai, S. *Tetrahedron Lett.* **1996**, 37, 73.

205
206
207
208
a) R = CH2OCH2C≡CH
b) R = CH2Cl
c) R = CH2SH
d) R = CH2OCH2CH2OH
a) X = CH2OCH2CH2OCH2
b) X =
c) X =
d) X =
e) X =
f) X =
a) X = CH2OCH2C≡CC≡CCH2OCH2
b) X =
c) X =
d) X =
e) X = N=N-Ar-N=N

spanning either the A,B/C,D/E,F/G,H rings[514a] or the A,C/B,D/E,G/F,H rings,[514b] although both assignments have been questioned (see footnote 318 in ref. 14c).





5.2.11.2 *Intermolecular Bridges*

Compound **200e** provides one example in which a pair of calixarenes are intermolecularly joined by a pair of upper rim to lower rim bridges. Other examples of upper rim to upper rim bridging are illustrated by (a) **215a**, obtained in 48% yield by treating *p*-A,C-bis(hydroxymethyl)calix[4]arene with *p*-A,C-bis(chloromethyl)calix[4]arene in the presence of CsOH;[485] (b) **215b** and **215c**, obtained in low yield by double (tandem) Claisen rearrangement of **215b, 215c, 216a** and **216b** from **161c, 166a** and **166b**[368,515] and (c) **215d**, obtained *via* reduction of the Schiff base produced

[514] (a) Chawla, H. M.; Srinivas, K. *Tetrahedron Lett.* **1994**, 35, 2925; (b) Chawla, H. M.; Srinivas, K. *J. Chem. Soc., Chem. Commun.* **1994**, 2593.

[515] Also obtained in 5% yield from a ruthenium-catalyzed reaction of A,C-*p*-diallylcalix[4]arene.[369]

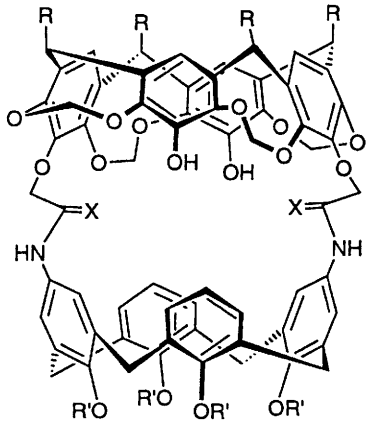
by the condensation of A,C-di-*p*-aminocalix[4]arene with A,C-di-*p*-formylcalix[4]arene.[516]

A rather intriguing example of this type of bridging is compound **215e**, obtained by treating **203a** with dipyrrylmethane. However, in this case the product was isolated in only 0.4% yield and as an incompletely characterized purple microcrystalline powder.[517] Chelation provides still another way for creating juncture, a calixarene carrying *p*-$CH_2CH(COMe)_2$ groups on the A,C rings reacting with Cu^{2+} to form **215f** which contains one metal atom and two calixarene moieties.[518] The 1,3-alternate conformer of **205b**, which can undergo intramolecular bridging to give **208**, can also be intermolecularly bridged, as exemplified by the construction of the 'nano-tube' molecule **217** (Y = Pr).[519] Similarly, the cone conformer of **205b**, which can produce intramolecular bridges, can be intermolecularly bridged to give the 'multiple ansa compound' **218** (Y = $EtOCH_2CH_2$).[520] Another calix[4]arene containing both intra- and intermolecular bridges is **219**, obtained *via* acetylene coupling reactions.[323]

The upper rim to upper rim joining of a pair of calix[4]arenes with four bridges has met with difficulties. An attempt to achieve this by reaction of the cone conformer of **205b** with catechol led instead to intramolecular products,[511] as described above. Another attempt involving the reaction of the cone conformer of **205c** (Y = CH_2CH_2OEt) with CH_2I_2 was initially thought to yield the tetra-bridged dimer,[478a] but later discovered to be an intramolecularly-bridged monomer.[478b] Success has been achieved, however, by treating the cone conformer of the conformationally inflexible tetrapropyl ether **205d** (Y = Pr) with the conformationally flexible tetramethyl ether **205b** (Y = Me) to produce **220** in 12% yield.[521] Using procedures similar to those employed for converting calix[4]resorcarenes to carcerands,[2] $\mathbf{6}^{CH_2Cl}$ has been treated with $\mathbf{6}^{CH_2SH}$ to produce what is believed to be a 'calixarene carcerand' in which the two calixarene units are joined by six spanners.[522] The quadruple linking of a pair of calixarenes of different sizes is represented by **155**, in which the upper rim of a calix[4]arene is joined to the lower rim of a calix[8]arene.[390]

A strategy used by Reinhoudt,[523,524] and others for constructing artificial receptor molecules as biochemical mimics makes use of medium-sized molecules as platforms to which functional groups can be attached. Included among such platforms are calix[4]arenes, calix[4]resorcarenes, cyclodextrins, and porphyrins (see Section 5.1.3.1), which have been combined in various ways. Several striking examples involve the intermolecular linking of calix[4]resorcarenes with

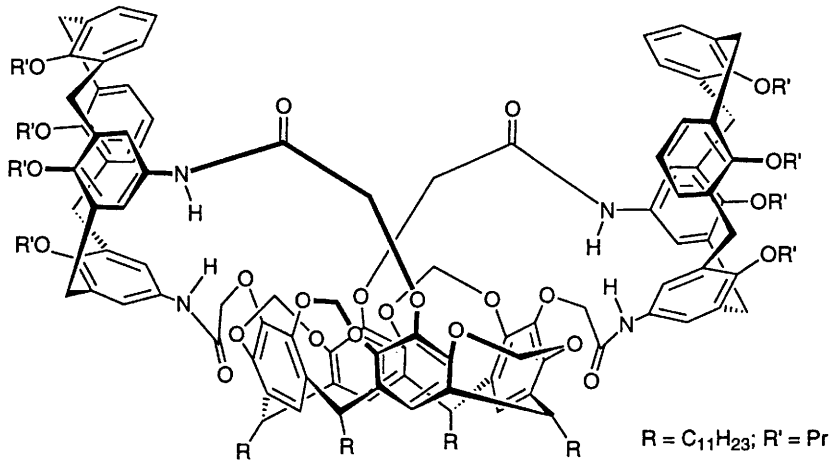
[516] Struck, O.; Chrisstoffels, L. A. J.; Lugtenberg, R. J. W.; Verboom, W.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1997**, 62, 2487.
[517] Asfari, Z.; Vicens, J.; Weiss, J. *Tetrahedron Lett.* **1993**, 34, 627.
[518] Fujimoto, K.; Shinkai, S. *Tetrahedron Lett.* **1994**, 35, 2915.
[519] Ikeda, A.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* **1994**, 2375.
[520] Siepen, A.; Zett, A.; Vögtle, F. *Liebigs Ann. Chem.* **1996**, 757.
[521] Araki, K.; Sisido, K.; Hisaichi, K.; Shinkai, S. *Tetrahedron Lett.* **1993**, 34, 8297.
[522] Arimura, T.; Matsumoto, S.; Teshima, O.; Nagasaki, T.; Shinkai, S. *Tetrahedron Lett.* **1991**, 32, 5111.
[523] Timmerman, P.; Boerrigter, H.; Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1995**, 114, 103.
[524] van Wageningen, A. M. A.; Verboom, W.; Reinhoudt, D. N. *Pure Appl. Chem.* **1996**, 68, 1273.



212

a) X = O

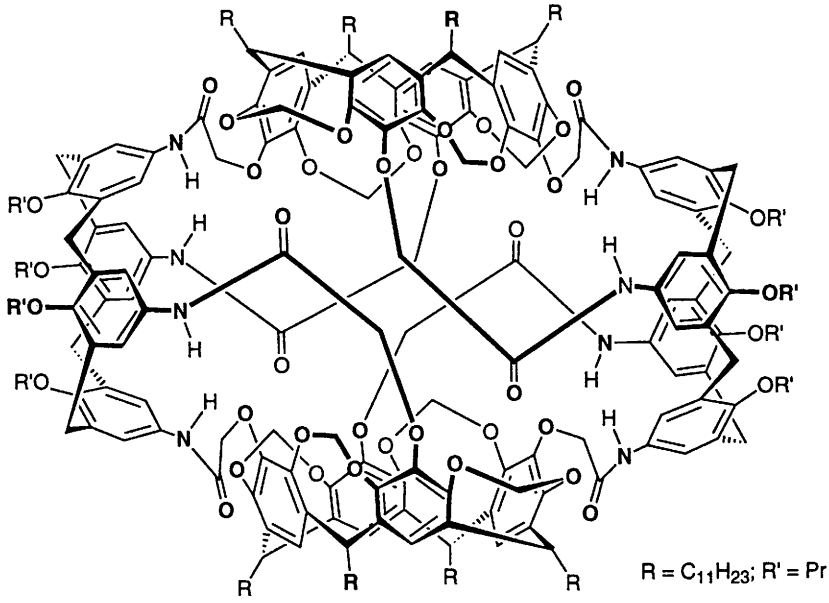
b) X = S



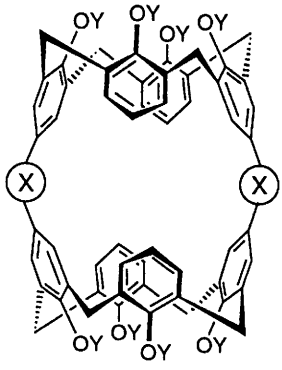
213

calix[4]arenes to give **212**,[120] **213**,[525] and **214**, which is heralded as an organic molecule with a rigid cavity of nanosize dimensions.[120] The advantageous use of Cs_2CO_3 in combination with NaH in creating some of the intermolecular links in these compounds is cited as a good example of a template effect as well as an illustration of the importance of preorganization.[435b]

[525] (a) Timmerman, P.; Verboom, W.; van Veggel, F. C. J. M.; van Duynhoven, J. P. M.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 2345; (b) van Wageningen, A. M. A.; van Duynhoven, J. P. M.; Verboom, W.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1995**, 1941.

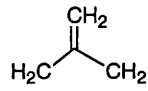


214



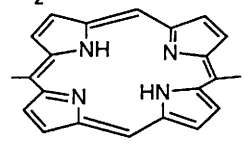
215

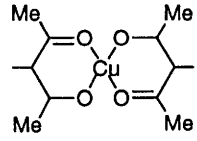
a) X = CH_2OCH_2

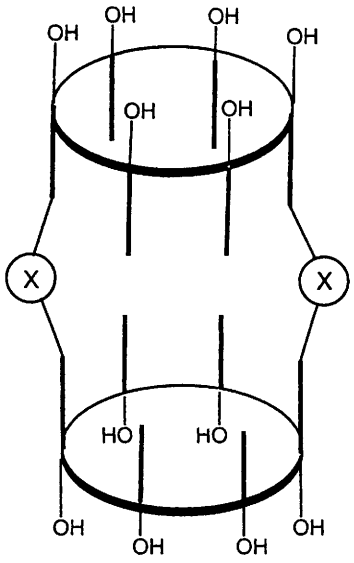
b) X = 

c) X = $CH_2CH{=}CHCH_2$

d) X = $NHCH_2$

e) X = 

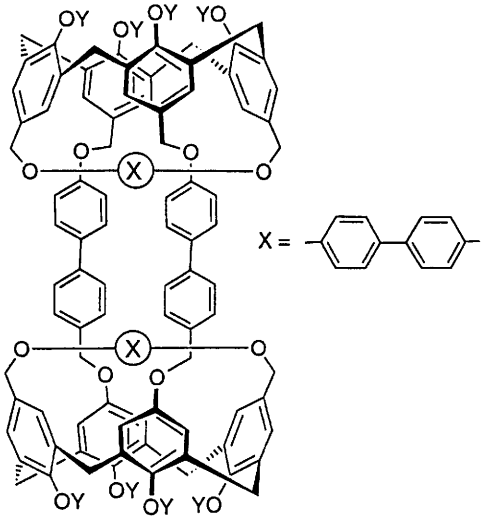
f) X = 



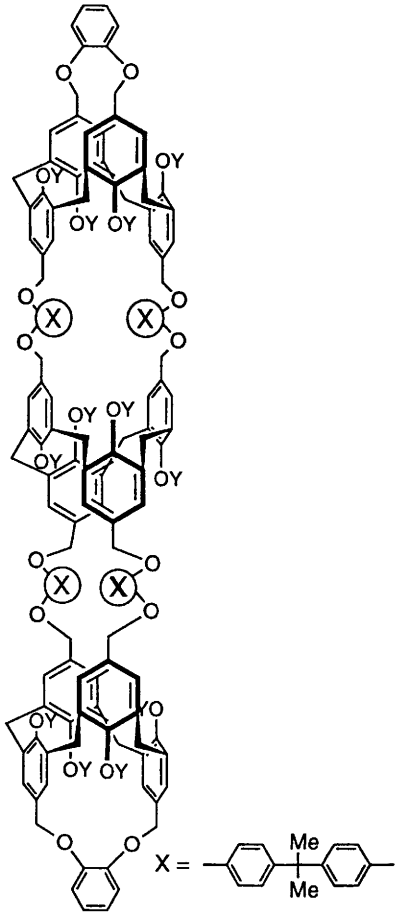
a) X = $OCH_2C(=CH_2)CH_2O$

b) X = $OCH_2CH{=}CHCH_2O$

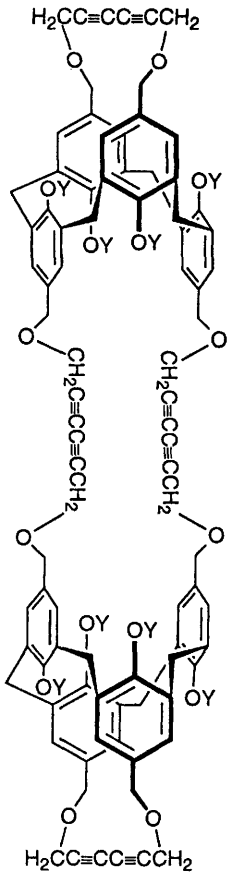
216



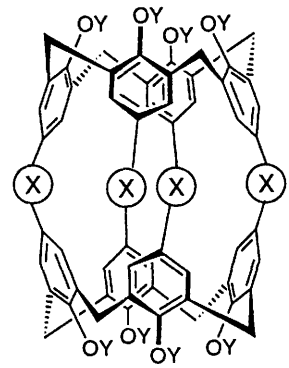
218



217



219



220

X = $CH_2OCH_2CH_2OCH_2$

5.3 Oxidation of Calixarenes

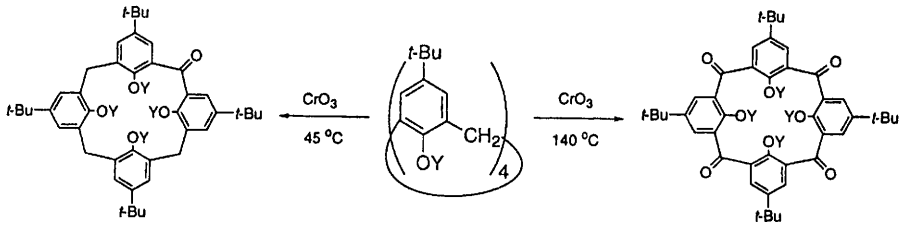
5.3.1 Methylene Group Oxidation

Treatment of the acetates of **4**$^{t\text{-Bu}}$, **6**$^{t\text{-Bu}}$, and **8**$^{t\text{-Bu}}$ with CrO_3 is reported to yield products in which one $ArCH_2Ar$ methylene group is converted to a carbonyl group in the case of **4**$^{t\text{-Bu}}$ and **6**$^{t\text{-Bu}}$ and three methylene groups are converted to carbonyl groups in the case of **8**$^{t\text{-Bu}}$ (regiochemistry of C=O groups unspecified).[526] A more recent study[527] confirms the formation of the monooxo compound **221** from **4**$^{t\text{-Bu}}$ and shows that under more strenuous conditions the tetraoxo compound **222** can be obtained in 90% yield. Wolff–Kishner reduction of **222** yields **4**$^{t\text{-Bu}}$, showing that no alteration of the basic ring system has occurred. Reduction of **222** with $NaBH_4$ converts the four ArCOAr groups to ArCH(OH)Ar groups. Calixarenes possess two important advantages over calix-

[526] Ninagawa, A.; Cho, K.; Matsuda, H. *Makromol. Chem.* **1985**, 186, 1379.

[527] Görmar, G.; Seiffarth, K.; Schulz, M.; Zimmermann, J.; Flämig, G. *Makromol. Chem.* **1990**, 191, 81.

resorcarenes: they can be easily altered at both the top and bottom rims, and they are inherently available in a variety of ring sizes. The calixresorcarenes can claim one important advantage, however: they are readily obtainable with various substituents at the sites of the bridging methylene groups. Ketocalixarenes such as **221** and **222** now offer the potential of allowing the incorporation of this structural feature in the phenol-derived calixarenes, but to date there have been no reports exploring this possibility.



221 **222**

5.3.2 Aromatic Ring Oxidation to Quinones

The first detailed publication of a calixquinone describes three multi-step conversions of $\mathbf{4}^{t\text{-Bu}}$ to the tetraquinone **224a**.[206a,b] One sequence involves the Fries rearrangement of the tetraacetate of $\mathbf{4}^{H}$ to the *p*-tetraacetyl compound **223a** followed by esterification to **223b**, Baeyer–Villiger oxidation to **223c**, hydrolysis to the hydroquinone **223d**, and oxidation to the tetraquinone **224a**. A second sequence involves a Hofmann rearrangement of **223a** to the *p*-tetraacetylamino compound **223e** followed by oxidation to **224a**. A third sequence involves the synthesis of the diazo compound **223f** by diazo coupling followed by reduction to the aminophenol **223g** and oxidation to **224a**.

A one-step method for generating calixquinones was introduced in the 1980s (see ref. 1, p. 146), but details did not appear until 1992 showing that chlorine dioxide converts $\mathbf{4}^{H}$, $\mathbf{5}^{H}$, and $\mathbf{6}^{H}$ to the corresponding calixquinones **224a**, **224b**, and **224c** in *ca.* 30% yields and that thallium trifluoroacetate converts $\mathbf{4}^{t\text{-Bu}}$ directly to calix[4]quinone (**224a**) in 14% yield.[230,528] Unfortunately, the thallium trifluoroacetate procedure does not work with $\mathbf{5}^{t\text{-Bu}}$ and $\mathbf{6}^{t\text{-Bu}}$.

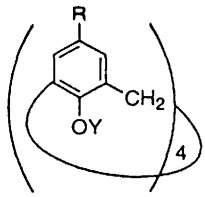
Calix[4]mono- and diquinones have been made by selective removal of *p-tert*-butyl groups from the upper rim and/or by selective etherification or esterification[529] followed by oxidation with $Tl(NO_3)_3$ or ClO_2. Thus, compounds **225a** ($Y^{2\text{-}4} = CH_2CO_2Et$[530] or Y^2Y^3 = the bridging group $CH_2(CH_2OCH_2)_2CH_2$, $Y^4 = Et$)[531] and compounds **225b** ($Y^{2,4}$ = Me, *i*-Pr,[207,424] or Y^2Y^4 = bridging

[528] A similar observation has been reported for the NO_2BF_4 induced oxidation of the bis-dihydroxylated compound **95b** which yields a diquinone.[304]

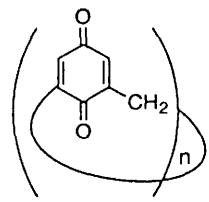
[529] Nam, K. C.; Kim, D. S.; Yang, S. J. *Bull. Korean Chem. Soc.* **1992**, 13, 105.

[530] Toth, K.; Lan, B. T. T.; Jeney, J.; Horváth, M.; Bitter, I.; Grün, A.; Auai, B.; Toke, L. *Talanta* **1994**, 41, 1041.

[531] Yamamoto, H.; Ueda, K.; Samankumara Sandanayake, K. R. A.; Shinkai, S. *Chem. Lett.* **1995**, 497.



223



224

a) R = $COCH_3$; Y = H

b) R = $COCH_3$; Y = Ac

c) R = $OCOCH_3$; Y = Ac

d) R = OH; Y = H

e) R = $NHCOCH_3$; Y = H

f) R = N=NAr; Y = H

g) R = NH_2; Y = H

a) n = 4

b) n = 5

c) n = 6

group $CH_2(CH_2OCH_2)_2CH_2$; $Y^{1,3}$ = H)[532] undergo selective oxidation of the phenolic rings to give the corresponding monoquinones **226**[533] and A,C-diquinones **228** in 40–70% yields. In the case of **225b** ($Y^{2,4}$ = Et), two conformers of the A,C-diquinone were isolated, one with the ArOEt rings *syn* and one with them *anti*.[207] In similar fashion, **225c** ($Y^{2,4}$ = Et) containing *tert*-butyl groups on the B,D residues and OH groups on the A,C residues undergoes $Tl(NO_3)_3$ induced oxidation to the diquinone **228b**.[424] With $Tl(OCOCF_3)_3$ as the oxidizing agent, removal of the *tert*-butyl groups is unnecessary, and compounds **225d–g** etherified or esterified on one, two, or three of the phenolic oxygens provide the monoquinone **226b**,[230] the A,B-diquinone **227**,[230] the A,C-diquinone **228b** ($Y^{2,4}$ = COAr,[230] Et, *n*-Pr,[534] or CH_2CO_2Et[535]), and the triquinone **229**.[230] The yields are generally in the 50–70% range but fall to only 12% for the triquinone.

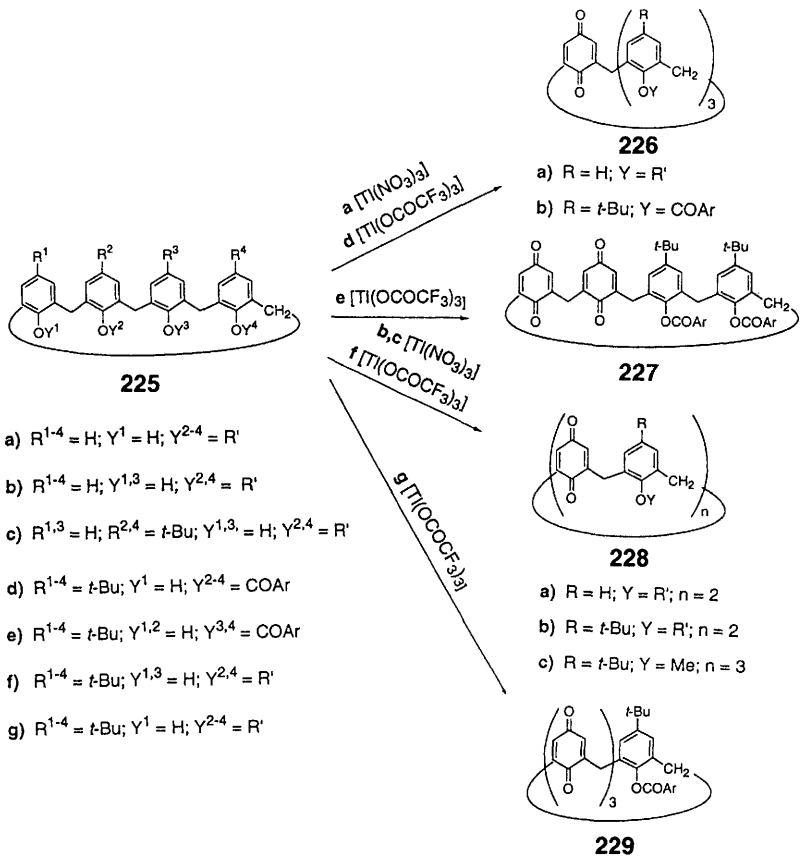
Only a few examples of calix[6]quinones are known in addition to the calix[6]hexaquinone (**224c**). Oxidation of the A,B,D,E-tetrakis(*p*-nitrobenzoate) of $\mathbf{6}^{t\text{-Bu}}$ with $Tl(OCOCF_3)_3$ affords a 49%yield of the A,D-bisquinone **230**,[230] and oxidation of the A,C,E-trimethyl ether of $\mathbf{6}^{t\text{-Bu}}$ yields the A,C,E-triquinone **228c**.[430] Treatment of calixarenes with $K_3Fe(CN)_6$ in the presence of 4-diethylamino-2-methylaniline yields indoanilinocalixarenes, a procedure that has

[532] Yamamoto, H.; Ueda, K.; Suenaga, H.; Sakaki, T.; Shinkai, S. *Chem. Lett.* **1996**, 39.

[533] A calix[4]arene monohemiketal carrying NO_2 groups at the *m*-positions of the quinone ring is obtained in 5% yield from the nitration of the $EtOCH_2CH_2$ ether of $\mathbf{4}^{H}$.[206c]

[534] Reddy, P. A.; Gutsche, C. D. *J. Org. Chem.* **1993**, 58, 3245.

[535] (a) Beer, P. D.; Chen, Z.; Gale, P. A.; Heath, J. A.; Knubley, R. J.; Ogden, M. I.; Drew, M. G. B. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 343; (b) Beer, P. D.; Chen, Z.; Gale, P. A. *Tetrahedron* **1994**, 50, 931; (c) Chen, Z.; Gale, P. A.; Heath, J. A.; Beer, P. D. *J. Chem. Soc., Faraday Trans.* **1994**, 90, 2931.



been applied to the synthesis of a series of indoanilinocalix[4]arenes **231a–c**[536] as well as a mono(indolamino)calix[6]arene **231d**.[537]

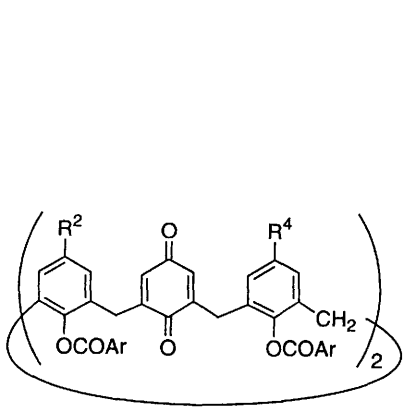
The reactions of the monoquinone **226b** (Y = Et) and diquinone **228b** (Y = *n*-Pr) have been studied in some detail.[534] The diquinone reacts with 2 equiv of malononitrile (pathway involves carbonyl addition, 1,6-conjugate addition, HCN elimination) to give a 68% yield of the tricyano compound **234** which, when treated with a secondary amine, affords dicyanoamines **235**. The calixarene monoquinone undergoes 1,4-conjugate addition with a variety of nucleophiles to give, *inter alia*, compounds **236**, **237**, and **238**.

5.3.3 Aromatic Ring Oxidation to Spirodienones

(for a review, see ref. 12m)

Strong oxidizing agents convert the phenolic rings of calixarenes to quinones, as discussed above, but milder oxidizing agents produce compounds in which one

[536] Kubo, Y.; Tokita, S.; Kojima, Y; Osano, Y. T.; Matsuzaki, T. *J. Org. Chem.* **1996**, 61, 3758.
[537] Kubo, Y.; Maeda, S.; Nakamura, M.; Tokita, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1725.



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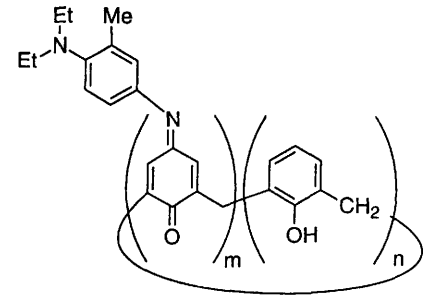


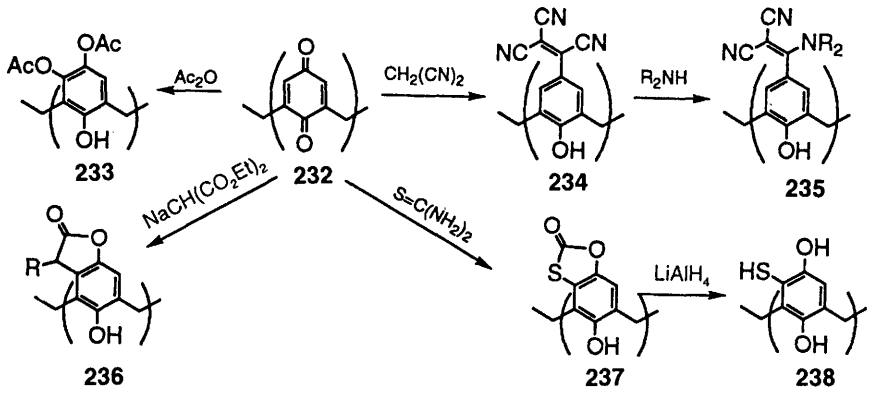
231

a) m = 1; n = 3

b) m = 2; n = 2

c) m = 4; n = 0

d) m = 1; n = 5



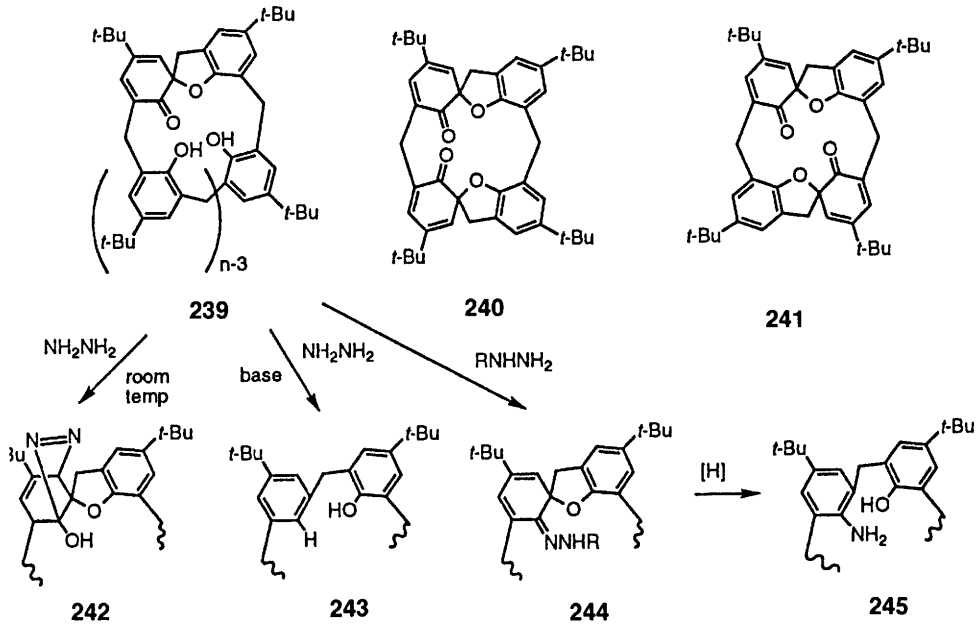
or more of the phenolic rings of the calixarenes are converted to a spirodienone moiety. Thus, the action of 1 equiv of trimethylphenylammonium tribromide on $4^{t\text{-Bu}}$ yields the monospirodienone **239**,[247] while with a larger amount of oxidant the product is a mixture of two A,B-dispirodienones **240** (*R,S* and *R,R/S,S* diastereoisomers) and one of the possible A,C-dispirodienones **241** (*R,S*).[538] The larger calixarenes behave in similar fashion,[539] mild oxidation yielding the monospirodienones **239** (n = 5, 6, 8) and more strenuous oxidation yielding the A,C-dispirodienone from $\mathbf{5}^{t\text{-Bu}}$, the A,B,E- and A,C,E-trispirodienones from $\mathbf{6}^{t\text{-Bu}}$, and the A,C,E,G-tetraspirodienone (1–2% yield) from $\mathbf{8}^{t\text{-Bu}}$.

The calix-spirodienones undergo a variety of reactions and are useful intermediates for effecting alterations at the lower rim. Treatment with NH_2NH_2 at room temperature yields the bridged compound **242**,[418] while under the more

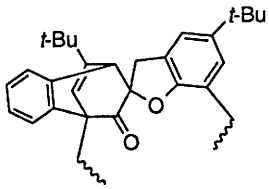
[538] (a) Litwak, A. M.; Biali, S. E. *J. Org. Chem.* **1992**, 57, 1943; (b) Litwak, A. M.; Grynszpan, F.; Aleksiuk, O.; Cohen, S.; Biali, S. E. *J. Org. Chem.* **1993**, 58, 393.

[539] (a) Grynszpan, F.; Biali, S. E. *J. Chem. Soc., Chem. Commun.* **1994**, 2545; (b) Grynszpan, F.; Aleksiuk, O.; Biali, S. E. *Pure Appl. Chem.* **1996**, 68, 1249; (c) Grynszpan, F.; Biali, S. E. *J. Org. Chem.* **1996**, 61, 9512.

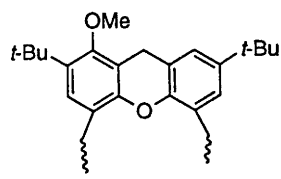
strenuous conditions of the Wolff–Kishner reduction the monodehydroxycalixarene **243** (*cf.* **95a**)[418] is produced. 2,4-Dinitrophenylhydrazine reacts with a calix-spirodienone to yield **244** (R = 2,4-dinitrophenyl) which can be reduced to the monoaminocalixarene **245**[539b] (see Section 5.1.4). The amine, in turn, can be diazotized and converted to the corresponding chloride, bromide, or iodide, although the reactions are complicated by the simultaneous formation of the xanthene **247**.[540] A *p-tert*-butylcalix[4]arene carrying two OH groups and two methyl groups on the lower rim has been prepared by treatment of dispirodienone **241** with MeLi followed by reduction with $MeCO_2H$–Et_3SiH.[541] Diels–Alder addition of benzyne yields **246**,[538,539] and treatment with acid in MeOH yields the xanthene **247**. In a three-step sequence, **247** (from **239**, $n = 6$) can be converted to the xanthone **248** which has been reductively dimerized (Zn/HCl) to **250**.[542] Upper rim alteration has also been observed, as exemplified by the reaction of **241** with conc HCl in MeCN to yield the mono-*p*-chlorocalix[4]arene **249**.[538b] The monospirodienone of a calix[4]arene provides a means for protecting two proximal aromatic rings, thereby allowing reaction to take place at the other two rings as, for example, in the conversion of **239** ($n = 4$) to the monophosphate which can be reduced with K/NH_3 to the calix[4]arene-aminetriol **168b**.[248]



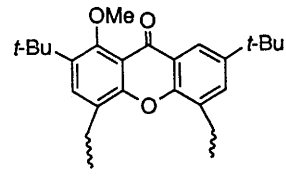
[540] Van Gelder, J. M.; Aleksiuk, O.; Biali, S. E. *J. Org. Chem.* **1996**, 61, 8419.
[541] Van Gelder, J. M.; Brenn, J.; Thondorf, I.; Biali, S. E. *J. Org. Chem.* **1997**, 62, 3511.
[542] Aleksiuk, O.; Biali, S. E. *J. Org. Chem.* **1996**, 61, 5670.



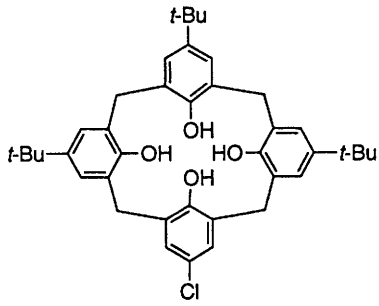
246



247



248



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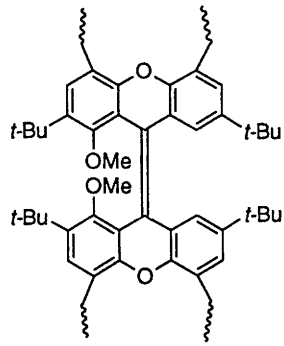

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5.4 Reduction of Calixarenes

In the only report of the reduction of the calixarene framework,[543] **4**^{H} undergoes complete reduction with Raney Ni–PrOH and H_2 at 1450 psi to a mixture of stereoisomeric perhydrocalix[4]arene diethers from which the *trans-syn-trans* isomer was isolated in 15% yield, the structure verified by X-ray crystallography.

5.5 Chiral Calixarenes

(for a review, see ref. 14e)

5.5.1 Chirality *via* External Attachment

The most obvious way to generate a chiral calixarene is by attachment of a chiral moiety. This was achieved as far back as 1979 by esterification with camphorsulfonyl chloride,[544] a chiral moiety which has again more recently been incorporated into a calix[4]arene.[545] Several other examples have also been published describing the attachment of the chiral moiety at the lower rim *via* ether linkage.

[543] Grynszpan, F.; Biali, S. E. *J. Chem. Soc., Chem. Commun.* **1996**, 195.
[544] Gutsche, C. D.; Muthukrishnan, R.; No, K. H. *Tetrahedron Lett.* **1979**, 2213.
[545] Motta, L.; Regnouf-De-Vains, J.-B.; Bavoux, C.; Perrin, M. *J. Chem. Crystallogr.* **1995**, 25, 401.

Included among the ether moieties that have been used are 2-methylbutyl,[546] $CH_2CONHCH(R)CO_2R'$,[547] glycidyl,[548] and bisnaphthol.[549] Perhaps also falling into this category of chiral calixarenes are those in which the chirality is induced by the incorporation of a chiral guest molecule as, for example, the induced circular dichroism that is observed with the complexes between *p*-sulfonatocalixarenes and chiral guests such as trimethyl-1-phenylethylammonium iodide[550] and amino acid methyl esters.[551] It is postulated that steric repulsions between host and guest induce asymmetric deformation of the calixarene, thereby giving rise to its circular dichroism.

5.5.2 Chirality *via* Upper and Lower Rim Substitution Patterns

(for a review, see ref. 14e)

A more subtle way to generate a chiral calixarene is to create dissymmetry or asymmetry within the molecule itself. One of the means for doing this with a calix[4]arene is to establish a substitution pattern of AABC or ABCD on the upper or lower rim, producing a compound that is inherently chiral in all possible conformations. Tabulations of the cone, partial cone, 1,2-alternate, and 1,3-alternate conformers of unsubstituted, mono-*O*-substituted, di-*O*-substituted, tri-*O*-substituted, and tetra-*O*-substituted calix[4]arenes and the specification of the chiral members of this group have been reported by Shinkai[552] and Böhmer.[553] For the temporal resolution of enantiomers of this type to be possible, however, conformational interconversion must be curtailed by placing suficiently large groups on the phenolic oxygens or by building bridges at the upper or lower rim, thus freezing the compound into a cone, partial cone, 1,2-alternate or 1,3-alternate conformation. For a calix[4]arene frozen in the partial cone, 1,2-alternate, or 1,3-alternate conformation, additional substitution patterns may also confer inherent chirality if one or another of the arrangements depicted in Figure 5.3 is established. For example, methanolysis of the bisanhydride **208d** ($Y = SO_2Ar$) yields the conformationally immobile and inherently chiral 1,3-alternate conformer **251** with an AABB substitution pattern.[272] A variety of examples of calix[4]arenes that are inherently chiral by virtue of the upper/lower rim substitution patterns are now known, the earliest being the 1982 report of the adventitious preparation of **252a** carrying two

[546] (a) Shinkai, S.; Arimura, T.; Satoh, H.; Manabe, O. *J. Chem. Soc., Chem. Commun.* **1987**, 1495; (b) Arimura, T.; Edamitsu, S.; Shinkai, S.; Manabe, O.; Muramatsu, T.; Tashiro, T. *Chem. Lett.* **1987**, 2269; (c) Shinkai, S. *J. Inclusion Phenom.* **1989**, 7, 193; (d) Arimura, T.; Kawabata, H.; Matsuda, T.; Muramatsu, T.; Satoh, H.; Fujio, K.; Manabe, O.; Shinkai, S. *J. Org. Chem.* **1991**, 56, 301; (e) Ikeda, A.; Nagasaki, T.; Shinkai, S. *J. Phys. Org. Chem.* **1992**, 5, 699.

[547] (a) Okada, Y.; Kasai, Y.; Nishimura, J. *Tetrahedron Lett.* **1995**, 36, 555; (b) Peña, M. S.; Zhang, Y; Thibodeaux, S.; McLaughlin, M. L.; de la Peña, A. M.; Warner, I. M. *Tetrahedron Lett.* **1996**, 37, 5841.

[548] Neri, P.; Bottino, A.; Geraci, C.; Piattelli, M. *Tetrahedron: Asymmetry* **1996**, 7, 17.

[549] Kubo, Y.; Maeda, S.; Tokita, S.; Kubo, M. *Nature* **1996**, 382, 522.

[550] Morozumi, T.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1219.

[551] Morozumi, T.; Shinkai, S. *Chem. Lett.* **1994**, 1515.

[552] Iwamoto, K.; Shimizu, H.; Araki, K.; Shinkai, S. *J. Am. Chem. Soc.* **1993**, 115, 3997.

[553] Böhmer, V.; Kraft, D.; Vogt, W. *Supramol. Chem.* **1994**, 3, 299.

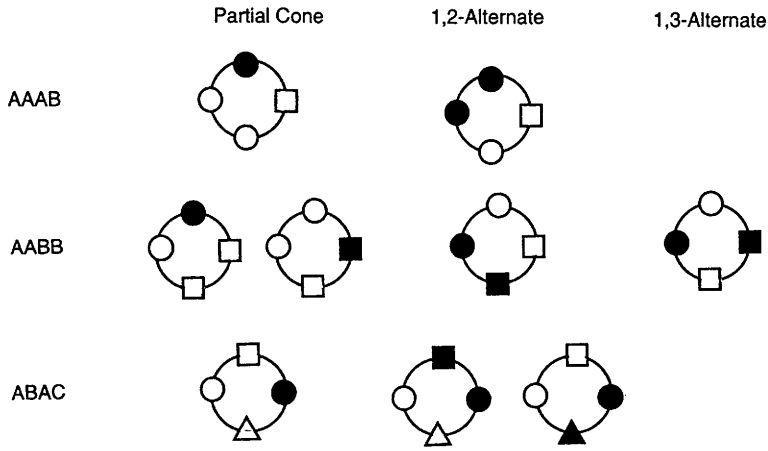
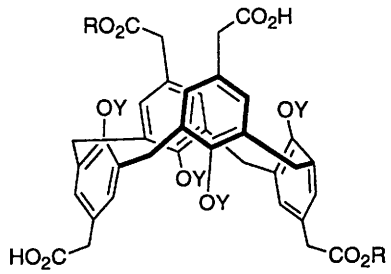


Figure 5.3 *Inherently chiral calix*[4]*arenes with AAAB, AABB, and ABAC substitution patterns*

p-tert-butyl groups, a *p*-acetylphenyl group, and a *p*-acetoxyphenyl group on the upper rim,[554] which establishes an AABC pattern of substitution. By stepwise



251

syntheses, chiral calixarenes as exemplified by **252b**[48] were constructed in the 1980s. However, no attempt was made at that time to separate these compounds into their enantiomers, and it was not until 1990 that the first resolution of an inherently chiral calixarene was accomplished by passing a solution of **252c** (see Table 5.1) through a chiral column.[555] Examples added more recently include compounds **252d–p** shown in Table 5.1. The test for chirality used for some of the examples shown in this table employs the doubling of the ^{1}H NMR resonance patterns in the presence of an optically active shift reagent [*e.g.* (*S*)-(+)-(9-anthryl)trifluoroethanol]; for others it involves the actual resolution, generally by using a chiral column but in at least one instance (**252h**) by conversion to the (−)-menthoxyacetate followed by separation of the diastereoisomers.[552]

[554] No, K. H.; Gutsche, C. D. *J. Org. Chem.* **1982**, 47, 2713.
[555] Iwamoto, K.; Yanagi, A.; Arimura, T.; Matsuda, T.; Shinkai, S. *Chem. Lett.* **1990**, 1901.

Table 5.1 *Chiral calix[4]arenes via upper/lower rim substitution*

Cmpd	*Pattern*	R^1	R^2	R^3	R^4	Y^1	Y^2	Y^3	Y^4	*Conformation*	*Ref.*
252a	AABC	*t*-Bu	*t*-Bu	Ac	OAc	OAc	Ac	Ac	Ac	paco?	554
252b	ABCD	Ph	*t*-Bu	Me	CO_2Et	H	H	H	H	cone	48
252c	AABC	*t*-Bu	*t*-Bu	*t*-Bu	*t*-Bu	CH_2Py	Pr	Pr	H	cone/paco	555
252d	AAAB	*t*-Bu	*t*-Bu	*t*-Bu	*t*-Bu	Pr	Pr	Pr	H	paco/1,2-alt	272
252e	AABB	CH_2CO_2Me	CH_2CO_2Me	CH_2CO_2H	CH_2CO_2H	SO_2Ar	SO_2Ar	SO_2Ar	SO_2Ar	1,2-alt	272
252f	AABB	*t*-Bu	*t*-Bu	*t*-Bu	*t*-Bu	Pr	Pr	H	H	paco/1,2-alt/1,3-alt	552
252g	AABC	*t*-Bu	*t*-Bu	*t*-Bu	*t*-Bu	Pr	Pr	CH_2Py	H	cone/paco	552
252h	AABC	*t*-Bu	*t*-Bu	*t*-Bu	*t*-Bu	Pr	Pr	CH_2Ph	H	cone/paco	552
252i	ABCD	*t*-Bu	*t*-Bu	*t*-Bu	*t*-Bu	CH_2Ph	Pr	CH_2Py	H	cone/paco	552
252j	AABC	*t*-Bu	*t*-Bu	Me	C_8H_{17}	CH_2CO_2Et	CH_2CO_2Et	CH_2CO_2Et	CH_2CO_2Et	cone	62
252k	ABCD	Me	Me	*t*-Bu	*t*-Bu	CH_2CO_2Et	H	CH_2CO_2Et	H	pinched cone	556
252l	ABCD	Ph	Ph	*t*-Bu	*t*-Bu	CH_2CO_2Et	H	CH_2CO_2Et	H	pinched cone	556
252m	AABC	*t*-Bu	*t*-Bu	*t*-Bu	*t*-Bu	CH_2Py	CH_2Py	R′	H	cone/paco	557
252n	AABC	*t*-Bu	*t*-Bu	*t*-Bu	*t*-Bu	$CH_2(CH_2OCH_2)_nCH_2$		CH_2Py	H	cone/paco	558
252o	AAAB	*t*-Bu	*t*-Bu	*t*-Bu	*t*-Bu	Ms	Ms	Ms	H	1,2-alt	559
252p	AABC	H/*t*-Bu	H/*t*-Bu	H/*t*-Bu	H/*t*-Bu	$P(O)(OEt)_2$	$P(O)(OEt_2)$	PhCO	H	cone	560

[556] Böhmer, V.; Wolff, A.; Vogt, W. *J. Chem. Soc., Chem. Commun.* **1990**, 968.
[557] Pappalardo, S.; Caccamese, S.; Giunta, L. *Tetrahedron Lett.* **1991**, 32, 7747.
[558] Pappalardo, S.; Parisi, M. F. *Tetrahedron Lett.* **1996**, 37, 1493.
[559] González, J. J.; Nieto, P. M.; Prados, P.; Echavarren;, A. M.; de Mendoza, J. *J. Org. Chem.* **1995**, 60, 7419.
[560] Markovsky, L. N.; Visotsky, M. A.; Pirozhenko, V. V.; Kalchenko, V. I.; Lipkowski, J.; Simonov, Y A. *J. Chem. Soc., Chem. Commun.* **1996**, 69.

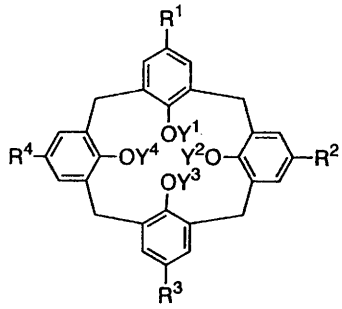
Table 5.2 *Chiral calix*[4]*arenes via* meta *substitution*

Cmpd	R	Z^1	Z^2	Z^3	Z^4	Y^1	Y^2	*Sym*	*Ref.*
253a	*i*-Pr	Me	H	H	H	H	H	C_1	64a
253b	three *i*-Pr; one Ph	Me	H	H	H	H	H	C_1	64a
253c	Me	Me	Me	Me	Me	CH_2CO_2Et	H	C_4	40b, 563
253d	one *i*-Pr; three *t*-Bu	Me	H	H	H	Pr	Pr	C_1	64b, 562
253e	Me or *i*-Pr or Cl	Me	Me	Me	Me	H	H	C_4	40b
253f	H or CH_2Cl or Me_2NCH_2	Me	Me	Me	Me	H	H	C_4	41
253g	four R–Z $(CH)_n$ bridges					CH_2CO_2Et	H	C_4	40b, 563
253h	four R–Z CH=CHCH=CH bridges (*i.e.* naphthalene rings)					CH_2CO_2Et	H	C_4	40b
253i	one R–Z CH=C(COMe)C=CH bridge (*i.e.* acetoxynaphthalene ring); three H					Pr	Pr	C_1	512
253j	*i*-Pr	Me	Me	Me	Me	CH_2CO_2Et	CH_2CO_2Et	C_4	40b
253k	*i*-Pr	Me	Me	Me	Me	CH_2CO_2Et	H	C_2	563
253l	*i*-Pr	Me	Me	Me	Me	one CH_2Ar; three H		C_1	40b
253m	Me	Me	Me	Me	Me	one Bu; three H		C_1	563

Table 5.3 *Chiral calix*[4]*arenes via* meta *substitution*

Cmpd	R^1	R^2	R^3	R^4	Z^1	Z^2	Y	*Sym*	*Ref.*
254a	OH	*t*-Bu	*t*-Bu	*t*-Bu	Nu	H	one H; three Et	C_1	534
254b	OAc	*t*-Bu	OAc	*t*-Bu	OAc	H	two OAc; two Et	C_2	534
254c	NHAc	*t*-Bu or H	*t*-Bu or H	*t*-Bu or H	Br or NO_2	H	four $EtOCH_2CH_2$	C_1	180
254d	NHAc	H	NHAc	H	Br	Br	four Pr	C_2	180

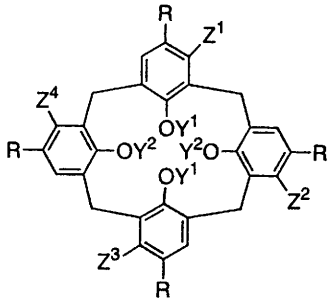
A pair of inherently chiral compounds fixed in the partial cone and 1,2-alternate conformations, respectively, have been made by forming the complex of the tetrapropyl ether of **4**^{H} with $Cr(CO)_3$, which becomes attached to only one of the rings, thereby establishing an AAAB substitution pattern.[561]



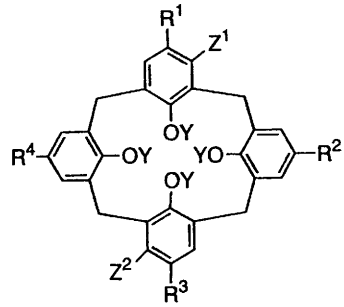
252a-p (See Table 5.1)

5.5.3 Chirality *via meta* Substitution

Still another way to create an inherently chiral calixarene is to introduce a substituent into one or more of the *meta* positions of the calixarene ring. This was first accomplished in 1987 with the synthesis of **253a** (carrying a single methyl group on the A ring; see Table 5.2) and **253b** (carrying methyl groups on both the



253a-m (See Table 5.2)



254a-d (See Table 5.3)

A and C rings, conferring C_2 symmetry).[64a] The first experimental demonstration that calix[4]arenes of this type are chiral appeared in 1990 with **253c**,[40] which showed a doubling of the ^{1}H NMR patterns in the presence of a chiral shift reagent, and with **253d** which was resolved on a chiral column.[64b,562] A variety of other chiral calix[4]arenes based on this principle have been made, as shown in Tables 5.2 and 5.3, including **253g**, **253h**,[40b,563] and **253i**[512] in which the *meta*

[561] (a) Iki, H.; Kikuchi, T.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 669; (b) Iki, H.; Kikuchi, T.; Shinkai, S. *J. Chem. Soc., Perkin Trans.* 1 **1993**, 205.

[562] Shinkai, S.; Arimura, T.; Kawabata, H.; Murakami, H.; Araki, K.; Iwamoto, K.; Matsuda, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1734.

[563] Pickard, S. T.; Pirkle, W. H.; Tabatabai, M.; Vogt, W.; Böhmer, V. *Chirality* **1993**, 5, 310.

and *para* positions are bridged. The resolution of **253f** (R = Me) has been accomplished *via* its tungsten complex, which upon treatment with an optically active diol such as (*S,S*)-(−)-hydrobenzoin yields a pair of diastereoisomers separable by ordinary HPLC procedures.[400] For the compounds shown in Table 5.2 the *meta* substituents are incorporated during the construction of the calixarene framework. Another approach is to introduce them at a later point, as illustrated by **253a,b** (see Table 5.3)[534] which are made from the calix[4]mono- and diquinones **226** and **228**, respectively, and by **254c,d**[180] which are made by bromination or nitration of the mono- and A,C-di-*p*-acetylamino compounds derived from the precursor *p*-nitro compounds (*e.g.* **180e,d**). Compounds such as **206e** and **206f**, which contain unsymmetrical upper rim bridges, resemble the *m*-substituted calix[4]arenes except that the handedness in the molecule now resides in the bridge rather than in the calixarene ring. If the substitution pattern is A,B/A,B the compound is chiral; if it is A,B/B,A the compound has a plane of symmetry and is achiral. The HPLC resolution of chiral **206f** on a chiral column shows a particlularly large separation factor of 3.17.[512]

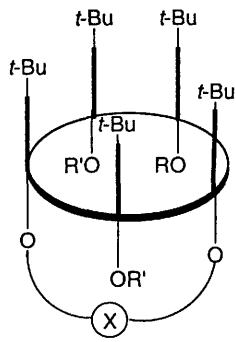
Far less attention has been given to the generation of chirality in the larger calixarenes. Of course, possibilities for establishing inherent chirality by appropriate upper/lower rim substitution are the same for the larger calixarenes as for the cyclic tetramer. For example, a BBAAAA-substituted calix[6]arene is achiral in the **u**,u,u,u,u,u conformation but chiral, *inter alia*, in the **u**,d,u,u,u,u conformation; a BBABAA-substituted calix[6]arene is chiral in all conformations. Only a few of the many chiral compounds that are possible in these larger systems have been synthesized at the present time. Several *p-tert*-butylcalix[5]arenes **255a** have been made that contain an A,C bridge along with a substituent on the oxygen of the D ring, establishing an ABACA substitution pattern that renders them inherently chiral.[216] The inherently chiral A,B-dibenzyl ether of $\mathbf{6}^{t\text{-Bu}}$ with the **u**,d,u,u,u,u conformation,[145] the A,B,D trisubstituted calix[6]arene **98f**,[226] and the A,D-bridged B,E-diarylmethyl ether **150i** (two Y = CH_2Ar)[124] have been prepared, although no tests for chirality were reported. The chiral calix[6]arene **256** has been synthesized by inserting a lower rim 4-methoxyxylenyl bridge across the A,C rings.[564] Its chirality was proved by resolution, and its temperature independent ^1H NMR spectrum was cited in support of the conformational immoblity of the system. Chiral calix[8]arene systems may be established by the formation of dimetallic complexes in which the chirality arises from the coordination geometry at the metal centers[565] and have also been generated through double bridging, compound **139** containing A,D and B,E bridges being inherently chiral.[374]

[564] Otsuka, H.; Shinkai, S. *J. Am. Chem. Soc.* **1996**, 118, 4271.

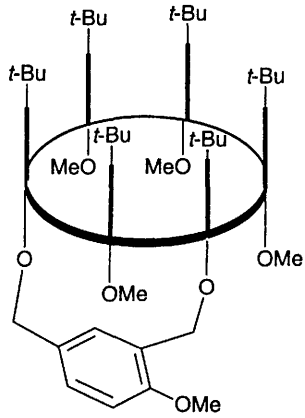
[565] (a) Furphy, B. M.; Harrowfield, J. M.; Kepert, D. L.; Skelton, B. W.; White, A. H.; Wilner, F. R. *Inorg. Chem.* **1987**, 26, 4231; (b) Hofmeister, G. E.; Hahn, F. E.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, 111, 2318; (c) Hofmeister, G. E.; Alvarado, E.; Leary, J. A.; Yoon, D. I.; Pedersen, S. F. *J. Am. Chem. Soc.* **1990**, 112, 8843.

5.5.4 Chirality in Calixarene-related Systems

The interesting stereochemical possibilities for the large-ring spherand-type calixarenes **16**, which include compounds with D_3 and D_4 symmetry, are discussed in ref. 14e. The intriguing stereochemistry of the calixarene spirodienones



255



256

a) X = $CH_2(CH_2OCH_2)_3CH_2$; R = Me, CH_2CO_2Et, COEt, COAr; R' = H

b) X = $CH_2CH_2OCH_2CH_2O$ (t-Bu) $OCH_2CH_2OCH_2CH_2$; R = R' = Me or 2-Pyridyl

239–241 is discussed in refs. 538 and 539. The concept of 'pseudo-C_2-symmetry' as applied to the dimethyl ether of *p-tert*-butyldihomooxacalix[4]arene (**67**) is discussed in refs. 14e and 566 for an A,B-diether in the u,d,u,u conformation.

5.6 Selective Functionalization

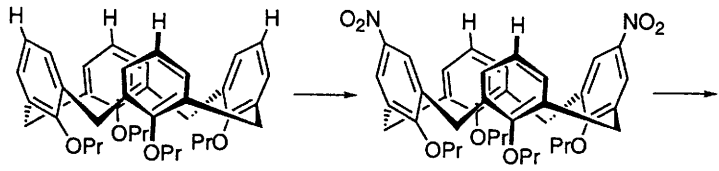
Selective functionalization of calixarenes is of central importance for the construction of compounds to serve in various capacities such as polyfunctional ion binders, molecular complexing agents, and enzyme mimics. Many examples of selective functionalization have already been included in the preceding sections, and only a few additional ones are presented in this section as representative of the present state of the art.

The European consortium of calixarene chemists have provided several good illustrations of polyfunctionalization sequences with a calix[4]arene which rely solely on upper rim selectivities. For example, starting with the tetrapropyl ether **257**, prepared by alkylation of $\mathbf{4}^{H}$, nitro groups were introduced on the A and C rings by treatment with HNO_3 at room temperature[106] to give **258**, a single iodine atom was added using 1 equiv of CF_3CO_2Ag/I_2 to yield **259**, and this was

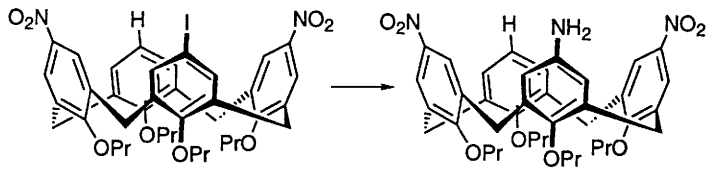
[566] Araki, K.; Inada, K.; Shinkai, S. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 72.

treated with phthalimide followed by NH_2NH_2 cleavage to produce the amino compound **260**.[432]

In contrast to the example just presented, most routes for selective functionalization on the upper rim take advantage of the relative ease with which selective functionalization on the lower rim can be effected. Procedures have been described in Section 5.1 for preparing mono-, di-, tri-, and tetraethers and -esters of calix[4]arenes. Comparably selective procedures are less available at the present



257 **258**



259 **260**

time for the larger calixarenes but will, no doubt, be forthcoming in the future. The great virtue of selective esterification and etherification is that it creates a significant difference in the reactivity at the *p*-positions, *viz.* the ArOH moieties are more susceptible to electrophilic substitution. This makes possible the selective removal of *tert*-butyl groups and, in turn, the selective introduction of other groups by one or another of the methods discussed in Section 5.2.

5.7 Calixarene Polymers

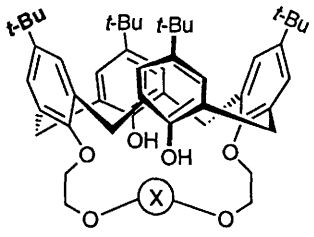
Interest in calixarene-containing polymers emerged in the mid 1980s, and a number of patents describing their preparation were issued during that period (see ref. 1, pp. 187–189). Interest continues today, and a variety of approaches have been taken for the construction of calixarene-containing polymers. One of these involves attachment of calixarene moieties to preformed polymeric matrices, for example by treating $\mathbf{8}^{t\text{-Bu}}$ with the acid chloride of a carboxyl-containing polymer derived from a styrene–divinylbenzene copolymer.[567] Similarly, treatment of polyethyleneimine with mono-*p*-3-bromopropylcalix[4]arene yields a water soluble functionalized polymer.[568] With $\mathbf{4}^{CH_2Cl}$ and polyethyleneimine an insoluble cross-linked polymer is obtained. A calixarene carry-

[567] Pathak, R.; Rao, G. N. *Anal. Chim. Acta* **1996**, 335, 283.
[568] Georgiev, E. M.; Troev, K.; Roundhill, D. M. *Supramol. Chem.* **1993**, 2, 61.

ing an epoxide-containing moiety on its upper rim yields a polymer upon treatment with poly(acryloyl chloride).[569]

Another approach is to generate polymers from polymerizable calixarene monomers. For example, attachment of methacryl groups to the lower rim[570] or the upper rim[571] of a calixarene to give **168** [$Y^{1-3} = OCH_2CO_2Et$; $Y^4 = OCH_2CO_2CH_2CH_2OCOC(Me)=CH_2$] and **178** [$X^{1-3} = H$; $X^4 = CH_2CH_2CH_2OCOC(Me)=CH_2$; Y = *n*-Bu], respectively, provides monomers that can be homopolymerized (with azobisisobutyronitrile as initiator) or copolymerized, *e.g.* with 2-(6-sulfo-2-naphthoxy)ethyl methacryate. Starting with the lower rim-bridged calix[4]arene **261a**, polymer **261b** has been generated by treatment with $Bu_3SnCH=CHSnBu_3$ and polymer **261c** by treatment with a bis-thiophene carrying a Me_3Sn moiety.[572]

Calixcrown telomers with $\bar{M}_n$ 5000–7000 have been prepared from calixcrown monomers **130a** [R = *t*-Bu; Y = H or CO_2H or $(CH_2)_{11}SiCl_2Me$] in which the linkages are ether groups, ester groups, or Si–O–Si groups, respectively.[573] An analogous copolymer with M_w = 15,000–24,000 has been prepared[574] by treating a mixture of the A,C-dimethyl ether of calix[4]arene and bisphenol-A with NaH followed by CH_2Br_2. Star polymers with molecular weights as high as *ca.* 250,000 are produced[575] when the calix[8]arene **167** (R = CMe_2OMe; Y = OMe; *n* = 8) is treated with isobutylene in the presence of BCl_3–$TiCl_4$.



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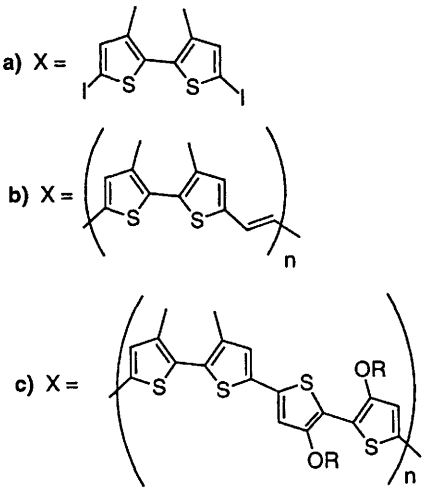

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[570] Harris, S. J.; Barrett, G.; McKervey, M. A. *J. Chem. Soc., Chem. Commun.* **1991**, 1224.
[571] Gravett, D. M.; Guillet, J. E. *Macromolecules* **1996**, 29, 617.
[572] Marsella, M. J.; Newland, R. J.; Carroll, P. J.; Swager, T. M. *J. Am. Chem. Soc.* **1995**, 117, 9842.
[573] Zhong, Z.-L.; Tang, C.-P.; Wu, C.-Y.; Chen, Y.-Y. *J. Chem. Soc., Chem. Commun.* **1995**, 1737.
[574] Dondoni, A.; Ghiglione, C.; Marra, A.; Scoponi, M. *J. Chem. Soc., Chem. Commun.* **1997**, 673.
[575] Jacob, S.; Majoros, I.; Kennedy, J. P. *Macromolecules* **1996**, 29, 8631.

CHAPTER 6

Filling the Baskets: Complex Formation with Calixarenes

'Scarce any Tale was sooner heard than told:
And all who told it, added something new,
And all who heard it, made Enlargements too,
In ev'ry Ear it spread, on ev'ry Tongue it grew'
Alexander Pope, *Temple of Fame: Poems of Alexander Pope*

The striking proliferation of publications in the calixarene field in the 1990s can be ascribed to some extent to the increasing attention being paid to the synthesis and functionalization of these compounds, as discussed in the previous chapters of this book. However, the major factor contributing to this growth is the wide variety of studies involving the calixarenes as complexing agents, for it is here that the potential utility of these compounds gains significant prominence.

The interaction between a host and a guest to form a complex can involve one or more of the following features: hydrogen bonding, electrostatic attraction, π–π stacking, van der Waals attraction, charge-transfer interactions. The experimental measure of the collective magnitude of such interactions can be expressed in a variety of ways, including the rate of transport through a membrane (liquid or supported liquid), stability constants as determined by spectroscopy or potentiometry, or the percentage of extraction in phase transfer processes from water into an immiscible solvent. It should be realized, however, that there is not necessarily exact parallelism in the values produced by these various measurements. For example, the rate of transport through a membrane is influenced by features that are not operative in other types of measurements, including the rate of complexation, the rate of transport within the membrane, and the rate of decomplexation.

The actual acquisition of the data for determining complexation capabilities similarly employs a variety of experimental techniques. In addition to the powerful spectrophotometric methods now available, most often NMR and/or UV–Vis spectrometry (picrate salts are frequently used in complexaton measurements because of the advantage provided by the color of the picrate anion), various other techniques are also being used. Mass spectrometry,[576] for example,

[576] Linnemayr, K.; Schmid, E. R.; Ailmaier, G. *Rapid Commun. Mass Spectr.* **1997**, 11, 427.

has been found to be useful in measuring the complexation of calixarenes with metal cations and onium ions[577] (including ammonium, sulfonium, and oxonium), the complexations being driven by the cation–π interaction. Not surprisingly, the order of complex stability is different in the solution and gas phases. Induced circular dichroism is applicable to the measurement of the complexation behavior of chiral calixarenes.[550,551,578] The inclusion properties of calixarenes with neutral molecules have been studied by means of capillary gas chromatography.[579] Conductivity measurements have been used to study the complexation behavior of calixcrowns with metal ions.[580] Using conductometric and potentiometric techniques, Danil de Namor and coworkers have made careful studies of the complexation of calixarenes with metal cations and have provided thermodynamic parameters for these processes.[581]

The precise structures of complexes are most directly obtained by X-ray crystallography, and the reasonable assumption is generally made that the solid state architecture reflects that of the solution state. It is certainly true, however, that frequently there are subtle differences between the two and that in some instances there are marked differences. In many cases the solution state structure can be inferred from ^{1}H NMR and ^{13}C NMR measurements, and modeling studies have also provided additional insights.[152,153] It should be noted that the significance and utility of the complexation effectiveness of a calixarene focuses not only on the absolute magnitude of its complexation constant but also on its ability as a host to discriminate among a group of guests.

6.1 Metal Ion Complexes with Calixarenes Carrying *endo* OH, SH, or C=O Groups

X-Ray crystallographic structures of solid state complexes of several of the parent calixarenes with metal ions have been obtained, early examples including the titanium complexes of **4**$^{t\text{-Bu}}$ [582] and **6**$^{t\text{-Bu}}$,[217] a complex containing two Eu^{3+} atoms and two **4**$^{t\text{-Bu}}$ molecules (each Eu^{3+} is coordinated to two OH groups from one of the calixarene residues and one OH from the other),[583] and a di-europium complex with **8**$^{t\text{-Bu}}$ (each Eu^{3+} is coordinated to three OH

[577] Inokuchi, F.; Araki, K.; Shinkai, S. *Chem. Lett.* **1994**, 1383; Inokuchi, F.; Miyahara, Y.; Inazu, T.; Shinkai, S. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 1364; Laali, K. K.; Liang, T.-M. *J. Chem. Res. (S)* **1995**, 240.

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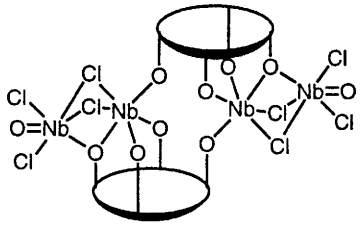
Table 6.1 *Cation transport by* p-tert-*butylcalix*[4,6,8]*arenes in basic solution*

Cation	*Diameter*, Å	*Cation transport*, mol s^{-1} m^{-2} × 10^8		
		[4]	[6]	[8]
Li^+	1.52		10	2
Na^+	2.04	2	22	9
K^+	2.76	< 0.7	13	10
Rb^+	3.04	6	71	340
Cs^+	3.40	260	810	996



262

groups)[565a] (see ref. 1, pp. 116–119 and ref. 11, p. 231). Similar complexes with Lu^{3+}, La^{3+}, and Tm^{3+} have more recently been prepared.[238] *p-tert*-Butylcalix[4]arene forms complexes (a) with niobium(V) (**262**), tantalum(V),[584] silicon(IV) and titanium(IV)[585] to give what have been called 'koilands', (b) with Al^{3+} and Zn^{2+} to form similar bis-calixarenes,[586,587] and (c) with Eu^{3+} to give a complex in which the calixarene is viewed[588] as a 'third sphere ligand' for the metal ion. With molybdenum a quadruply-bonded di-molybdenum [$Mo_2(OAc)_2(H_2$-*p-tert*-butylcalix[4]arene(THF)] complex is obtained.[589] Solution state complexes of parent calixarenes with alkali metal cations were first demonstrated in the 1980s by Izatt and coworkers,[590] who showed that a strongly basic environment is necessary for complexation to be effective (see ref. 1, pp. 158–160), indicating that it is the calixarene anion that is forming the complex. The solution state complexation of $\mathbf{8}^{t\text{-Bu}}$ with lanthanides has also been studied (see ref. 11, pp. 220–224).[591] A rough correlation between the size of the calixarene and the diameter of the alkali cations is noted, as illustrated by the data in Table 6.1. A study of the variations in cesium transport efficiency of

[584] Corazza, F.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *J. Chem. Soc., Chem. Commun.* **1990**, 1083.
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[589] Acho, J. A.; Lippard, S. J. *Inorg. Chim. Acta* **1995**, 229, 5.
[590] Izatt, R. M.; Lamb, J. D.; Hawkins, R. T.; Brown, P. R.; Izatt, S. R.; Christensen, J. J. *J. Am. Chem. Soc.* **1983**, 105, 1782; Izatt, S. R.; Hawkins, R. T.; Christensen, J. J.; Izatt, R. M. *J. Am. Chem. Soc.* **1985**, 107, 63.
[591] Arnaud-Neu, F. *Chem. Soc. Rev.* **1994**, 23, 235.

calix[4]arenes carrying bridges of various lengths on the upper rim (**46**)[56d] suggested that the cation resides within the cavity. This has been substantiated by ^{133}Cs NMR studies[592] and by the X-ray structure of the cesium complex of $\mathbf{4}^{t\text{-Bu}}$,[593] which shows the cesium to be inside the cavity and to be closer to the faces of the aromatic residues than to the oxygen atoms. *Endo* complexation may be unique to cesium,[594] however, and a study of the complexation of the monoanion of $\mathbf{4}^{t\text{-Bu}}$ with the alkali metals shows that the stability constants fall in the order $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$, which agrees with calculations indicating *exo* structures.[595] *Endo* complexation, based on NOE measurements[596a] (see ref. 1, pp. 164–167), has been suggested for the complex of $\mathbf{4}^{t\text{-Bu}}$ with *tert*-butylamine in MeCN solution. However, a molecular dynamics study[596b] comes to the conclusion that although the *endo* complex is inherently more stable, solvation in MeCN will favor the *exo* complex.

p-tert-Butylcalix[4]arenedithiol (**95h**) and *p-tert*-butylcalix[4]arenetetrathiol (**95j**)[203] both form complexes with Hg, the first containing a single metal atom[204] and the second a pair of metal atoms.[205] Although the X-ray crystal structure and the ^1H NMR spectrum of the tetrathiol show it to exist in the 1,3-alternate conformation, it appears to be able to undergo inversion to the cone conformer to form a complex on a rough Ag surface.[597] Molecular mechanics calculations[203] indicate an energy difference between the 1,3-alternate and cone conformations of *ca.* 4 kcal mol^{-1}, large enough to preclude observation of the cone conformer in the ^1H NMR spectrum but small enough to account for its formation under the influence of the Ag surface.

The electrochemical behavior of calixquinones[207,535b,c,598-600] has been studied in some detail, and the complexation characteristics of several diquinones [*e.g.* **228** (R = *t*-Bu; Y = Me, CH_2CO_2Et, and CH_2CONEt_2)] have been investigated. Complexation constants ranging from 10^3 M^{-1} to 4.8×10^5 M^{-1} are observed,[535] the latter with the complex of the ester with Ba^{2+}. The calix[4]arene monoquinone **226** (R = *t*-Bu; Y = Et) binds Na^+ and shows an enhancement in the complexation constant of *ca.* 10^6 when reduced to the radical anion.[598]

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[593] Harrowfield, J. M.; Ogden, M. I.; Richmond, W. R.; White, A. H. *J. Chem. Soc., Chem. Commun.* **1991**, 1159.

[594] Metalation of calix[4]arene with $NbCl_5$ and $TaCl_5$ produces metal complexes which, when treated with alkali phenoxides, entrap the alkali metal ions within the calix, as indicated by X-ray crystallography: Zanotti-Gerosa, A.; Solari, E.; Giannini, L.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *J. Chem. Soc., Chem. Commun.* **1997**, 183.

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[596] (a) Gutsche, C. D.; Iqbal, M.; Alam, I. *J. Am. Chem. Soc.* **1987**, 109, 4314; (b) Fraternali, F.; Wipff, G. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1997**, 28, 63.

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6.2 Metal Cation Complexes with Calixarenes Carrying Substituents on the Lower Rim

(for a short review, see ref. 13c; for extensive reviews, see refs. 14b and 14d)

Following shortly on the heels of the early complexation studies with unsubstituted calixarenes were studies with calixarenes carrying substituents on the lower rim. Some involve calixarenes whose pendant arms are unconnected with one another, while others involve calixarenes carrying lower rim bridges of various sorts, as discussed in the following sections.

6.2.1 Separate Pendant Arms on Lower Rim

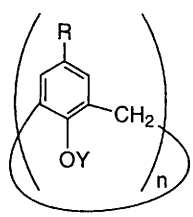
6.2.1.1 *Lower Rim Ethers*

The earliest examples of lower rim-substituted calixarenes investigated for their complexation properties are the ethyleneoxy compounds **263a**,[224,337,601] which show only a modest degree of cation binding capacity. Surprisingly, however, the simple *n*-propyl ether **263b** (R = H; $n = 4$) shows strong complexation with K^+ (log $K_{assoc} = 4.7$) and Ag^+ (log $K_{assoc} = 4.3$) if it is in the 1,3-alternate conformation.[476,602,603] Much weaker complexation is observed for the other conformers and for **263b** (R = *t*-Bu; $n = 4$). The special ability of the 1,3-alternate conformer to form tight complexes is attributed to coordination of the cation with the ether oxygens combined with π-donor participation with the aryl rings of the calixarene. The π-donor participation is supported by the X-ray crystal structure of the Ag^+ complex of the partial cone conformer of **263b** (R = H; $n = 4$).[476] However, the Na^+ complex of the conformationally flexible tetramethyl ether of $\mathbf{4}^{t\text{-Bu}}$ exists in a cone conformation in the solid state with the sodium ion located *exo*-calix on the lower rim and a molecule of toluene located *endo*-calix.[604] The kinetics of the complexation of **263a** with Na^+, measured by means of ^{23}Na NMR and 2D-EXSY ^1H NMR, give a rate constant for dissociation of 37 s^{-1} at 300 K with $\Delta H^{\ddagger} = 11.18$ kcal mol^{-1} and $\Delta S^{\ddagger} = -14.5$ cal mol^{-1} K^{-1}.[605]

6.2.1.2 *Lower Rim Esters*

Much more effective than the simple ethers in most cases are members of a family of compounds with the general structure **128** (see ref. 1, pp. 162–164; ref. 11, pp. 127–172), which have been studied with great zeal by a number of groups in recent years, particularly by McKervey and coworkers, as discussed in the next several subsections.

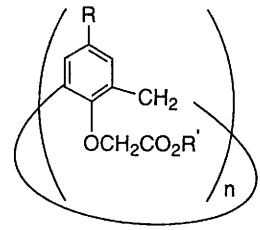
[601] Ungaro, R.; Pochini, A.; Andreetti, G. D.; Ugozzoli, F. *J. Inclusion Phenom.* **1985**, 3, 409.
[602] Ikeda, A.; Shinkai, S. *Tetrahedron Lett.* **1992**, 33, 7385.
[603] However, an X-ray structure of the Ag^+ complex of the tetramethyl ether of calix[4]arene shows it to be in the partial cone conformation: Xu, W.; Puddephatt, R. J.; Muir, K. W.; Torabi, A. A. *Organometallics* **1994**, 13, 3054.
[604] Bott, S. G.; Coleman, A. W.; Atwood, J. L. *J. Am. Chem. Soc.* **1986**, 108, 1709.
[605] Blixt, J.; Detellier, C. *J. Am. Chem. Soc.* **1995**, 117, 8536.



263

a) Y = $(CH_2CH_2O)_nR'$

b) Y = *n*-Pr



264

a) R = *t*-Bu; R' = H; n = 4

b) R = *t*-Bu; R' = Et; n = 4

c) R = H; R' = H; n = 4

d) R = H; R' = Et; n = 4

e) R = *t*-Bu; R' = H; n = 6

f) R = *t*-Bu; R' = Et; n = 6

g) R = H; R' = Et; n = 6

Earliest to be studied among this family of compounds were esters (**264**)[214,325a,328,606] for which it was determined, using phase transfer extraction[325] measurements, that (a) the cyclic tetramers, pentamers, and hexamers extract all of the alkali cations; the cyclic tetramer works best with Na^+, the cyclic pentamer better with K^+, Rb^+, and Cs^+, and the cyclic hexamer best with Rb^+ and Cs^+ but very poorly with Na^+; and (b) the cyclic heptamer and octamer are quite ineffective. An X-ray crystal structure of the K^+ complex of **264b** shows it to have a cone conformation with C_4 symmetry.[273] The strength and/or discrimination of complexation with these esters can, of course, be adjusted not only by changing the ring size but also by changing the ester group R', the *p*-substituent R, and the conformation. For example, the *tert*-butyl esters **264** (R' = *t*-Bu) are stronger complexers than the ethyl esters (R' = Et) for $n = 4$ and 5, illustrating the effect of the ester group. The de-*tert*-butyl ester **264g** shows a four-fold greater discrimination than **264f** between Cs^+ and Na^+, illustrating the influence the *p*-substituent may sometimes exert.[607] The cone conformer of **264b** is more selective for Na^+ (for X-ray crystal structure of complex, see ref. 608) than the other three conformers which are more effective for K^+ complexation[275] (*vide infra*), illustrating the importance of conformation. A more subtle conformation effect is operative with the upper rim-bridged calixarenes **46a**

[606] McKervey, M. A.; Seward, E. M.; Ferguson, G.; Ruhl, B.; Harris, S. J. *J. Chem. Soc., Chem. Commun.* **1985**, 388.

[607] Arnaud-Neu, F.; Fanni, S.; Guerra, L.; McGregor, W.; Ziat, K.; Schwing-Weill, M.-J.; Barrett, G.; McKervey, M. A.; Marrs, D.; Seward, E. M. *J. Chem. Soc., Perkin Trans.* 2 **1995**, 113.

carrying CH_2CO_2Et moieties on all four of the lower rim oxygen atoms. When $n = 7$ and 9 selective complexation of Na^+ is observed, but when $n = 5$ or 6 complexation falls drastically by a factor of $> 10^5$ due to the inability of the system to assume the necessary four-fold symmetry.[609] The kinetics of complexation of **264b** show that a 1:1 complex is formed in a slow exchange with solvated calixarene and Na^+ and that a 2:1 calixarene: Na^+ complex is formed in a fast exchange.[610]

Stability constants for esters determined in MeOH or MeCN generally mimic the results obtained from extraction experiments; the values for K_{assoc}, which range from 10^2 to $10^{6.5}$, are comparable to those for dibenzo-18-crown-6 but lower than those for the cryptands by factors of 10^3 to 10^5. Calorimetric measurements,[611,612] have provided $\Delta G°$, $\Delta H°$, and $T\Delta S°$ values for the complexation of **264b**, and they show that with Li^+ the complexation is entropy driven whereas with the other alkali cations it is enthalpy driven. The Na^+ complex of **264b** undergoes reversible decomposition upon irradiation with a low-pressure Hg lamp, the decomposition being both solvent dependent (occurs in toluene but not in MeOH) and anion dependent (iodide and thiocyanate most labile; perchlorate least labile).[613]

6.2.1.3 *Lower Rim Ketones*

Ketones of the general structure **265** have complexing features[325,335] rather similar to those of the esters **264**. Stability constant measurements and extraction data indicate that the cyclic tetrameric ketones are better than their ester analogs for the extraction of Li^+ and also for Rb^+ and Cs^+. The ketone **265c** has a broader range of extraction capability than its cyclic tetramer and hexamer counterparts but shows little selectivity among the cations.

6.2.1.4 *Lower Rim Amides*

Amides of the general structure **266** were first prepared and studied by Ungaro and coworkers[273] and subsequently in considerable detail by McKervey and coworkers[607,612,614] and Beer and coworkers.[615] The cyclic tetrameric amides

[608] Ikeda, A.; Tsuzuki, H.; Shinkai, S. *Tetrahedron Lett.* **1994**, 35, 8417.

[609] Böhmer, V.; Vogt, W.; Goldmann, H.; McKervey, M. A.; Owens, M.; Cremin, S.; Collins, E. M. *J. Org. Chem.* **1990**, 55, 2569; Arnaud-Neu, F.; Böhmer, V.; Guerra, L.; McKervey, M. A.; Paulus, E. F.; Rodriquez, A.; Schwing-Weill, M.-J.; Tabatabai, M.; Vogt, W. *J. Phys. Org. Chem.* **1992**, 5, 471.

[610] Israëli, Y.; Detellier, C. *J. Phys. Chem. B* **1997**, 101, 1897.

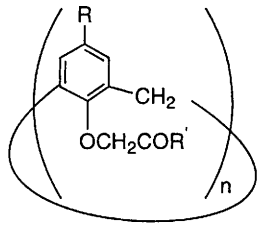
[611] Danil de Namor, A. F.; de Apaza Sueros, N.; McKervey, M. A.; Barrett, G.; Neu, F. A.; Schwing-Weill, M.-J. *J. Chem. Soc., Chem. Commun.* **1991**, 1546.

[612] Arnaud-Neu, F.; Barrett, G.; Fanni, S.; Marrs, D.; McGregor, W.; McKervey, M. A.; Schwing-Weill, M.-J.; Vetrogon, V.; Wechsler, S. *J. Chem. Soc., Perkin Trans.* 2 **1995**, 453.

[613] Barrett, G.; Corry, D.; Creaven, B. D.; Johnston, B.; McKervey, M. A.; Rooney, A. *J. Chem. Soc., Chem. Commun.* **1995**, 363.

[614] Arnaud-Neu, F.; Schwing-Weill, M.-J.; Ziat, K.; Cremin, S.; Harris, S. J.; McKervey, M. A. *New J. Chem.* **1991**, 15, 33.

[615] Beer, P. D.; Drew, M. G. B.; Leeson, P. B.; Ogden, M. I. *J. Chem. Soc., Dalton Trans.* **1995**, 1273; Beer, P. D.; Drew, M. G. B.; Kan, M.; Leeson, P. B.; Ogden, M. L.; Williams, G. *Inorg. Chem.*



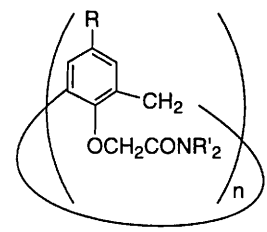
265

a) R = *t*-Bu; R' = Me; n = 4

b) R = *t*-Bu; R' = Et; n = 4

c) R = *t*-Bu; R' = *t*-Bu; n = 5

d) R = *t*-Bu; R' = Et; n = 6



266

a) R = *t*-Bu; R' = Et; n = 4

b) R = *t*-Bu; R'R' = $(CH_2)_4$; n = 4

c) R = *t*-Bu; R' = $CH_2C{\equiv}CH$; n = 4

d) R = *t*-Bu; R' = Et; n = 6

e) R = H; R' = Et; n = 6

266 ($n = 4$) qualitatively resemble the esters and ketones with respect to the complexation of alkali cations in showing a preference for Na^+, but quantitatively are considerably more effective. For example, the K_{assoc} for the complex of **266a** with Na^+ is almost 10^3 greater than that for **264b** or **265a** and comparable with that of cryptand-221. This increased strength of complexation, however, does not necessarily mean increased selectivity; **266a** is less selective for Na^+ relative to K^+ than **264b**, although it is more selective than cryptand-221. On the other hand, the amides are particularly selective for Na^+ relative to Rb^+ as well as for K^+ relative to Rb^+. The identity of the R and R' groups in the amides **266** can affect the complexation characteristics to some extent.[607] Calixarene **266c**, for example, shows a particularly high complexing ability with Na^+ relative to Li^+, K^+, Rb^+, and Cs^+, although overall it is less effective than **266a,b**; calixarene **266e** shows superior Cs^+/Na^+ selectivity relative to that of **266d**.[616]

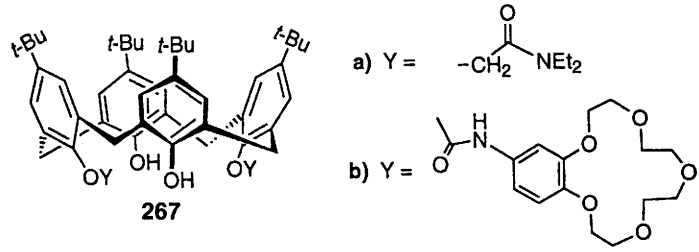
In contrast to the ethers **263**, esters **264**, and ketones **265**, the amides very effectively complex the alkaline earth cations, first shown in the case of secondary amides[331b] and later studied in considerable detail with the tertiary amides **266a** and **266b** ($n = 4, 5, 6$).[273,607] The cations Ca^{2+}, Sr^{2+}, and Ba^{2+} are much more tightly complexed than Mg^{2+}, the complex of Ca^{2+} with **266a** in MeOH being as strong as that with cryptand-221 ($\log K_{assoc} = 9.3$), although the cryptand is better for the other alkaline earth cations. The Ca^{2+}/Mg^{2+} selectivity with **266a,b**, with a value approaching 10^8, is the highest reported with a neutral ligand. A study of the complexation of Sr^{2+} as a function of ring size shows **266a,b** ($n = 6$) to be among the most effective members of the group, **266a,b**

1996, 35, 2202; Beer, P. D.; Drew, M. G. B.; Grieve, A.; Kan, M.; Leeson, P. B.; Nicholson, G.; Ogden, M. I.; Williams, G. *J. Chem. Soc., Chem. Commun.* **1996**, 1117; Beer, P. D.; Drew, M. G. B.; Leeson, P. B.; Ogden, M. I. *Inorg. Chim. Acta* **1996**, 246, 133.

[616] Fanni, S.; Arnaud-Neu, F.; McKervey, M. A.; Schwing-Weill, M.-J.; Ziat, K. *Tetrahedron Lett.* **1996**, 37, 7975.

($n = 4$) to be somewhat less effective, and **266 a,b** ($n = 5$) to be considerably less effective (see ref. 14b, p. 573). The identity of the R′ group in the host **266** has more impact on the complexation of alkaline earth cations than alkali cations. For example, **266c** is far less effective than **266a,b** in extracting Sr^{2+}. Calorimetric measurements[612] show that Ca^{2+} and Sr^{2+} but not Ba^{2+} have favorable enthalpy terms in complexation with **266a,b** and that all three cations show favorable entropy terms, this being the controlling factor. A molecular dynamics study predicts that **266a** should complex the alkaline earth cations in the diminishing order $Ca^{2+} > Sr^{2+} > Ba^{2+} > Mg^{2+}$, in agreement with experiment.[617]

Trivalent cations are also effectively bound by the amides.[618] For example, **266a** forms 1:1 complexes with Pr^{3+} (log K_{assoc} 8.5), Eu^{3+} (log K_{assoc} 8.7), and Yb^{3+} (log K_{assoc} 8.1). In extraction studies the cyclic tetramers are shown to prefer Eu^{3+} over Pr^{3+} and Yb^{3+}; with Eu^{3+} the cyclic hexamers are better than the cyclic tetramers, **266b** ($n = 6$) showing the highest extraction effectiveness (see ref. 14b, p. 580). X-Ray crystal structures of the Tm^{3+}, Ce^{3+}, and Pr^{3+} complexes of the diamide **267a** have been obtained.[619]



267

Among the metal cations in other groups, Ag^+ has been particularly well studied, and its stability constants for a broad range of hosts in MeOH have been determined. The amides[326] prove to be superior to the esters and ketones for complexing this cation,[273] and within the amide series the cyclic pentamer **266a** ($n = 5$) is an especially strong complexing agent (see ref. 14b, p. 583). The larger Tl^+ cation forms weaker complexes than Ag^+.

6.2.1.5 *Lower Rim Carboxylic Acids*

Carboxylic acids of the general structure **264a**[620,621] differ from the esters, ketones, and amides in having ionizable groups, the pK_a values in MeOH for the

[617] Muzet, N.; Wipff, G.; Casnati, A.; Domiano, L.; Ungaro, R.; Ugozzoli, F. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1065.

[618] Sabbatini, N.; Guardigli, M.; Mecati, A.; Balzani, V.; Ungaro, R.; Ghidini, E.; Casnati, A.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1990**, 878; Georgiev, E. M.; Roundhill, D. M. *Inorg. Chim. Acta* **1997**, 258, 93; Beer, P. D.; Drew, M. G. B.; Ogden, M. I. *J. Chem. Soc., Dalton Trans.* **1997**, 1489.

[619] Beer, P. D.; Drew, M. G. B.; Grieve, A.; Ogden, M. I. *J. Chem. Soc., Dalton Trans.* **1995**, 3455.

[620] Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1984**, 981.

[621] (a) Arnaud-Neu, F.; Barrett, G.; Harris, S. J.; Owens, M.; McKervey, M. A.; Schwing-Weill, M.-J.; Schwinté, P. *Inorg. Chem.* **1993**, 32, 2644; (b) Arnaud-Neu, F.; Barrett, G.; Ferguson, G.; Gallagher, J. F.; McKervey, M. A.; Moran, M. B.; Schwing-Weill, M.-J.; Schwinté, P. *Supramol. Chem.* **1996**, 7, 215.

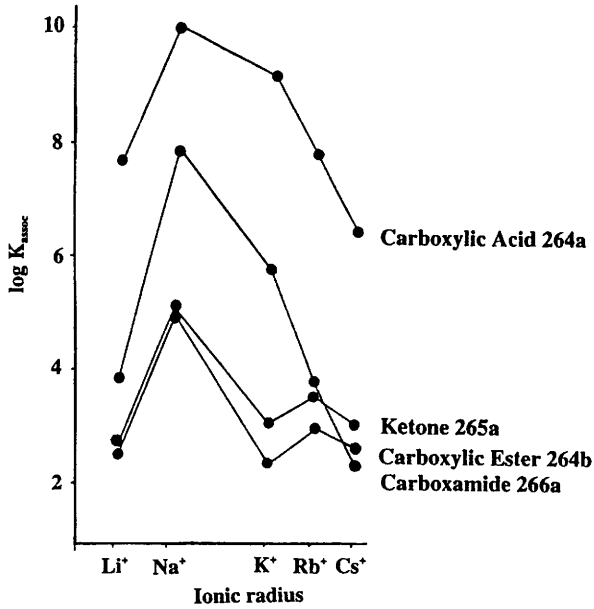


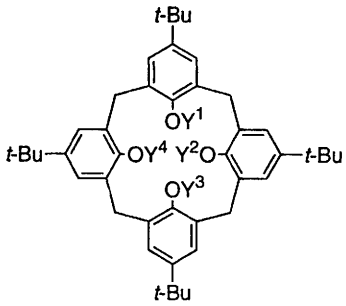
Figure 6.1 *Plot of log* K_{assoc} *values in MeOH for calix*[4]*arenes carrying ester, ketone, amide, and acid moieties on the lower rim (Taken from McKervey* et al.[146])

four carboxyl groups of **264a** being 8.3, 9.2, 10.9, and 13.4. The first of these values is somewhat higher than the pK_a of the monomeric phenoxyacetic acid (pK_a 7.7) and is attributed to stabilization of the protonated forms of **264a** by intramolecular hydrogen bonding. The pK_a of the triester monocarboxylic acid **268d**, for example, is 10.0, and its X-ray crystal structure shows the carboxyl group to be pointing into the cavity where it is hydrogen-bonded to neighboring ether oxygen atoms.[622] As illustrated in Figure 6.1, the carboxylic acids are all more effective complexing agents for alkali cations than are the corresponding esters, ketones, and amides [if only the log β_{110} (see ref. 14b, pp. 546, 563) value for the amide is used for comparison]. The conformation of both the uncomplexed and complexed species appears to be a distorted cone. Compounds **268a** and **268b** are interesting in being able to form $M_2L^{(n-2)-}$ binuclear complexes with the alkali cations, and the trifunctional compound **268e** forms $M_2Li_2H_4$ binuclear complexes with the alkali cations (except Li^+) in MeOH, as confirmed by an X-ray structure of the K^+ complex.[621b]

Although the calixarene carboxylic acids form complexes with some of the alkali metal cations,[623] the fact that they have an even greater capacity for alkaline earth cations was first realized in the mid 1980s[224,327] and subsequently studied in some detail.[621] As a consequence of their greater charge the alkaline

[622] Barrett, G.; Böhmer, V.; Ferguson, G.; Gallagher, J. F.; Harris, S. J.; Leonard, R. G.; McKervey, M. A.; Owens, M.; Tabatabai, M.; Vierengel, A.; Vogt, W. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1595.

[623] Montavon, G.; Duplâtre, G.; Asfari, Z.; Vicens, J. *New J. Chem.* **1996**, 20, 1061.



268

a) $Y^{1,3} = CH_2CO_2H$; $Y^{2,4} = H$

b) $Y^{1,3} = CH_2CO_2H$; $Y^{2,4} = CH_2CO_2Bu^t$

c) $Y^1 = CH_2CO_2H$; $Y^{2,3,4} = H$

d) $Y^1 = CH_2CO_2H$; $Y^{2,3,4} = CH_2CO_2Et$

e) $Y^1 = CH_2CO_2H$; $Y^3 = CH_2CO_2Et$; $Y^{2,4} = H$

f) $Y^{1,3} = CH_2CO_2H$; $Y^{2,4} = CH_2CONEt_2$

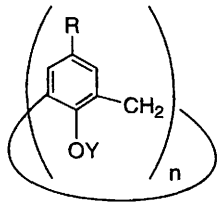
g) $Y^{1-3} = CH_2CO_2H$; $Y^4 = CH_2CONHR$

h) $Y^{1,3} = CH_2CO_2Et$; $Y^{2,4} = CH_2COCH_3$

earth cations are more strongly bound than the alkali cations. In fact, **264a** binds these cations more strongly (log K_{assoc} = 12.9 in MeOH) than does cryptand-222, which is the cryptand of choice for Ba^{2+} complexation. All of these carboxylic acids are selective for Ca^{2+}, especially **264a** for which the Ca^{2+}/Mg^{2+} selectivity is 2.7×10^{11} which is 10^4 higher than that of the amide **266b**. The cone conformer of the mixed carboxylic acid amide **268f** has a particularly striking selectivity for Ca^{2+}, showing an infinitely greater attraction[624] for this ion than for Mg^{2+}, Sr^{2+}, and Ba^{2+}. As with the alkali cations, under certain conditions **268e** can form $M_2L_2H_4^{2+}$ binuclear species with the alkaline earth cations in MeOH. Included among other divalent cations that form complexes with the carboxylic acids such as **269** (R = 1,1,3,3-tetramethylbutyl; Y = CH_2CO_2H; $n = 4$) is Cu^{2+} which, interestingly, also requires the presence of Na^+. This unusual behavior[625] is attributed to the ability of Na^+ to preorganize the extractant to accept the Cu^{2+}.

The acids form stronger complexes with lanthanide cations than with alkali and alkaline earth cations, the log K_{assoc} values for **264a** (as a tetraanion) with Pr^{3+}, Eu^{3+}, and Yb^{3+} being 20.7, 25.0, and 24.8, respectively (see ref. 80 in ref. 14b). The complexing ability of the acids, however, is pH dependent, and only at high pH is **264a** more effective than the amide **266a** (see Figure 6.1). Extraction experiments[626] indicate that the cyclic hexamer **264e** is better than the cyclic tetramer **264a**, with the order of extractability being $Nd^{3+} \approx Eu^{3+} > La^{3+} > Er^{3+} > Yb^{3+}$, but it is also strongly influenced by the presence of the cation of the background electrolyte (see ref. 14b, p. 82). The tricarboxylic acid monoamide **268g** has been used to form a neutral complex[627]

[624] Ogata, M.; Fujimoto, K.; Shinkai, S. *J. Am. Chem. Soc.* **1994**, 116, 4505.
[625] Ohto, K.; Shiratsuchi, K.; Inoue, K.; Goto, M.; Nakashio, F.; Shinkai, S.; Nagasaki, T. *Solvent Extr. Ion Exch.* **1996**, 14, 459.
[626] Ludvig, R.; Inoue, K.; Yamato, T. *Solvent Extr. Ion Exch.* **1993**, 11, 311.
[627] Rudkevich, D. M.; Verboom, W.; van der Tol, E.; van Staveren, C. J.; Kaspersen, F. M.; Verhoeven, J. W.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans. 2* **1995**, 131.



269

a) R = SO_3H; Y = CH_2CO_2H

b) R = *t*-Bu; Y = $CH_2CONHOH$

c) R = *t*-Bu; Y = R'_2P

d) R = *t*-Bu; Y = $CH_2CSNR'_2$

e) R = *t*-Bu; Y = $CH_2CONH(CH_2)_mSEt$

f) R = $CH_2CH_2NH_2$; Y = $SO_2C_6H_4Br$

g) R = $CH_2PO_3H_2$; Y = Me

h) R = $(C_6H_5)_2P$; Y = Me

i) R = NHC(=NOH)CH=NOH; Y = Me

j) R = *t*-Bu; Y = $(CH_2)_4NHC(=X)NHC_6H_5$

k) R = *t*-Bu; Y = $CH_2CH_2P(O)(C_6H_5)_2$

l) R = $NHCOCH_2P(O)(C_6H_5)_2$; Y = Alkyl

m) R = *t*-Bu; Y = $CH_2P(O)R_2$

n) R = *t*-Bu; Y = $CH_2CH_2C(S)NMe_2$

with Eu^{3+} and Tb^{3+}. The calix[4]arene dicarboxylic acid **268** ($Y^{1,3} = CH_2CO_2H$; $Y^{2,4}$ = Me) and the calix[6]arene ester **269** (R = 1,1,3,3-tetramethylbutyl; Y = CH_2CO_2R; $n = 6$) are useful extractants for the rare earth cations.[628,629]

Some of the carboxylic acids of the general structure **264a** and **269a** have proved to be highly effective complexation agents for the uranyl cation (see ref. 1, p. 190).[459c,630] Not only are the high complexation constants of the water soluble *p*-sulfonato calixarenes **269a** (n = 5 and 6) noteworthy (log K_{assoc} = 18.4 and 18.7), but the large discrimination factors of 10^{12}–10^{17} relative to Cu^{2+}, Zn^{2+}, and Ni^{2+} are quite remarkable. The analogous *p-tert*-butylcalix[5]- and -[6]arenes are somewhat less effective uranophiles, but the corresponding hydroxamic acid **269b** ($n = 6$) is even better than **269a** ($n = 6$) and competes efficiently with CO_3^{2-} ions.[631] The special effectiveness of the 'superuranophiles' has been interpreted in terms of a certain degree of preorganization, although this has been questioned on the basis of the X-ray structure[101] of

[628] Soedarsono, J.; Hagége, A.; Burgard, M.; Asfari, Z.; Vicens, J. *Ber. Bunsenges. Phys. Chem.* **1996**, 100, 477.

[629] Ohto, K.; Yano, M.; Inoue, K.; Yamamoto, T.; Goto, M.; Nakashio, F.; Shinkai, S.; Nagasaki, T. *Anal. Sci.* **1995**, 11, 893.

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[631] Nagasaki, T.; Shinkai, S.; Matsuda, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2617; Nagasaki, T.; Shinkai. S. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1063. For a *N*-substituted analog, see Agrawal, Y. K.; Sanyal, M. *J. Radioanal. Nucl. Chem.* **1995**, 198, 349.

Na_8\{calix[6]arene sulfonate\} which shows no preorganization into a pseudo-planar hexacoordinate structure.

6.2.1.6 *Lower Rim Phosphorus- and Sulfur-containing Groups*

(for a brief review, see ref. 12i)

The calixarene **269c** ($n = 4$) containing four OPR_2 groups on the lower rim reacts with $[Cu(CO)Cl]_n$ to form a complex containing eight Cu atoms and two calixarene molecules.[296] It also reacts with $[Fe(CO)_3(\eta_2\text{-}C_8H_{14})_2]$ to form a complex containing two Fe atoms, one calixarene, and six molecules of CO.[632] The complexation behavior of a series of calixarenes carrying two lower rim OPR_2 groups, **186** (R = *t*-Bu; $Y^{1,3} = R'_2P$; $Y^{2,4}$ = H, alkyl, or CH_2CO_2R'), has been studied with Pd(II), Pt(II), and Rh(II). Evidence for the formation of oligomeric complexes containing two or more calixarene moieties was adduced.[633] The calixarene **269m** ($n = 4$) containing four $OCH_2P(O)Ph_2$ groups forms a palladium complex in which a Pd^{2+} is coordinated with each of the phosphorus centers.[634]

A class of hosts that forms only weak complexes with the alkali and alkaline earth cations but strong complexes with Ag^+, Pb^{2+}, and Cd^{2+} are the thioamides **269d**.[635] The cyclic pentamer **269d** (R = *t*-Bu; R′ = Pr; $n = 5$) is particularly effective for the extraction of Cd^{2+}, and the cyclic hexamer **269d** (R = *t*-Bu; R′ = Et; $n = 6$) shows a high Ag^+/Cu^{2+} and Ag^+/Pb^{2+} selectivity. Calixarenes **269e** ($n = 4$), containing 'hard' binding sites at the oxygen atoms and 'soft' binding sites at the sulfur atoms, have the potential for forming ditopic bimetallic complexes. There is some evidence that this has been accomplished with Ag^+ and Na^+ for the compound in which $n = 6$, although the same compound with Cd^+ excludes the Na^+ ion.[636] Calixarenes **269l** and **269k** ($n = 4$–8) carrying diphenylphosphoryl acetamide moieties on the upper rim[637] and lower rim,[638] respectively, are highly efficient extractants for Eu^{3+}, Th^{3+}, Np^{3+}, Pu^{3+}, and Am^{3+}. The *N*,*N*-dimethyldithiocarbamoylethyl ether **269n** (R = *t*-Bu; $n = 4$) is an effective extractant[639] for Pd^{2+} and other heavy metals.

6.2.1.7 *Nitrogen-containing Chelating Groups on Lower Rim*

p-tert-Butylcalix[4]arenes carrying one, two, three, and four *O*-bipyridylmethyl

[632] Jacoby, D.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *J. Chem. Soc., Dalton Trans.* **1993**, 813.

[633] Loeber, C.; Matt, D.; Briard, P.; Grandjean, D. *J. Chem. Soc., Dalton Trans.* **1996**, 513.

[634] Dielman, C.; Loeber, C.; Matt, D.; De Cian, A.; Fischer, J. *J. Chem. Soc., Dalton Trans.* **1995**, 3097.

[635] Arnaud-Neu, F.; Barrett, G.; Corry, D.; Cremin, S.; Ferguson, G.; Gallagher, J. F.; Harris, S. J.; McKervey, M. A.; Schwing-Weill, M.-J. *J. Chem. Soc., Perkin Trans. 2* **1997**, 575.

[636] Koh, K. N.; Imada, T.; Nagasaki, T.; Shinkai, S. *Tetrahedron Lett.* **1994**, 35, 4157.

[637] Arnaud-Neu, F.; Böhmer, V.; Dozol, J.-F.; Grüttner, C.; Jakobi, R. A.; Kraft, D.; Mauprivez, O.; Rouquette, H.; Schwing-Weill, M.-J.; Simon, N.; Vogt, W. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1175.

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[639] Yordanov, A. T.; Mague, J. T.; Roundhill, D. M. *Inorg. Chim. Acta* **1995**, 240, 441; Yordanov A. T.; Mague, J. T.; Roundhill, D. M. *Inorg. Chem.* **1995**, 34, 5084; Yordanov, A. T.; Roundhill, D. M.; Mague, J. T. *Inorg. Chim. Acta* **1996**, 250, 295.

groups on the lower rim have been synthesized and their interactions with Cu^+ investigated.[640] The mono(bipyridylmethyl) ether forms a 2:1 intermolecular complex, and the A,B- and A,C-diethers both form 1:1 intramolecular complexes. Treatment with Cu^+ of a similar calixarene carrying two bipyridylmethyl and two pyridylmethyl groups produces an air-stable chiral complex, the structure of which has been established by X-ray crystallography.[641] With Cu^{2+} in MeOH solution, however, a complex is obtained that rapidly transforms to the Cu^+ complex, the result of reduction by MeOH which is oxidized to HCHO. *p-tert*-Butylcalix[4]arenes carrying *O*-alkylamino moieties on the lower rim have also been synthesized and their interactions with metal ions, particularly Pb^{2+}, Hg^{2+}, and Cd^{2+}, briefly explored.[642] The complexation of similar bipyridylmethyl and phenanthrolinylmethyl compounds as well as the lower rim-bridged calixarene **131b** (Ar = pyridyl)[643] with Eu^{3+} and Tb^{3+} have been studied for their luminescence characteristics.[644] Attachment of a pair of 1,4,7-triazacyclononane moieties to the bottom rim of a calix[4]arene produces a compound that contains three azide bridging ligands[645] and is capable of forming a ferromagnetic complex with Ni^{2+}.

6.2.2 Bridges on Lower Rim

6.2.2.1 *Calixcrowns*

The calixarenes called calixcrowns, carrying bridging polyethyleneoxy moieties on the lower rim, are described in previous chapters and include **130a**, **131**, **132**, **133–140**, **161d**, and **255**. First prepared by Ungaro and coworkers[347] in 1983, they have proved to be very effective cation complexing agents. In contrast to the esters, ketones, and amides discussed above, which are selective for Na^+, the calixcrowns show a preference for the larger cations. Several calixcrown dialkyl ethers **270** (Y = alkyl) have been studied,[302,351,375,646] and an interesting effect of conformation has been noted in the case of **270b** for which the structures of the cone, partial cone, and 1,3-alternate conformers have been established by X-ray crystallography. As illustrated by the data in Table 6.2,[351] the partial cone conformer forms the strongest complexes, and its K^+/Na^+ selectivity of 1.18×10^4 is among the highest values yet observed for a synthetic ionophore. In transport through a supported membrane, however, the selectivity is less dra-

[640] Regnouf-de-Vains, J.-B.; Lamartine, R. *Helv. Chim. Acta* **1994**, 77, 1817.

[641] Regnouf-de-Vains, J.-B.; Lamartine, R.; Fenet, B.; Bavoux, C.; Thozet, A.; Perrin, M. *Helv. Chim. Acta* **1995**, 78, 1607.

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[644] Sabbatini, N.; Guardigli, M.; Manet, I.; Ungaro, R.; Casnati, A.; Fischer, C.; Ziessel, R.; Ulrich, G. *New J. Chem.* **1995**, 19, 137; Casnati, A.; Fischer, C.; Guardigli, M.; Isernia, A.; Manet, I.; Sabbatini, N.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1996**, 395.

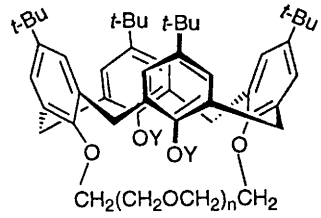
[645] Beer, P. D.; Drew, M. G. B.; Leeson, P. B.; Lyssenko, K.; Ogden, M. I. *J. Chem. Soc., Chem. Commun.* **1995**, 929.

[646] Nijenhuis, W. F.; Buitenhuis, E. G.; de Jong, F.; Sudhölter, E. J. R.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, 113, 7963.

Table 6.2 *Association constants for the cone, partial cone, and 1,3-alternate conformers of* **270b** *with alkali picrates in* $CDCl_3$

	K_{assoc}, M^{-1}			
Conformation	Na^+	K^+	Rb^+	Cs^+
Cone	1.3×10^5	1.2×10^7	4.0×10^5	9.8×10^4
Partial cone	7.5×10^5	8.9×10^9	1.5×10^9	1.6×10^6
1,3-Alternate	2.9×10^5	1.4×10^8	5.4×10^7	9.3×10^5

matic, and it has been shown that with **270b**, in contrast to **270a**, the transport rate is affected by the rate of cation release.[647]



270

a) Y = Me; n = 3

b) Y = Et; n = 3

c) Y = *i*-Pr; n = 3

d) Y = Me; n = 4

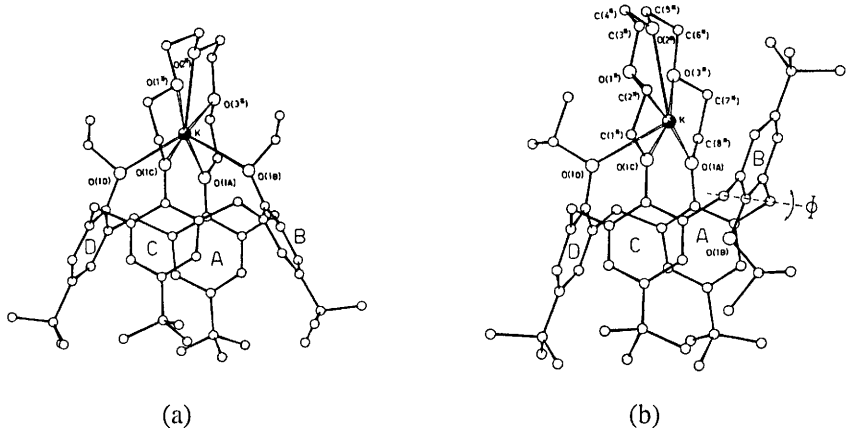
e) Y = *i*-Pr; n = 4

f) Y = H; n = 4

The X-ray crystal structures for the complexes of K^+ with the cone (**270b**) and partial cone (**270c**) conformers, shown in Figure 6.2, reveal that the K–O bond distances are shorter for the cone complex than the partial cone complex,[648] which might lead one to predict that the cone conformer should bind K^+ more tightly. However, in the partial cone conformation the cation–π interaction between K^+ and the phenyl moiety of the calixarene comes into play and proves to be especially effective. That the 1,3-alternate conformer is not an even stronger K^+ binder is attributed to the steric hindrance between the *p-tert*-butyl groups in this conformation. In fact, the de-*tert*-butyl analog of **270c** does prove to be a stronger K^+ binder and is even more selective than valinomycin, showing a K^+/Na^+ selectivity of *ca.* 3.4×10^5.

[647] Reichwein-Buitenhuis, E. G.; Visser, H. C.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, 117, 3913.

[648] Ugozzoli, F.; Ori, O.; Casnati, A.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Supramol. Chem.* **1995**, 5, 179.



(a) (b)

Figure 6.2 *X-Ray crystallographic structures of K^+ complexes of calixcrowns* (a) **270b** *in cone conformation and* (b) **270c** *in partial cone conformation (Taken from Ugozzoli* et al.[648])

The X-ray crystal structure of the Cs^+ complex of the conformationally mobile dimethyl ether de-*tert*-butylated **270a** shows that the system adopts a 1,3-alternate conformation,[350] maximizing the cation–π interaction. Acting on this lead, the diisopropyl ether **270e** fixed in the 1,3-alternate conformation was prepared and was found to be notably selective for Cs^+. Its especially high Cs^+/Na^+ selectivity factor of *ca.* 4000 is attributed to the size of the crown ether (which is intermediate between an 18-crown-6 and a 21-crown-7) and to its inability to wrap around the smaller cations because of steric hindrance from the calixarene skeleton.[356]

The complexing behavior of calix[4]arenes doubly-bridged with polyethyleneoxy chains (**271**)[357,359,408b] (see ref. 560 for the X-ray crystal structure) has been studied both in experimental[580,651] and theoretical detail.[652] The bis-calix[4]arenecrown-6 **271a** is selective for Cs^+, although the Cs^+/Na^+ factor of 850 is not quite as high as that for **270e**. The bis-calix[4]arenecrown-6 **271b** forms a binuclear complex with CsI, one Cs^+ residing in each of the crown ether moieties.[653] The doubly-bridged calix[8]arene **139** ($X = OCH_2CH_2OCH_2CH_2O$) shows a Cs^+/Na^+ selectivity factor of 1400, but conversion to the tetramethyl ether reduces it to 67.[372]

The bis-calixarene **272**, referred to as an 'ionophoric tube',[654] contains binding

[649] Casnati, A.; Pochini, A.; Ungaro, R.; Bocchi, C.; Ugozzoli, F.; Egberink, R. J. M.; Struijk, H.; Lugtenberg, R.; de Jong F.; Reinhoudt, D. N. *Chem. Eur. J.* **1996**, 2, 436.

[650] Abidi, R.; Asfari, Z.; Harrowfield, J. M.; Sobolev, A. N.; Vicens, J. *Aust. J. Chem.* **1996**, 49, 183.

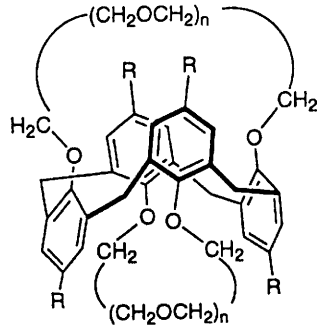
[651] Arnaud-Neu, F.; Asfari, Z.; Souley, B.; Vicens, J. *New J. Chem.* **1996**, 20, 453.

[652] Varnek, A.; Wipff, G. J. *Comput. Chem.* **1996**, 17, 1520; *idem. J. Mol. Struct. (Theochem)* **1996**, 363, 67.

[653] Thuéry, P.; Nierlich, M.; Lamare, V.; Dozol, J.-F.; Asfari, Z.; Vicens, J. *Acta. Crystallogr.* **1996**, *C*52, 2729.

[654] Ohseto, F.; Shinkai, S. *Chem. Lett.* **1993**, 2045; Ohseto, F.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1103. Also see Ohseto, F.; Sakaki, T.; Araki, K.; Shinkai, S. *Tetrahedron Lett.* **1993**, 34, 2149.

sites at each of its calixarene units and forms both 1:1 and 2:1 complexes with Na^+. In the 1:1 complex the lone cation can oscillate between the two sites by an intermolecular pathway (concentration dependent) and/or an intramolecular pathway (concentration independent). Both pathways have been detected and have been measured by ^1H NMR spectroscopy, the former occurring at room temperature (25 °C) and the latter at lower temperature (− 25 °C). The intramolecular exchange occurs more rapidly with **272** ($n = 2$) than with **272** ($n = 3$, 4). A similar phenomenon has been noted in other systems as well. For example, in the 1:1 Ag^+ complex of the 1,3-alternate conformer of **263b** (R = H; $n = 4$) it is postulated that the Ag^+ passes from one site to the other through the interior of the molecule,[476] *viz.* 'tunneling across a π-basic tube'; and, in the 1:1 complexes of **271c** the cations K^+, Rb^+, Cs^+, and NH_4^+ all are postulated to tunnel in the same fashion.[655] The 1,3-alternate conformer of molecule **130** (X = $[OCH_2CH_2OCH_2CH_2]_2NC_6H_{13}$; $Y^{1,2}$ = OCH_2CH_2OEt; R = H) acts as a 'molecular syringe', accepting Ag^+ in the azacrown cavity in the neutral state but expelling it to the polyether cavity upon protonation.[656]

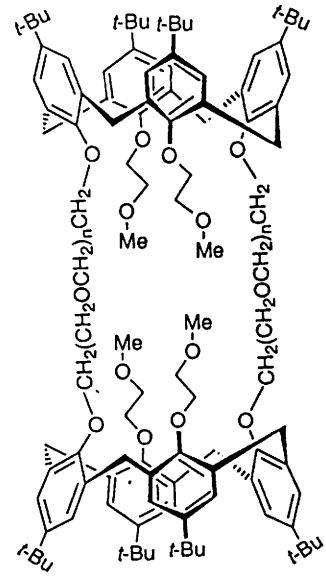


271

a) R = *t*-Bu; n = 4

b) R = H; n = 3

c) R = H; n = 4



272

6.2.2.2 *Calixspherands*

A particularly good example of the power of preorganization combined with conformational adaptation is seen in the calix[4]spherands (**142a**), compounds in which a hemispherand moiety is affixed to the lower rim of a calix[4]arene.[302,375,657] Although the hemispherand part of the molecule is

[655] Koh, N. K.; Araki, K.; Shinkai, S.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **1995**, 36, 6095.

[656] Ikeda, A.; Tsudera, T.; Shinkai, S. *J. Org. Chem.* **1997**, 62, 3568.

[657] Iwema-Bakker, W. I.; Reinhoudt, D. N. *New Separation Chemistry Techniques for Radioactive Waste and Other Specific Applications*; Elsevier Applied Science: London; **1991**, p. 142.

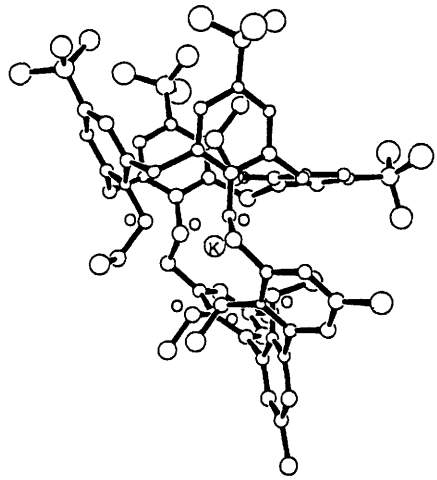


Figure 6.3 *X-Ray crystallographic structure of the K^+ complex of calixspherand* **142a** *(R = Me) (Taken from Bakker* et al.[660])

constrained in a rigid conformation that already is most appropriate for metal ion complexation, the calixarene part retains some conformational mobility. In the uncomplexed state the calixspherand exists in the cone conformation, both in solution as shown by ^{1}H NMR (NOESY) experiments and in the solid state as shown by X-ray crystallography.[658] Upon complexation with a cation, however, it transforms to a flattened partial cone conformer, as illustrated in Figure 6.3. The calixspherand **142a** (R = Me) forms very tight complexes with Na^+ ($K_{assoc} = 2.1 \times 10^{12}$ M^{-1}), K^+ ($K_{assoc} = 2.2 \times 10^{13}$ M^{-1}), and Rb^+ ($K_{assoc} = 3.6 \times 10^9$ M^{-1}), but the rate of decomplexation of Rb^+ ($k_d = 6.9 \times 10^{-5}$ s^{-1}), measured by a radioactive metal ion exchange method,[659] is considerably greater than that of Na^+ ($k_d = 6.0 \times 10^{-9}$ s^{-1}) and K^+ ($k_d = 1.0 \times 10^{-8}$ s^{-1}). High kinetic stability of the Rb^+ complex is desirable for its intended use as an organ imaging reagent, and it was discovered that this can be achieved by introducing larger alkyl groups onto the middle oxygen of the hemispherand. Thus, **142a** (R = Et) shows $K_{assoc} = 4.4 \times 10^9$ M^{-1} and $k_d = 1.4 \times 10^{-6}$ s^{-1}; **142a** (R = *i*-Pr) shows $K_{assoc} = 7.5 \times 10^9$ M^{-1} and $k_d = 4.4 \times 10^{-8}$ s^{-1}, corresponding to an increase in the half-time for decomplexation of 2.8 h for **142a** (R = Me) to 139 h for **142a** (R = Et) and 180 days for **142a** (R = *i*-Pr).[660] The corresponding Na^+ and K^+ complexes have decomplexation half-lives of several years. The decomplexation rate[661] of the complex of Ag^+ with **142a** (R = Et), though somewhat greater than that of the Rb^+ complex, is nevertheless the

[658] Groenen, L. C.; Brunink, J. A. J.; Iwema-Bakker, W. I.; Harkema, S.; Wijmenga, S.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1899.

[659] Iwema-Bakker, W. I.; Haas, M.; den Hertog, H. J., Jr.; Verboom, W.; de Zeeuw, D.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans. 2* **1994**, 11.

[660] Iwema-Bakker, W. I.; Haas, M.; Khoo-Beattie, C.; Ostaszewski, R.; Franken, S. M.; den Hertog, H. J., Jr.; Verboom, W.; de Zeeuw, D.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1994**, 116, 123.

[661] Iwema-Bakker, W. I.; Verboom, W.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1994**, 71.

lowest yet reported.[662] The increased kinetic stability of the complexes with **142a** (R = Et and *i*-Pr) is attributed to the greater ability of the larger alkyl groups to shield the cation imbedded in the calixspherand from solvent molecules. A functionalized calixspherand **142d** has been attached to a low molecular weight protein.[663]

6.3 Metal Cation Complexes with Calixarenes Carrying Substituents on the Upper Rim

Relatively fewer papers have been published dealing with metal cation complexation involving groups on the upper rim of the calixarene. One early example deals with the interaction of Ni^{2+}, Cu^{2+}, Co^{2+}, Fe^{2+}, and Pd^{2+} with the cone conformer of **269f** ($n = 4$) in which the four ethylamine appendages behave more or less independently of one another rather than as a single trialkylenetetraamine-like moiety.[294] Calixarenes **269a**[459c,664] and **269g**[665] ($n = 5$ and 6) with SO_3H and $CH_2PO_3H_2$ groups in the *p*-positions have proved to be excellent uranophiles, showing complexation constants of *ca.* 10^{19} and $10^{17.5}\,M^{-1}$, respectively, and a high selectivity relative to Ni^{2+}, Zn^{2+}, and Cu^{2+}. The complexes of $\mathbf{4}^{SO_3H}$ with Cr^{3+}, Yb^{3+}, and Cu^{2+} and of $\mathbf{5}^{SO_3H}$ with Co^{2+} and Ni^{2+} have been obtained for X-ray crystal structure determination by crystallization from water,[666] and the complex of $\mathbf{6}^{SO_3H}$ with Fe^{3+} in solution has been studied spectrophotometrically.[667] X-Ray crystallography of the sodium salts of the *p*-sulfonatocalixarenes shows them to consist of alternating hydrophilic and hydrophobic layers, characterized as 'organic clays',[668] with an interlayer separation of *ca.* 13.9 Å and a layer thicknesses of *ca.* 8.7 and 5.2 Å, respectively. Complexes of $\mathbf{4}^{SO_3H}$ with $Ni(C_5H_5N)_3(NO_3)_2$[669] or protonated adenine[670] are stated to be bilayers of anionic calixarenes intercalated with bilayers of cations separated by a bed of water molecules. The diphenylphosphinocalixarene **269h** ($n = 4$) forms complexes with a variety of cations, as measured by extraction efficiency with the following descending order of extractability being ob-

[662] Izatt, R. M.; Pawlak, J. S.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, 91, 1721.
[663] Iwema-Bakker, W. I.; Haas, M.; den Hertog, H. J., Jr.; Verboom, W.; de Zeeuw, D.; Bruins, A. P.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, 59, 972.
[664] Nagasaki, T.; Kawano, K.; Araki, K.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1325.
[665] Nagasaki, T.; Arimura, T.; Shinkai, S. *Bull. Chem. Soc. Jpn.* **1991**, 64, 2575.
[666] Atwood, J. L.; Orr, G. W.; Means, N. C.; Hamada, F.; Zhang, H.; Bott, S. G.; Robinson, K. D. *Inorg. Chem.* **1992**, 31, 603; Johnson, C. P.; Atwood, J. L.; Steed, J. W.; Bauer, C. B.; Rogers, R. D. *Inorg. Chem.* **1996**, 35, 2602.
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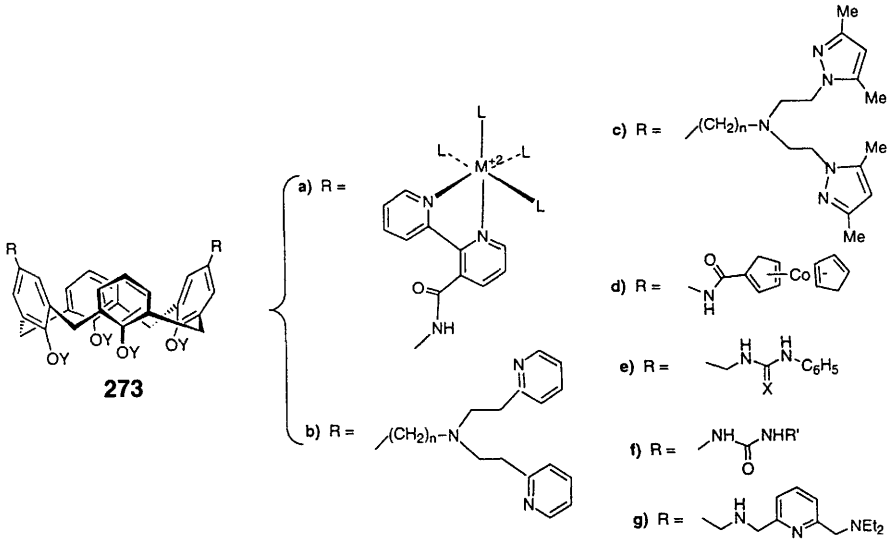
[669] Atwood, J. L.; Orr, G. W.; Hamada, F.; Vincent, R. L.; Bott, S. G.; Robinson, K. D. *J. Am. Chem. Soc.* **1991**, 113, 2760.
[670] Atwood, J. L.; Barbour, L. J.; Dawson, E. S.; Junk, P. C.; Kienzle, J. *Supramol.Chem.* **1996**, 7, 271.

served:[671] $Hg^{+} > Cu^{2+} > Cd^{2+} > Zn^{2+} > Ni^{2+} > Al^{3+} > Na^{+} > K^{+}$. The complex with Cu^{2+} appears to involve a pair of the cations.

A variety of chelating moieties have been attached to the upper rim of calixarenes. The calix[6]arene **269i** ($n = 6$) carrying *vic*-dioxime groups forms complexes with Cu^{2+}, Co^{2+}, and Ni^{2+} containing three metal ions.[447] Calixarenes carrying bipyridyl residues on the upper rim interact with metals such as Ru^{2+} and Re^{2+} accompanied by other external ligands such as pyridine, bipyidyl, or CO to form complexes containing two metal ions (**273a**) that are useful as anion receptors (*vide infra*).[453,672] Calixarenes **273b** and **273c** interact



with Cu^{+} and Cu^{2+} to form complexes containing two metal ions that are useful in redox systems.[673] Calixarenes carrying *p*-phenylazo groups show highly selective binding for Ag^{+}, Hg^{+}, and Hg^{2+} cations.[674] An interesting example of cooperativity (allosteric effect) is seen with **274** which complexes two Na^{+} cations. Binding of the first Na^{+} occurs at the lower rim, thereby imposing the required four-fold symmetry on the system and promoting the binding of the second Na^{+} at the upper rim by a factor of more than two orders of magnitude.[492] (see p. 156 for a related example with a calix[4]arene carboxylic acid with Cu^{2+} and Na^{+}).

6.4 Anion Complexes with Calixarenes

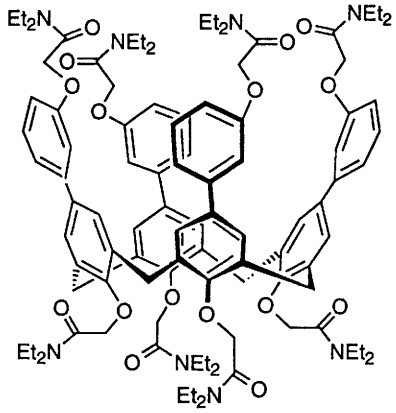
For every metal cation there is a counter anion, the latter considered to be merely a passive passenger in most of the complexation phenomena discussed above.

[671] Hamada, F.; Fukugaki, T.; Murai, K.; Orr, G. W.; Atwood, J. L. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1991**, 10, 57.

[672] Beer, P. D.; Drew, M. G. B.; Hesek, D.; Shade, M.; Szemes, F. *J. Chem. Soc., Chem. Commun.* **1996**, 2161.

[673] Xie, D. J.; Gutsche, C. D. unpublished results.

[674] Nomura, E.; Taniguchi, H.; Otsuji, Y. *Bull. Chem. Soc. Jpn.* **1993**, 66, 3797.



274

This may not always be the case, however, and recent attention has also focused on the anion with the goal of developing anion-specific receptors, stimulated by a desire to understand how Nature utilizes negatively charged species in its biological systems. Selective complexation of anions can be more difficult than that of cations, however, because of the higher free energies of solvation of anions and because of the frequently encountered pH dependence of the complexation. Ways for accomplishing anion complexation with *in vitro* systems include the attachment of positively charged or electron deficient moieties to an appropriate framework.

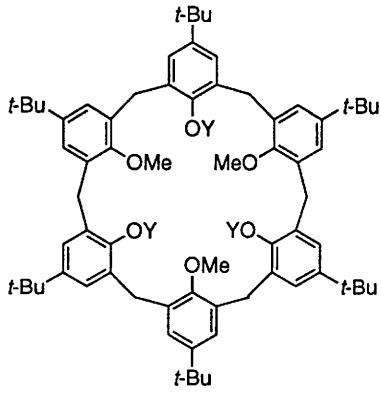
Among the earliest investigations of this facet of calixarene chemistry are those of Beer and coworkers,[454] who attached cobalticinium moieties to the upper rim of a calix[4]arene to obtain **273d** which recognizes Cl^-, Br^-, $H_2PO_4^-$, HSO_4^-, and $^-O_2C(CH_2)_4CO_2^-$ with stability constants in DMSO-d_6 of 5035, 1680, 2800, 990, and 11,510 M^{-1}, respectively[455] (different values for some of the anions are shown in a later paper[675]). In more recent work[504] they have shown that the bis-calixarene **200e** is selective for F^- relative to Cl^-, HSO_4^-, and $H_2PO_4^-$, the anion stability constants being 1330, 172, 21, and 91 M^{-1}, respectively. The calixarene **130h**, bridged on the lower rim with a bipyridyl residue, forms a complex with Ru^{2+} accompanied by two external bipyridyl molecules that selectively electrochemically senses $H_2PO_4^-$ in the presence of 10-fold excess amounts of HSO_4^- and Cl^- (cation is tetrabutylammonium).[366,453] Calixarene **273a**, substituted in a similar fashion on the upper rim, also forms complexes with anions,[672] including $H_2PO_4^-$. A calixarene carrying Ar–Ru^{2+} groups at the aryl faces has been made by refluxing a trifluoroacetic acid solution of $[Ru(Ar)(acetone)_3](BF_4)_2$ with $\mathbf{4}^H$. Its X-ray crystal structure shows that one of the BF_4^- ions is firmly embedded in the cavity.[676]

Anion complexing agents need not be restricted to those containing positively

[675] Beer, P. D.; Drew, M. G. B.; Hesek, D.; Nam, K. C. *J. Chem. Soc., Chem. Commun.* **1997**, 107.

[676] Steed, J. W.; Juneja, R. K.; Atwood, J. L. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 2456; Staffilani, M.; Hancock, K. S. B.; Steed, J. W.; Holman, K. T.; Atwood, J. L.; Juneja, R. K.; Burkhalter, R. S. *J. Am. Chem. Soc.* **1997**, 119, 6324.

charged or electron deficient centers, and certain neutral molecules bind anions selectively *via* hydrogen bond interactions. For example,[463] calixarene **184e** (R′ = H; R″ = *n*-Pr; $n = 4$) complexes $H_2PO_4^-$, HSO_4^-, Cl^-, NO_3^-, and ClO_4^- with association constants of 350, 970, 360, 240, and < 1, respectively, and **184e** (R′ = H; R″ = $CH_2CH_2NHC(O)Me$; $n = 4$) shows an especially high complexation constant of 103,400 for HSO_4^-. A variety of urea- and thiourea-containing calixarenes, including the lower rim-substituted **269j** ($n = 4$; X = O or S)[677] and **275a**[678] and the upper rim-substituted **273e** (Y = Pr; X = O or S),[679] have been prepared. The first set of compounds binds anions in the order $Cl^- > Br^- > CN^-$, has only a small affinity for I^- and SCN^-, and has no affinity for F^- and $H_2PO_4^-$. The second set of compounds, possessing C_3 symmetry and containing three urea or thiourea groups, shows selectivity for Br^- over Cl^- and a high affinity for tricarboxylate anions such as benzene-1,3,5-tricarboxylate (K_{assoc} = 87,000 M^{-1} when X = O; 190,000 M^{-1} when X = S), benzene-1,2,4-tricarboxylate (K_{assoc} = 23,000 M^{-1} when X = O; 2500 M^{-1} when X = S) and cyclohexane-1,3,5-tricarboxylate (K_{assoc} = 101,000 M^{-1} when X = O and 29,000 M^{-1} when X = S). The third set of compounds, containing two urea or thiourea groups on the upper rim, shows considerable selectivity for acetate (K_{assoc} = 2200 M^{-1}) over butyrate, the phthalates, and the halide anions when X = O. The analog of **273e** carrying a single urea or thiourea on the upper rim shows modest selectivity for butryate over acetate when X = O or S.



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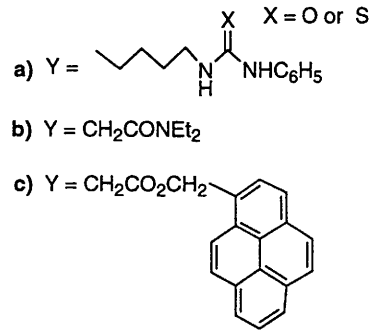
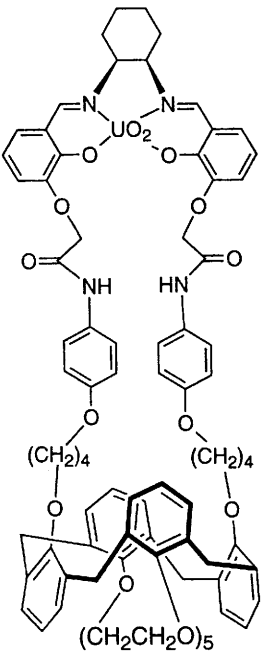


6.5 Salt Complexes with Calixarenes

The experiments described above in Sections 6.1–6.4 focus on the cation or the anion of a salt as separate, essentially non-interacting, entities. The experiments

[677] Scheerder, J.; Fochi, M.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, 59, 7815.
[678] Scheerder, J.; Engbersen, J. F. J.; Casnati, A.; Ungaro, R.; Reinhoudt, D. N. *J. Org.Chem.* **1995**, 60, 6448.
[679] Casnati, A.; Fochi, M.; Minari, P.; Pochini, A.; Reggiani, M.; Ungaro, R.: Reinhoudt, D.N. *Gazz. Chim. Ital.* **1996**, 126, 99.

described in this section focus on them collectively. Calixarene **200d** (Y = CH_2CO_2Et),[450] for example, contains an upper rim bridge that forms a complex with UO_2^{2+} which, along with the amide moieties, provides an anion-binding site; it also contains four lower rim ester groups that provide a cation-binding site. As a consequence, it acts as a bifunctional receptor and complexes NaH_2PO_4 with a K_{assoc} of 390 M^{-1}. In a similar vein, **276** effectively transports CsCl through a supported liquid membrane,[355] while **273f** (Y = CH_2CO_2Et) solubilizes NaCl, NaBr, NaI, KBr, and KI in $CHCl_3$ but not KCl or the Cs salts.[680] In the latter case, complexation of Na^+ induces a structural change that is prerequisite for anion complexation, still another example of an allosteric effect. A second approach involves the amide- and crown ether-containing calixarene **267b** which forms 1:1 stoichiometric complexes with potassium salts and shows the following association constants:[681] Cl^- (3500 M^{-1}), NO_3^- (1300 M^{-1}), HSO_4^- (5600 M^{-1}), $H_2PO_4^-$ ($> 10^4$ M^{-1}).



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[680] Scheerder, J.; van Duynhoven, J. P. M.; Engbersen, J. F. J.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 1090.

[681] Beer, P. D.; Drew, M. G. B.; Knubley, R. J.; Ogden, M. I. *J. Chem. Soc., Dalton Trans.* **1995**, 3117.

6.6 Molecular Complexes with Calixarenes

(see ref. 14b, p. 589)

6.6.1 Solid State Complexes

The first solid state complex to be studied involving a calixarene was that between $\mathbf{4}^{t\text{-Bu}}$ and toluene, the X-ray crystal structure of which was published in 1979[166] (see ref. 1, pp. 149–158). This complex has since been studied *via* inelastic neutron scattering to probe the tunneling of the methyl group of the guest,[682] as well as by variable temperature solid state ^{13}C NMR spectroscopy and differential scanning calorimetry which show that it undergoes a symmetry lowering phase transition at $-25\,^{\circ}C$, the high symmetry at room temperature being due to dynamic disorder of the toluene guest.[683] X-Ray crystal structures of numerous other molecular complexes of calixarenes have also been obtained more recently. Included among this large and growing group are first the calix[4]-arenes: (a) the nitrobenzene complex of $\mathbf{4}^{t\text{-Bu}}$ showing guest-induced asymmetry,[684] (b) the toluene complex of $\mathbf{4}^{t\text{-Bu}}$ to higher resolution,[685] (c) the *n*-pentane and cyclohexane complexes of $\mathbf{4}^{t\text{-Bu}}$ to probe the π-methyl theory of complexation,[686] (d) the *p*-xylene[687] and toluene[168] complexes of $\mathbf{4}^{i\text{-Pr}}$, (e) the MeCN complexes $\mathbf{4}^{t\text{-Bu}}$ [688] (f) the acetone complex of the chiral calixarene **60b** ($R^{1,3,4,5} = i$-Pr),[172] (g) the 1:4 picoline complex of *p*-(4-nitrophenylazo)calix-[4]arene,[689] (h) the CH_2Cl_2 complex of an Al-fused bis-*p*-*tert*-butylcalix[4]-arene,[586] (i) the Et_4N^+ salt of $\mathbf{4}^{t\text{-Bu}}$ [690] (j) the H_2O complex of the sodium salt of $\mathbf{4}^{SO_3H}$ (evidence for hydrogen bonding between H_2O and aromatic π electrons),[691] (k) the Me_4N^+ complexes of $\mathbf{4}^{SO_3H}$ [692] and $\mathbf{4}^{H}$,[693] (l) the pyridine complex of the calixcrown **270f** (evidence for hydrogen bonding between CH_3 of

[682] Caciuffo, R.; Francescangeli, O.; Melone, S.; Prager, M.; Ugozzoli, F.; Andreetti, G. D.; Amoretti, G.; Coddens, G.; Blank, H. *Physica B (Amsterdam)* **1992**, 180, 691; Caciuffo, R.; Amoretti, G.; Carlile, C. J.; Fillaux, F.; Francescangeli, O.; Prager, M.; Ugozzoli, F. *ibid.* **1994**, 202, 279; Prager, M.; Caciuffo, R.; Amoretti, G.; Carlile, C. J.; Coddens, G.; Fillaux, F.; Francescangeli, O.; Ugozzoli, F. *Mol. Phys.* **1994**, 81, 609; Caciuffo, R.; Amoretti, G.; Fillaux, F.; Francescangeli, O.; Melone, S.; Prager, M.; Ugozzoli, F. *Chem. Phys. Lett.* **1993**, 201, 427.

[683] Facey, G. A.; Dubois, R. H.; Zakrzewski, M.; Ratcliffe, C. I.; Atwood, J. L.; Ripmeester, J. A. *Supramol. Chem.* **1993**, 1, 199.

[684] Brouwer, E. B.; Enright, G. D.; Ripmeester, J. A. *Supramol. Chem.* **1996**, 7, 7.

[685] Brouwer, E. B.; Enright, G. D.; Ratcliffe, C. I.; Ripmeester, J. A. *Supramol. Chem.* **1996**, 7, 79.

[686] Brouwer, E. B.; Enright, G. D.; Ripmeester, J. A. *Supramol. Chem.* **1996**, 7, 143. A useful method is described for making complexes that involves vapor diffusion of the guest into a *m*-nitrotoluene solution of the calixarene.

[687] Perrin, M; Gharnati, F.; Oehler, D.; Perrin, R.; Lecocq, S. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, 14, 257.

[688] Xu, W.; Puddephatt, R. J.; Manojlovic-Muir, L.; Muir, K. W., Frampton, C. S. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 277.

[689] Ehlinger, N.; Perrin, M. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1995**, 22, 33.

[690] Harrowfield, J. M.; Ogden, M. I.; Richmond, W. R.; Skelton, B W.; White, A. H. *J. Chem. Soc., Perkin Trans. 2* **1993**, 2183.

[691] Atwood, J. L.; Hamada, F.; Robinson, K. D.; Orr, G. W.; Vincent, R. L. *Nature* **1991**, 349, 683.

[692] Atwood, J. L.; Barbour, L. J.; Junk, P. C.; Orr, G. W. *Supramol. Chem.* **1995**, 5, 105.

[693] Harrowfield, J. M.; Richmond, W. R.; Sobolev, A. N.; White, A. H. *J. Chem. Soc., Perkin Trans. 2* **1994**, 5.

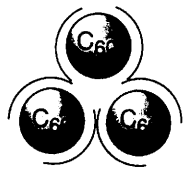
t-Bu and N of pyridine),[694] (m) the $MeNO_2$ complex of the calix bis-crown **131a** (R = cyclohexyl; $n = 1$),[181b] (n) the $CH_2(CN)_2$ and $MeNO_2$ complexes of the pyridine-bridged calixarene **202e** (Z = N; R = H),[266] (o) the *N*-methyl-*N'*-hydroxyethylpiperazine complex of *p*-(*N*-hydroxyethylpiperazino)-calix[4]-arene,[495] and (p) the X-ray diffraction (and solid state NMR spectrum) of the xenon complex of $\mathbf{4}^{t\text{-Bu}}$ which shows the Xe to occupy two cavity sites defined by static disordered host *tert*-butyl groups.[695] The calix[5]arenes include: (a) the EtOAc[211] and tetralin[210] complexes of $\mathbf{5}^{t\text{-Bu}}$; the toluene complex of $\mathbf{5}^{1,1,3,3\text{-tetramethylbutyl}}$;[213] and (c) the EtOH complex of the trisferrocenyl ester of $\mathbf{5}^{t\text{-Bu}}$.[696] The calix[6]arenes include: (a) the dimethylformamide complex of $\mathbf{6}^{\text{cumyl}}$;[218] (b) the Me_4N^+ complex of $\mathbf{6}^{t\text{-Bu}}$ (1,2,3-alternate conformations in both cases);[697] and (c) the MeCN complex of $\mathbf{6}^{t\text{-Bu}}$.[222]

In 1992, Williams and Verhoeven[698] obtained evidence for the formation of a complex between C_{60} and the water-soluble sodium salt of the $(CH_2)_3SO_3H$ ether of $\mathbf{8}^{H}$. Two years later a solid calixarene complex of C_{60} was isolated, almost simultaneously, by Williams and coworkers,[699] Atwood and coworkers,[700] and Shinkai and coworkers,[701] who mixed toluene solutions of $\mathbf{8}^{t\text{-Bu}}$ and C_{60}-containing soot. Two recrystallizations of the precipitate (initial composition 89% C_{60} and 11% C_{70}) yielded material of > 99.5% purity from which C_{60} was obtained by treating the solid complex with $CHCl_3$. Calix[8]arenes with *p*-H, Me, Et, *n*-Pr, *i*-Pr, *t*-pentyl, 1,1,3,3-tetramethylbutyl, and Ph groups are all less effective than *t*-Bu.[702] An X-ray crystal structure of the complex has yet to be obtained, but ^{1}H NMR and CP-MAS ^{13}C NMR spectral measurements indicate that the calix[8]arene asssumes a twisted double cone conformation with C_2 symmetry rather than a pleated loop. Molecular mechanics calculations suggest that the 1:1 complex of C_{60} and $\mathbf{8}^{t\text{-Bu}}$ is actually a micelle-like trimeric aggregate[703] schematically represented by **277**. A slightly different picture is presented by the calix[5]arene **278** (X = I) which forms a complex with C_{60} that is shown by X-ray analysis[704] to consist of two calixarene molecules acting as hemispherical caps around one C_{60}.

Another example of selective complexation is observed when $\mathbf{4}^{i\text{-Pr}}$ is added to a

[694] Andreetti, G. D.; Ori, O.; Ugozzoli, F.; Alfieri, C.; Pochini, A.; Ungaro, R. *J. Inclusion Phenom.* **1988**, 6, 523.
[695] Brouwer, E. B.; Enright, G. D.; Ripmeester, J. A. *J. Chem. Soc., Chem. Commun.* **1997**, 939.
[696] Beer, P. D.; Chen, Z.; Drew, M. G. B.; Gale, P. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1851; Beer, P. D.; Gale, P. A.; Chen, Z.; Drew, M. G. B. *Supramol. Chem.* **1996**, 7, 241.
[697] Harrowfield, J. M.; Richmond, W. R.; Sobolev, A. N. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 257.
[698] Williams, R. M.; Verhoeven, J. W. *Recl. Trav. Chim. Pays-Bas* **1992**, 111, 531.
[699] Williams, R. M.; Zwier, J. M.; Verhoeven, J. W.; Nachtegaal, G. H.; Kentgens, A. P. M. *J. Am. Chem. Soc.* **1994**, 116, 6965.
[700] Atwood, J. L.; Koutsantonis, G. A.; Raston, C. L. *Nature* **1994**, 368, 229.
[701] Susuki, T.; Nakashima, K.; Shinkai, S. *Chem. Lett.* **1994**, 699.
[702] Suzuki, T.; Nakashima, K.; Shinkai, S. *Tetrahedron Lett.* **1995**, 36, 249.
[703] Raston, C. L.; Atwood, J. L.; Nichols, P. J.; Sudria, I. B. N. *J. Chem. Soc., Chem. Commun.* **1996**, 2615.
[704] Haino, T.; Yanase, M.; Fukazawa, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 259; Haino, T.; Yanase, M.; Fukazawa, Y. *Tetrahedron Lett.* **1997**, 38, 3739.

solution containing the *o*-, *m*-, and *p*-xylenes, the complex with *p*-xylene precipitating preferentially.[149] The co-grinding or co-precipitation of *p-tert*-butyl-



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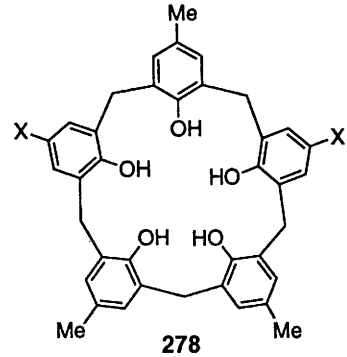


278

calixarenes with steroids is postulated to produce inclusion complexes that show some specificity among the steroid guests,[705] as discerned by FTIR and DSC analyses. No solution state complexation could be detected, however. A different sort of molecular complex is represented by those derived from $Cr(CO)_3$, described previously[490,561] as a means for selectively functionalizing calix[4]arenes (see ref. 1, p. 94) and from $[\{M(\eta^5\text{-}C_5Me_5)Cl(\mu\text{-}Cl)\}_2]$ where M = Rh or Ir. In these complexes the metallic moiety is associated with the face of an aromatic moiety, one moiety in the first case and two or even four in the second case.[706]

6.6.2 Solution State Complexes with Molecular Cations

The NH_4^+ cation acts, in many respects, like an inorganic cation and is often included in the complexation studies of the latter. Cations derived from amines, similarly, have considerable resemblance to inorganic cations, although the organic moiety introduces a significant steric factor, as previously shown for RNH_3^+ and **4**^{allyl} (see ref. 1, pp. 164–167).[596,707,708] Thus, with the calixcrown **130a** (R = *t*-Bu; *n* = 4) the binding strengths towards RNH_2 amines diminish in the order of increasing size of R in the amine,[709] *viz.* H > Me > Et ≈ Pr > Bu > *i*-Bu > *s*-Bu > *t*-Bu; with the calix-bis-crown **131** (R = H; *n* = 1) showing a small but significant preference for $MeNH_3^+$ over Me_4N^+ (evidence is adduced that a Me group is in the cavity);[181b] and with the calix-bis-quinone **228** [$R^{2,4}$ = *t*-Bu; $Y^2Y^4 = CH_2(CH_2OCH_2)_3CH_2$] there is a significantly greater binding of NH_4^+ than $BuNH_3^+$. Reciprocally, with the

[705] Parini, C.; Colombi, S.; Casnati, A. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 18, 341.

[706] Steed, J. W.; Juneja, R. K.; Burkhalter, R. S.; Atwood, J. L. *J. Chem. Soc., Chem. Commun.* **1994**, 2205.

[707] Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, 107, 6059.

[708] Also studied with *p-tert*-butylcalix[4]arene and *p-tert*-butylcalix[8]arene with various cyclic amines: Görmar, G.; Seiffarth, K.; Schulz, M.; Chachimbombo, C. L. *J. Prakt. Chem.* **1991**, 333, 475; Danil de Namor, A. F.; Garrido Pardo, M. T.; Munoz, L.; Pacheco Tanaka, D. A.; Sueros Velarde, F. J; Cabaleiro, M. C. *J. Chem. Soc., Chem. Commun.* **1992**, 855.

[709] Jung, Y. E.; Song, B. M.; Chang, S.-K. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2031. Also see Han, S.-Y.; Kang, M.-H.; Jung Y. E.; Chang, S.-K. *J. Chem. Soc., Perkin Trans. 2* **1994**, 835.

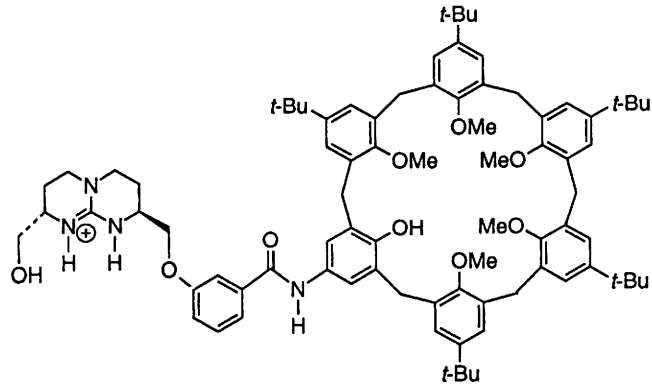
guest molecule *N*-methylpyridinium the size of the calixarene cavity has an effect, the K_{assoc} values with the methyl ethers of $\mathbf{4}^{t\text{-Bu}}$, $\mathbf{6}^{t\text{-Bu}}$, and $\mathbf{8}^{t\text{-Bu}}$ being 52, 190, and 132 M^{-1}, respectively.[710] The calix[5]arene-crown-5 compound **255b** forms complexes with *n*-$BuNH_3^+$ in which the guest is shown to be inside the host (*endo* complexation).[711] The observed K_{assoc} values of 48–86 M^{-1} are comparable to the values of 50–65 M^{-1} noted earlier[596] for the *endo*-calix complex of $\mathbf{4}^{allyl}$ and Me_3NH^+. A study with **264** (R = *t*-Bu; R′ = alkyl; *n* = 4, 6, 8) indicates that the cyclic hexamer is better than the cyclic tetramer or octamer for the complexation of butylamine.[712] A closely related study[713] of the complexes of **255a** with a variety of ammonium guests such as acetylcholine and *N*-methylquinuclidinium reaches the conclusion that the guest is in the cavity and that its ammonium portion is closely associated with the aromatic rings of the calixarene (π–cation interaction). Removal of the *tert*-butyl groups from **255a** significantly increases the effectiveness of its binding, a phenomenon also noted in other instances.[710] In this same study a solvent effect was observed that showed the strength of host to guest binding to be greater in $CHCl_2CHCl_2$ than in $CHCl_3$ and was interpreted to mean that only the smaller solvent is able to occupy the cavity of the host. In still another study employing ^1H NMR shift and relaxation time measurements of the complex formed from the calix[6]arene **264f** and $EtNH_3^+$, evidence is adduced that the Et group is embedded deep within the cavity,[714] a similar conclusion having been reached in the 1980s for the complex of $\mathbf{4}^{allyl}$ with *t*-$BuNH_3^+$ (see ref. 1, pp. 164–167). Thermodynamic studies of benzonitrile and nitrobenzene solutions of $\mathbf{4}^{t\text{-Bu}}$ and triethylamine indicate that the initial interaction is through hydrogen bonding or ion-pair formation.[715]

An interesting and surprising illustration of amine selectivity is shown by the pyridine-bridged calixarenes **202e** (Z = N) which form complexes with $MeNH_3^+$ OTs^- but not with the dimethyl-, trimethyl-, or tetramethylammonium counterparts,[502] the K_{assoc} in the case of **202e** (R = NMe_2; Z = N) being 1970 M^{-1}. Selective transport of amino acid esters through a $CHCl_3$ liquid membrane is effected *via* the calix[6]arene **265d**, tryptophane and phenylalanine esters traveling 12–23 times faster than glycine and alanine esters.[716] The upper rim-capped calix[6]arene **210** forms a complex with $PhNMe_3I$ in CD_2Cl_2 solution with K_{assoc} calculated to be *ca.* 14 at room temperature.[270]

Guanidinium cation is very selectively complexed[334] by the triamide **275b** with $K_{assoc} = 1.7 \times 10^7$ M^{-1}, while the hexaamide **266a** (*n* = 6) binds it even more tightly ($K_{assoc} = 9.6 \times 10^9$ M^{-1}) although less selectively. Two molecules

[710] Araki, K.; Shimizu, H.; Shinkai, S. *Chem. Lett*, **1993**, 205.
[711] Pappalardo, S.; Parisi, M. F. *J. Org. Chem.* **1996**, 61, 8724.
[712] Chang, S.-K.; Jang, M. J.; Han, S. Y.; Lee, J. H.; Kang, M. H.; No, K. T. *Chem. Lett.* **1992**, 1937.
[713] Arnecke, R.; Böhmer, V.; Cacciapaglia, R.; Dalla Cort, A.; Mandolini, L. *Tetrahedron* **1997**, 53, 4901.
[714] Ahn, S.; Chang, S.-K.; Kim, T.; Lee, J. W. *Chem. Lett.* **1995**, 297.
[715] Danil de Namor, A. F.; Garrido Pardo, M. T.; Pacheco Tanaka, D. A.; Sueros Velarde, F. J.; Cárdenas Garcia, J. D.; Cabaleiro, M. C.; Al-Rawi, J. M. A. *J. Chem. Soc., Faraday Trans.* **1993**, 69, 2727; Danil De Namor, A. F.; Wang, J.; Gomez Orellana, I.; Seueros Velarde, F. J.; Pacheco Tanaka, D. A. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 371.
[716] Chang, S. K.; Hwang, H. S.; Son, H.; Youk, J.; Kang, Y. S. *J. Chem. Soc., Chem. Commun.* **1991**, 217.

of imidazole are bound to the calixarenedicarboxylic acid **273** (R = *m*-carboxyphenyl; Y = H),[49b] the first with $K_{assoc} = 100\ M^{-1}$ and the second much more tightly with $K_{assoc} = 4000\ M^{-1}$. Molecular mechanics calculations suggest that one guest is bound between the two carboxylates solely by hydrogen bonding while the other is folded within the cavity and bound with the aromatic moieties of the calixarene both by hydrogen bonding and cation–π interaction. A striking example of complexation involves the calixarene **279** and dioctanoyl-D-α-phosphatidylcholine (**280**); the guanidinium moiety of **279** provides a binding site for the phosphate group, and the calixarene cavity provides a binding site for the ammonium group[717] (NMR spectral measurements indicate it to be in a cone conformation). The $K_{assoc} = 73{,}000\ M^{-1}$ in $CHCl_3$ solution, is quite similar to that of the natural receptor McPC603 antibody in water.



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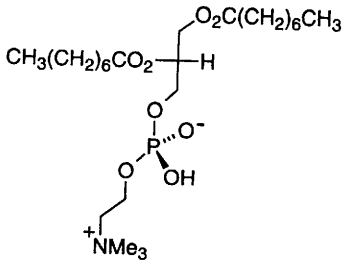

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The precise structures of complexes in solution remain in many cases less certain than those in the solid state, where X-ray structure determination usually reveals the orientation of the guest in the cavity of the host. In one study aimed at bridging this gap, the complex formed from tetrasodium $\mathbf{4}^{SO_3Na}$ and trimethylanilinium chloride was studied both in the solution and solid states.[718] In the solid state the X-ray crystal structure shows the phenyl group to reside

[717] Magrans, J. O.; Ortiz, A. R.; Molins, M. A.; Lobouille, P. H. P.; Sánchez-Quesada, J.; Prados, P.; Pons, M.; Gago, F.; de Mendoza, J. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 1712.

[718] Shinkai, S.; Araki, K.; Matsuda, T.; Nishiyama, N.; Ikeda, H.; Takasu, I.; Iwamoto, M. *J. Am. Chem. Soc.* **1990**, 112, 9053.

within the cavity, and the CP-MAS ^{13}C NMR spectrum is commensurate with this structure. In D_2O solution, however, the orientation of the guest is pD dependent, adopting the 'phenyl-in-the-cavity' orientation at pD 0.4 but a mixture of this and the 'trimethylammonium-in-the-cavity' orientation at pD 7.3. Another study involving the water soluble $\mathbf{5}^{SO_3H}$ provided the conclusion that the importance of extremely large scale self-assembly in the solid state cannot be overemphasized, the dominance of crystal packing forces highlighting the problem of comparing solution and solid state data for complexes.[103]

Several calixarene-like molecules have been shown to form complexes in solution, including a tetrahomodioxacalix[4]arene doubly-bridged on the lower rim with $(CH_2CH_2)_2O$ groups which forms fairly weak complexes with quaternary ammonium ions,[719] the bishomocalix[4]arene **62b** carrying chiral amino acid moieties as ether functions which efficiently extracts, with chiral recognition, certain amino acid esters and their corresponding carboxylates,[547a], and the naphthalene-1,8-diol-derived calixarene **12** which forms complexes with phenols[720] and with amino acids with K_{assoc} ranging from 0.4 for glycine to 140 for tryptophan.[721]

6.6.3 Solution State Complexes with Neutral Molecules

The K_{assoc} values for complexes of calixarenes and neutral molecules in organic solvents are often very small. For example, the results of an early study of complexation between calixarenes and toluene in $CHCl_3$ solution[707] (see ref. 1, pp. 167–168), using aromatic solvent induced shift (ASIS) measurements, indicated a K_{assoc} of *ca.* 1.1. This has been confirmed by a pulsed gradient spin echo (PGSE) NMR method[722] that promises to be of considerable utility in the study of complexation phenomena. The interactions of a variety of X–CH_2–Y molecules with the monomethyl ether of monodeoxy *p-tert*-butylcalix[4]arene **95a**[723] were measured in CCl_4 solution, which was chosen on the premise that its size and lack of a C–H bond prevent if from forming an *endo*-calix complex. The observed K_{assoc} constants range from 4.9 M^{-1} for CH_2Cl_2 to 46 M^{-1} for $ClCH_2CN$, the C–H acidity of the guest correlating well with the enthalpy of complexation. In a similar study the calix-bis-crown **132**[181b] showed a K_{assoc} with $MeNO_2$ of 230 M^{-1} in CCl_4 but only 27 in $CDCl_3$. The water soluble compound **264** (R = SO_3H; R′ = H; n = 4) forms an *endo*-calix complex with EtOH.[726b]

Complexation of urea, which is of special interest because of its medical implications, has been studied by Reinhoudt and coworkers.[724] Using the

[719] De Iasi, G.; Masci, B. *Tetrahedron Lett.* **1993**, 34, 6635.
[720] Poh, B.-L.; Lim, C. H.; Tan, C. M.; Wong, W. M. *Tetrahedron Lett.* **1993**, 49, 7259.
[721] Poh, B.-L.; Tan, C. M. *Tetrahedron* **1994**, 50, 3453.
[722] Mayzel, O; Aleksiuk, O.; Grynszpan, F.; Biali, S .E.; Cohen, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 1183.
[723] Yoshimura, K.; Fukazawa, Y. *Tetrahedron Lett.* **1996**, 37, 1435.
[724] Nijenhuis, W. F.; van Doorn, A. R.; Reichwein, A. M.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, 113, 3607; van Straaten-Nijenhuis, W. F.; van Doorn, A. R.; Reichwein, A. M.; de Jong, F.; Reinhoudt, D. N. *J. Org. Chem.* **1993**, 58, 2265; Reichwein, A. M.; Verboom, W.; Harkema, S.; Spek, A. L.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1167.

UO_2^{2+} complex of the calix-salophen-crown ether **130b** as the host, the electrophilic uranyl cation serving as a binding site for polar neutral compounds, they demonstrated that urea transport through a supported liquid membrane occurs with a flux of 18×10^{-8} mol cm^{-2} h^{-1}. When blood plasma containing urea was used as the source phase, an even slightly higher flux of 20×10^{-8} mol cm^{-2} h^{-1} was obtained.

All of the conformers of the tetra-*n*-propyl ether of $\mathbf{4}^{t\text{-Bu}}$ form 1:1 charge-transfer complexes with tetracyanoethylene (TCNE), but in varying degree; the strength of the complex diminishes from $K_{assoc} = 280$ to $K_{assoc} = 30$ in the order: 1,3-alternate > partial cone > 1,2-alternate > cone.[725]

Amino-,[496] carboxy-,[496] and sulfonato-calixarenes[726a] and the 1,8-naphthol-derived **12**[727] form moderately strong complexes with polycyclic aromatic compounds in aqueous solution (see ref. 1, pp. 180–185), with K_{assoc} values approaching 10^5 M^{-1}. The aminocalixarenes have been shown to be capable of being transported through a liquid membrane.[497] The water soluble β-cyclodextrin-calix[4]arene **281** (for attachment of β-cyclodextrin at the lower rim, see ref. 728) forms a complex[729] with 2-*p*-toluidino-6-naphthalenesulfonate with $K_{assoc} = 1.53 \times 10^5$ M^{-1}. The cysteine-substituted calixarenes **282** ($n = 4$ and 6)[730] form a complex with 8-anilino-1-naphthalenesulfonate (ANS) ($K_{assoc} = 2.46 \times 10^3$ M^{-1} for $n = 4$; 1.82×10^4 M^{-1} for $n = 6$) and with pyrene ($K_{assoc} = 8.5 \times 10^5$ M^{-1} for $n = 4$; 4.12×10^5 M^{-1} for $n = 6$). Similarly, oxyethylated $\mathbf{4}^{t\text{-Bu}}$ (average chain length 9 ethyleneoxy units; conformation a mixture of cone and partial cone) forms a complex[340c] with ANS ($K_{assoc} = 2 \times 10^4$ M^{-1}) and pyrene ($K_{assoc} = 2.2 \times 10^4$ M^{-1}). A complex of $\mathbf{6}^{SO_3H}$ and the aromatic-like hydroxymethylferrocene in aqueous solution[731] shows $K_{assoc} = 3.7 \times 10^3$ M^{-1}.

In organic solvents, aromatic compounds generally form much weaker complexes with calixarenes (*vide supra*) than in water, with K_{assoc} values less than 10^2. For example, the pyridine-bridged calix[6]arene **150e** forms a complex with 4-nitrophenol in $CHCl_3$ with $K_{assoc} = 12$ M^{-1} but not with 2,6-dimethyl-4-nitrophenol or 1,3-dinitrophenol, behavior similar to that of **148a**[378] (see ref. 1, pp. 171–172). 2,6-Naphthoquinone forms what is inferred from ^1H NMR spectral data and molecular modeling studies to be an *endo*-calix complex with $\mathbf{6}^{t\text{-Bu}}$ in $CHCl_3$, but no complexation constants are reported.[732a] A study of the complexation of several neutral molecules with $\mathbf{4}^{t\text{-Bu}}$ has been published.[732b]

[725] Ikeda, A.; Nagasaki, T.; Araki, K.; Shinkai, S. *Tetrahedron* **1992**, 48, 1059.

[726] (a) Shinkai, S.; Kawabata, H.; Arimura, T.; Matsuda, T.; Satoh, H.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1073; (b) Arena, G.; Casnati, A.; Contino, A.; Sciotto, D.; Ungaro, R. *Tetrahedron Lett.* **1997**, 38, 4685.

[727] Poh, B.-L.; Koay, L.-S.*Tetrahedron Lett.* **1990**, 31, 1911.

[728] D'Alessandro, F.; Gulino, F. G.; Impellizzeri, G.; Pappalardo, S.; Rizzarelli, E.; Sciotto, D.; Vecchio, G. *Tetrahedron Lett.* **1994**, 35, 629.

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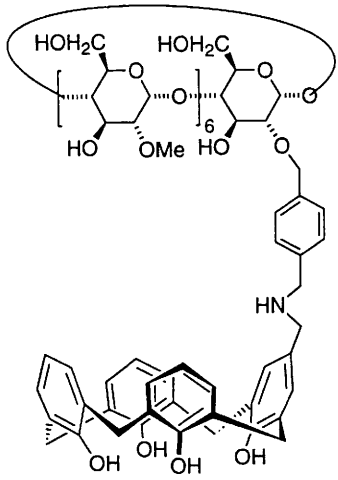
[730] Nagasaki, T.; Tajiri, Y.; Shinkai, S. *Recl. Trav. Chim. Pays-Bas* **1993**, 112, 407.

[731] Zhang, L.; Macias, A.; Lu, T.; Gordon, J. I.; Gokel, G. W.; Kaifer, A. E. *J. Chem. Soc., Chem. Commun.* **1993**, 1017; Zhang, L.; Macias, A.; Isnin, R.; Lu, T.; Gokel, G. W.; Kaifer, A. E. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 361.

[732] (a) Chawla, H. M.; Srinivas, K. *Indian J. Chem.* **1995**, 34*B*, 230; (b) Smirnov, S.; Sidorov, V.; Pinkhassik, E.; Havlicek, J.; Stibor, I. *Supramol. Chem.* **1997**, 8, 187.



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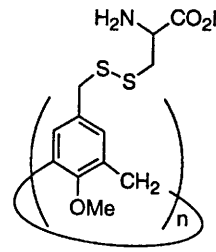


282

The complexation of C_{60}, discussed above for the solid state, has also been investigated in solution. First observed in aqueous solution with a water soluble calixarene,[698] a complex in toluene with $K_{assoc} = 110$ has been demonstrated using the triply-bridged calix[6]arene **211** as the host molecule.[513] An even tighter complex is formed with the calix[5]arene **278** (X = I), with a $K_{assoc} = 2120\ M^{-1}$ in toluene.[704] With **278** (X = Me or H) the K_{assoc} values fall to 1673 M^{-1} and 588 M^{-1}, respectively, and the K_{assoc} values in other solvents, particularly CS_2 and *o*-dichlorobenzene, also fall considerably. A survey of 28 calixarenes produced a similar conclusion, *viz* that the calix[5]arene system is particularly well suited for C_{60} complexation.[733]

Joining the quest to find artificial receptors for large guests, Reinhoudt and coworkers[734] have shown that the calix[4]resorcarene-substituted calix[4]arene **212** forms complexes with steroids with K_{assoc} values of 90–950 M^{-1} in $CDCl_3$. Surprisingly, however, the holand **214** fails to form a complex with these guests, presumably because its rigidity prevents it from accommodating to the requirements of the guest for effective binding. On the other hand, the calix-carcerand **213** does form host–guest complexes, albeit with much smaller molecules such as DMF[525] and various other molecules of comparable size.[735] The temperature dependent ^1H NMR spectrum of the DMF–carcerand complex indicates that the DMF is oriented in two different fashions inside the cavity (corresponding to an energy difference of 0.7 kcal mol^{-1}), providing an example of what has been called 'carceroisomerism'.

The complexation of sugars has been studied in some detail with the calix[4]resorcarenes but less so with the calixarenes themselves. Using the

[733] Ikeda, A.; Yoshimura, M.; Shinkai, S. *Tetrahedron Lett.* **1997**, 38, 2107.
[734] Higler, I.; Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, 61, 5920.
[735] van Wageningen, A. M. A.; Timmerman, P.; van Duynhoven, J. P. M.; Verboom, W.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *Chem. Eur. J.* **1997**, 3, 639.

bis-boronic acid calixcrown **179k** Shinkai and coworkers[438] detected 1:1 complexes with D-glucose, D-talose, and D-allose but not with D-mannose, D-galactose, D-fructose, or D-fucose. The conformationally semimobile calixarene is postulated to assume a cone conformation upon complexation. The addition of Li^+, Na^+, Mg^{2+}, and Ca^{2+} weakens the complexation, while the addition of K^+, Rb^+, or Cs^+ strengthens it, cited as examples of negative and positive allosterism, respectively.

6.6.4 Gas Phase Complexes

Only a few studies involving host–guest interactions of calixarenes in the gas phase have been carried out. Such studies are of interest because, in the absence of solvent effects, only the intrinsic interactions between the host and guest are operative. Acid/base character can be radically different in the solution and gas phases as, for example, the reversal in the acidities that occurs with toluene *vs.* water, the former becoming the more acidic in the gas phase. Although initial attempts to observe gas phase complexes using fluorine-containing compounds as putative guests were unsuccessful,[736] such complexation has been demonstrated more recently with the triamide **275b**[334] and the calixarene esters **264**[737] complexing Na^+ and K^+; with the calixfurans **79** complexing ammonium ions;[76c] with **4**$^{t\text{-Bu}}$ complexing alkali and alkaline earth cations;[738] and with the bridged calix[4]arenes **200a**, **200b** and **202c** complexing $MeCO_2R$, ROH, MeCOEt, MeCN, and benzene.[507,739] In the case of the bridged compounds, **200c** and **200d** are somewhat more effective as host molecules than **202d** and very much more so than their counterparts lacking the bridge. The ester, ketone, and nitrile guests are more tightly complexed than the alcohols or benzene, attributed to interactions between the acidic Me hydrogens of the guests and the π-electrons of the cavity and bridge moieties of the host.

6.7 Supramolecular Assemblies of Calixarenes

'Self assembly' is an integral aspect of the physical world: electrons, neutrons, and other subatomic particles assemble into atoms; atoms assemble into molecules; molecules react with one another to reassemble into new molecules; and molecules assemble with themselves and/or with other molecules *via* intermolecular non-covalent forces to form supramolecular arrays. The term 'self assembly', however, seems to have been selected to describe only the last of these phenomena and is currently a topic of great interest in chemistry as well as biology. The calixarenes, not surprisingly, are among the many types of molecules that have been chosen by the chemists for investigating this phenomenon.

[736] Liang, T.-M.; Laali, K. K.; Cordero, M.; Wesdemiotis, C. *J. Chem. Res. (S)* **1991**, 354.
[737] Inokuchi, F.; Shiomi, Y.; Kawabata, H.; Sakaki, T.; Shinkai, S. *Chem. Lett.* **1993**, 1595.
[738] Wong, P. S. H.; Yu, X. J.; Dearden, D. V. *Inorg. Chim. Acta* **1996**, 246, 259.
[739] Ungaro, R.; Arduini, A.; Casnati, A.; Pochini, A.; Ugozzoli, F. *Pure Appl. Chem.* **1996**, 68, 1213.

6.7.1 Dimeric Assemblies of Calixarenes

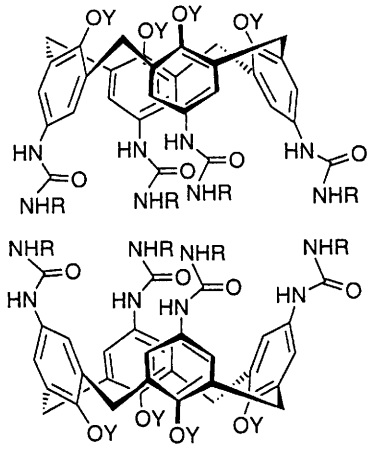
(for a brief, general review of molecular assembly, see ref. 740)

The linear bi- and tri-phenolic oligomers formed in the condensation of *p-tert*-butylphenol and formaldehyde (*i.e.* the precursors to calixarenes) have been shown to form intermolecular associated dimers[741] even at concentrations lower than 10^{-5} M.[110] These have been called 'hemicalixarenes' (see ref. 1, pp. 53–54) and presumably play a significant role in the proclivity of the linear oligomers to form cyclic oligomers.

Intermolecularly associated dimers derived from the calixarenes themselves have only recently been investigated. In 1992, Reinhoudt and coworkers[742] synthesized ethoxyethyl ethers of calix[4]arenes **285a,b** carrying two and four α-pyridone moieties on the upper rim. Compound **285a** does, indeed, form a dimer with $K_{assoc} = 100\ M^{-1}$, but **285i** gives primarily an oligomeric assembly (*vide infra*). Both the dimer and oligomer are denatured by the addition of *N*-methylimidazolidone, which forms a 1:1 complex with the calixarenes. In the same year, Atwood and coworkers[743] published an X-ray structure of a dimer from Na_4(pyridinium)[calix[4]arenesulfonate]·$8H_2O$. In 1993 a prediction of things to come appeared from the laboratories of Rebek and coworkers,[744] who pictured the dimerization of a calix[4]arene tetraamide. A well defined solution dimer appeared in 1994 from the laboratories of Shinkai and coworkers,[745] who demonstrated the upper rim-to-upper rim association of a pair of tetrapropyl ethers of calix[4]arene **285c**, carrying carboxyl groups in the *p*-position, and **285d**, carrying pyridyl-containing arms in the *p*-position. In 1995, Shimizu and Rebek[746,747] provided persuasive proof for a dimer from the tetrabenzyl ether of a calix[4]arene carrying *N*-phenylurea moieties in the *p*-position (**285e**). Rebek revised this system a year later, using the conformationally mobile tetramethyl ether which is driven to adopt the cone conformation upon dimerization.[748] In 1996 a set of similar compounds (**285f**) was described by Böhmer and coworkers,[456] and Reinhoudt and coworkers provided examples of upper rim-to-lower rim hydrogen-bonded dimers comprising *p*-carboxycalix[4]arene and the 3- and 4-pyridymethyl ethers of $\mathbf{4}^{t\text{-Bu}}$ with K_{assoc} values of 1300 and 7600 M^{-1}, respectively.[749] Support for the dimer structures in these various systems, initially based on ^{1}H NMR spectral interpretations and mass spectral observa-

[740] Rebek, J., Jr. *Acta Chem. Scand.* **1996**, 50, 707.
[741] Cairns, T.; Eglinton, G. *Nature* **1962**, 196, 535; *idem J. Chem. Soc.* **1965**. 5906.
[742] van Loon, J.-D.; Janssen, R. G.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron Lett.* **1992**, 33, 5125.
[743] Atwood, J. L.; Orr, G. W.; Hamada, F.; Bott, S. G.; Robinson, K. D. *Supramol. Chem.* **1992**, 1, 15.
[744] Andreu, C.; Beerli, R.; Branda, N.; Conn, M.; de Mendoza, J.; Galán, A.; Huc, I.; Kato, Y.; Tymoschenko, M.; Valdez, C.; Wintner, E.; Wyler, R.; Rebek, J., Jr. *Pure Appl. Chem.* **1993**, 65, 2313.
[745] Koh, K.; Araki, K.; Shinkai, S. *Tetrahedron Lett.* **1994**, 35, 8255.
[746] Shimizu, K. D.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. USA* **1995**, 92, 12403.
[747] For short reviews, see Rebek, J., Jr. *Pure Appl. Chem.* **1996**, 68, 1261; *idem. Chem.Soc. Rev.* **1996**, 25, 255.
[748] Castellano, R. K.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1996**, 118, 10002.
[749] Vreekamp, R. H.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, 61, 4282.

tions, has been reinforced by an X-ray crystal structure[750] of the dimer from **285f** (Ar = *p*-tolyl).



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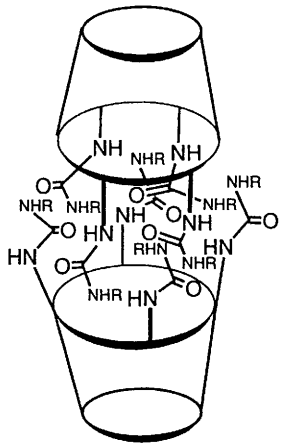
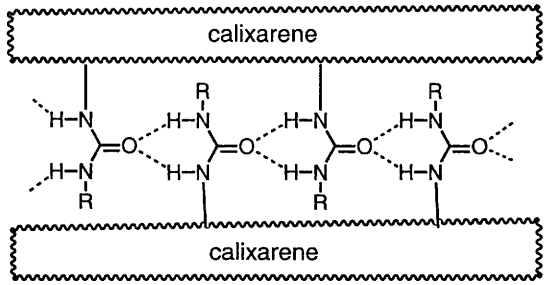
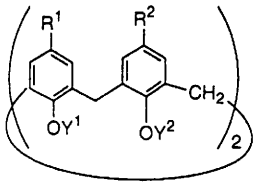




284

The dimers **283** derived from **285e,f**, represented schematically by **284**, have several interesting features. Although comprising two monomers with C_4 symmetry, the dimers have S_8 symmetry as a consequence of the uniform directionality of the intermolecular hydrogen bonds between the neighboring urea moieties, a fact manifested in the observed multiplicities in the ^{1}H NMR spectra. Another interesting feature is the ability of the dimers to act as complexing agents in which they hold a variety of molecules in the intermolecular cavity. Competition experiments with the dimer from **285e**[747] show that the tightness of complexation decreases in the order: benzene ≈ chloroform > toluene > *o*-xylene > *p*-xylene > ethylbenzene. Similar experiments with the dimer from **285f** (Ar = *p*-

[750] Mogck, O.; Paulus, E. F.; Böhmer, V.; Thondorf, I.; Vogt, W. *J. Chem. Soc., Chem. Commun.* **1996**, 2533.



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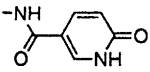
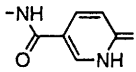
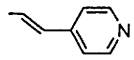
a) R^1 =  ; R^2 = H; $Y^{1,2}$ = $EtOCH_2CH_2$

b) $R^{1,2}$ =  : $Y^{1,2}$ = $EtOCH_2CH_2$

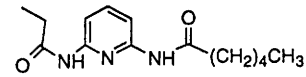
c) $R^{1,2} = CO_2H$; $Y^{1,2}$ = Pr

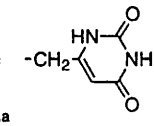
d) $R^{1,2}$ =  ; $Y^{1,2}$ = Pr

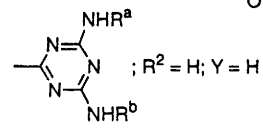
e) $R^{1,2} = NHCONHC_6H_6$; $Y^{1,2} = CH_2C_6H_5$

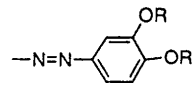
f) $R^{1,2}$ = NHCONHAr; $Y^{1,2} = CH_2CO_2Et$

g) $R^{1,2}$ = NHCONHAr; $Y^{1,2}$ = Me

h) $R^{1,2}$ = t-Bu; $Y^{1,2}$ = 

i) $R^{1,2}$ = H; Y^1 = H; Y^2 = 

j) R^1 =  ; R^2 = H; Y = H

k) $R^{1,2}$ = 

fluorophenyl) show the order of decreasing affinity to be: *p*-difluorobenzene > pyrazine > fluorobenzene > pyridine > benzene > phenol > aniline > chlorobenzene.[751] As noted above with the dimer from **285d**, the addition of strong hydrogen bond-forming small molecules 'denatures' the dimer to a monomer. This occurs with **285f** in the presence of *N*-phenyl-N′-phenylethylurea, which is too large to occupy the cavity of the dimer that is estimated to have a volume of *ca.* 210 Å^3. A third interesting feature is observed with the dimethyl ether **285g**, which is conformationally mobile and, as a monomer, exists primarily in the partial cone conformation. Upon dimerization, however, the conformation changes to the cone as a result of the advantage gained from the intermolecular hydrogen bonding between its urea moieties.[748]

6.7.2 Oligomeric and Polymeric Assemblies of Calixarenes

The 1992 attempt to create a calixarene dimer from **285b** (*vide supra*) resulted primarily in the formation of a polymeric assembly in $CDCl_3$ solution which

[751] Hamann, B. C.; Shimizu, K. D.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 1326.

could be denatured by treatment with imidazolidone.[743] A more recent approach,[752] designed specifically to create polymeric assemblies, makes use of the calix[4]arene **285h** substitued with diaminopyridine moieties on the lower rim. In the presence of dioctylbarbituric acid and Na^+ cations the hydrogen bonding in **285h** changes from intra- to intermolecular to give a polymeric assembly in which the calixarene and barbituric acid constitute 1:1 units with $K_{assoc} = 150$ M^{-1}. A somewhat similar approach, based on establishing predictable directionality of hydrogen bonding, makes use of calixarenes **285i,j** carrying uracil or diaminotriazine moieties.[434] The uracil **285i** forms an unusually strong dimer ($K_{assoc} = 3.4 \times 10^3$ M^{-1}), whereas the triazine **285j** ($R^{a,b} = COC_5H_{11}$) is strongly intramolecularly hydrogen-bonded (pinched cone conformation) and does not aggregate. Similarly, a mixture of **285i** and **285j** ($R^{a,b} = COC_5H_{11}$) fails to interact, but a mixture of **285j** ($R^{a,b} = COC_5H_{11}$) and 5-ethyl-5-phenylbarbituric acid in $CHCl_3$ solution produces a gel in which the aggregate is described as hydrogen-bonded ribbons that produce a network of fibers with a diameter up to *ca.* 100 nm. The closely related calixarene **285j** ($R^a = C_4H_9$; $R^b = H$; $Y = C_{12}H_{25}$) interacts with diethylbarbituric acid to produce a 'double rosette' aggregate[753] represented by **286**.

Another approach to aggregate building employs guest molecules capable of complexing two separate calixarene units, leading either to dimers or oligomers depending on the structures of host and guest. For example, the phenylazocalixarene **285k** ($R = C_{12}H_{25}$) reacts with $WOCl_4$ to form a complex[754] that aggregates in a columnar fashion, the W=O moiety of one calixarene unit inserting itself in the cavity of a neighboring molecule as depicted in **287**. In this case the tungsten moiety, although covalently bonded to a calixarene, can be considered to be the guest. An example in which the guest is completely noncovalently bonded is seen in the combination of calixarene **285k** with the diamide $HCONH(CH_2)_3NHCHO$ to produce a columnar array in which one end of the amide binds in the cavity of a calixarene and the other end forms hydrogen bonds with a neighboring calixarene.[755] In a similar vein a pair of calixarene units joined lower rim-to-lower rim *via* Si bridges (a 'koiland')[756] interact with $CH_3C{\equiv}C{-}C{\equiv}CCH_3$ to form a columnar array represented by **288** (a 'koilate'). The dipyridinium copper cation holds calix[4]arene sulfonates in like fashion to form aggregates for which X-ray crystallographic structures have been obtained.[757]

[752] Lhotak, P.; Shinkai, S. *Tetrahedron Lett.* **1995**, 36, 4829.

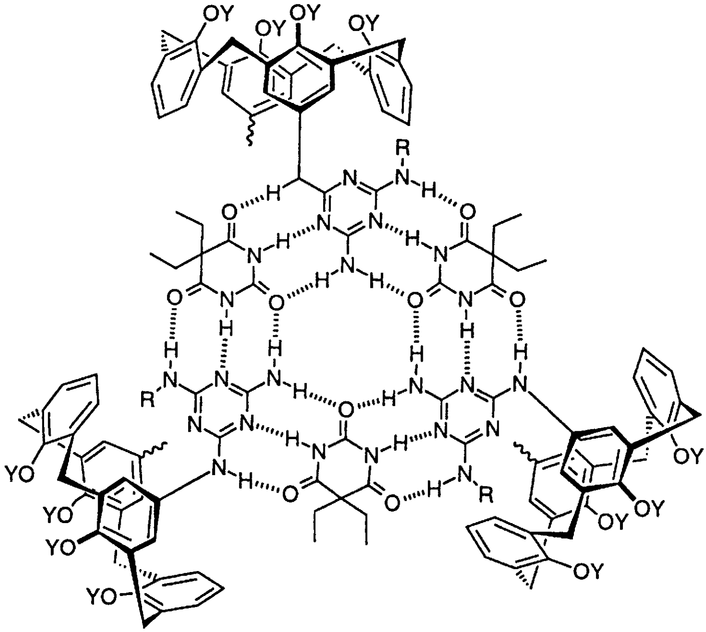
[753] Vreekamp, R. H.; van Duynhoven, J. P. M.; Hubert, M.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 1215.

[754] Xu, B.; Swager, T. M. *J. Am. Chem. Soc.* **1993**, 115, 1159.

[755] Xu, B.; Swager, T. M. *J. Am. Chem. Soc.* **1995**, 117, 5011.

[756] (a) Delaigue, X.; Hosseini, M. W.; De Cian, A.; Fischer, J.; Leize, E.; Kieffer, S.; Van Dorsselaer, A. *Tetrahedron Lett.* **1993**, 34, 3285; Delaigue, X.; Hosseini, M. W.; Graff, R.; Kintzinger, J.-P.; Raya, J. *ibid.* **1994**, 35, 1711; (b) Hajek, F.; Graf, E.; Hosseini, M. W.; Delaigue, X.; De Cian, A.; Fischer, J. *ibid.* **1996**, 37, 1401; Hajek, F.; Graf, E.; Hosseini, M. W. *ibid.* **1996**, 37, 1409.

[757] Atwood, J. L.; Orr, G. W.; Juneja, R. K.; Bott, S. G.; Hamada, F. *Pure Appl. Chem.* **1993**, 65, 1471.



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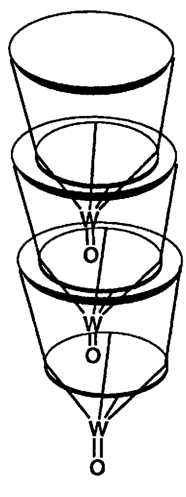

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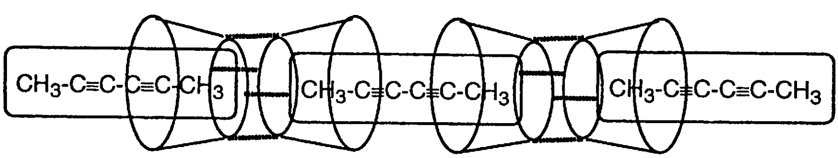

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The influence of molecular shape on aggregation properties is nicely illustrated by the tetrapropyl ethers of calix[4]arenes carrying $CH_2NMe_3^+$ or $CH_2O(CH_2)_nNMe_3^+$ groups in the *para* positions. The cone conformer aggregates in water to globular micelles, while the 1,3-alternate conformer forms stable vesicular arrays detectable by electron microscopy.[758] In a study of the simple aggregation properties in water, calixarenes carrying sulfonato or trimethylammonium groups have been categorized as non-micellar, micelle-forming, or unimolecular micellar.[449,759]

6.7.3 Calixarenes in Monolayers, Interfaces, and Colloids

Regen[339] (see Chapter 7) and Shinkai were among the first to experiment with calixarene-derived monolayers, the latter showing that monolayers of *p-tert*-butylcalixarenes respond selectively to the addition of cations[760] and that those of the calix[6]arene **264** (R = R′ = *t*-Bu; $n = 6$) respond selectively to butylammonium cations in the decreasing order *t*-Bu > *n*-Bu > *i*-Bu > *s*-Bu.[761] More recent detailed studies by Baglioni and coworkers,[762] aimed at characterizing the monolayers of $\mathbf{6}^{t\text{-Bu}}$ and the hexaamide **266a** ($n = 6$), have shown that in the former case the closely packed monomolecular films have only some of the phenolic groups immersed in the water (perpendicular orientation), whereas in the latter case all six of the amide groups are in the water (parallel orientation). A study of calix[4]arenes carrying various numbers of $CO(CH_2)_{10}Me$ groups on the upper rim and OCH_2CO_2Et on the lower rim concluded that the most stable monolayers are formed from the calixarene containing one of each.[763]

While a monolayer of the parent calix[6]arene shows a selective response to Cs^+ (which increases the parallel orientation), the hexaamide shows a selective response to guanidinium ion.[762b] Similar results are reported for $\mathbf{8}^{t\text{-Bu}}$ and its derived ester **264** (R = 1,1,3,3-tetramethylbutyl; R′ = Et) and amide, where the order of selection for cations is $Cs^+ > Rb^+ > Na^+ > K^+$ and for anions is $I^- > F^- > Br^- > Cl^-$.[764] Monolayers prepared from $\mathbf{8}^{t\text{-Bu}}$ and the fullerenes C_{60} and C_{70} have been tentatively interpreted in terms of *endo*-calix complexes, but the possibility is not dismissed that the fullerenes simply lie on top of the calixarene monolayer.[765]

The adsorption of calixarenes on metal surfaces has received recent study. The $Me(CH_2)_{11}S(CH_2)_{12}$ ethers of $\mathbf{4}^{H}$ and $\mathbf{4}^{t\text{-Bu}}$, for example, form a well-packed monolayer on a gold substrate, verified by IR spectroscopy and wetability

[758] Arimori, S.; Nagasaki, T.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **1995**, 679.
[759] Arimori, S.; Nagasaki, T.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 887.
[760] Ishikawa, Y.; Kunitake, T.; Matsuda, T.; Otsuka, T.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* **1989**, 736.
[761] Kawabata, H.; Shinkai, S. *Chem. Express* **1993**, 8, 765.
[762] (a) Dei, L.; Casnati, A.; Lo Nostro, P.; Baglioni, P. *Langmuir* **1995**, 11, 1268; (b); Dei, L.; Casnati, A.; Lo Nostro, P.; Pochini, A.; Ungaro, R.; Baglioni, P. *ibid.* **1996**, 12, 1589.
[763] Merhi, G.; Munoz, M.; Coleman, A. W.; Barrat, G. *Supramol. Chem.* **1995**, 5, 173.
[764] Davis, F.; O'Toole, L.; Short, R.; Stirling, C. J. M. *Langmuir* **1996**, 12, 1892.
[765] Castillo, R.; Ramos, S.; Cruz, R.; Martinez, M.; Lara, F.; Ruiz-Garcia, J. *J. Phys. Chem.* **1996**, 100, 709.

experiments.[766] The calix[4]arenetetrathiol (**95j**) adsorbs on a rough Ag surface, the calixarene undergoing an inverstion from the 1,3-alternate to the cone conformation in the process.[597] The latter system shows some ability to form complexes with aromatic hydrocarbons. In similar fashion a calixarene–calixresorcarene–DMF carceplex containing long disulfide arms on the calixresorcarene moiety forms a monolayer assembly on Au.[767] A mirror image situation exists in the system in which ferrocene-$CO(CH_2)_{10}SH$ is adsorbed on a gold surface and forms a complex with the dodecyl ether of $\mathbf{8}^{SO_3H}$.[768] A somewhat more elaborate procedure for depositing a calixarene on a metal surface involves first treating a silver surface with $HS(CH_2)_{10}C{\equiv}CC{\equiv}C(CH_2)_{10}CO_2H$, then polymerizing the adsorbed acetylenic chains followed by exposure to $SOCl_2$ (to convert the CO_2H to COCl groups) and treatment with $\mathbf{4}^{t\text{-Bu}}$ or $\mathbf{6}^{t\text{-Bu}}$.[769] The procedure has the advantage, however, of employing readily available calixarenes without the necessity of altering their upper or lower rim substituents. Evidence was adduced to indicate that the assemblies interact with volatile organic compounds by specific interaction with the calixarene cavities rather than by nonspecific adsorption. Calixarene-containing colloids have been made by heating the calixcrown **130a** [$Y^{1,2} = (CH_2)_{11}OH$] with Stöber silica spheres in *o*-nitrophenyl octyl ether at 145–160 °C for 4 days.[354] The formation of a complex in colloidal dispersion with Cs^+ was demonstrated by means of a ^1H MAS TOCSY experiment. Complexation of amphiphilic viologen guests by the calix[6]arene **184a** (Y = *n*-$C_{12}H_{25}$; $n = 6$) at an electrode/solution interface has been studied by electrochemical techniquies.[770]

X-Ray crystallography, although providing a detailed and definitive structure for a compound, is still an indirect procedure, not a direct photographic picture. With the advent of atomic force microscopy (AFM), however, direct imaging is now possible, and this technique has been applied to the calixarenes. A monolayer dispersion of $\mathbf{6}^{t\text{-Bu}}$ and octadecanol has been prepared and transferred to a treated mica surface and then studied by AFM.[771] Although the images are rather blurred, it is stated that their shape and size are in good accordance with dimensions estimated from inspection of CPK models.

[766] Huisman, B.-H.; van Delzen, E. U. T.; van Veggel, F. C. J. M.; Engbersen, J. F. J.; Reinhoudt, D. N. *Tetrahedron Lett.* **1995**, 36, 3273.

[767] Huisman, B.-H.; Rudkevich, D. M.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1996**, 118, 3523.

[768] Zhang, L.; Godinez, L. A.; Lu, T.; Gokel, G. W.; Kaifer, A. E. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 235.

[769] Dermody, D. L.; Crooks, R. M.; Kim, T. *J. Am. Chem. Soc.* **1996**, 118, 11912.

[770] Bernardo, A. R.; Lu, T.; Cordova, E.; Zhang, L.; Gokel, G. W.; Kaifer, A. E. *J. Chem. Soc., Chem. Commun.* **1994**, 529.

[771] Namba, M.; Sugawara, M.; Bühlmann, P.; Umezawa, Y. *Langmuir* **1995**, 11, 635.

CHAPTER 7

Using the Baskets: Calixarenes in Action

'It is not enough that you should understand about applied science in order that your work may increase man's blessings. Concern for the man himself and his fate must always form the chief interest of all technical endeavors; concern for the great unsolved problems of the organization of labor and the distribution of goods in order that the creations of our mind shall be a blessing and not a curse to mankind. Never forget this in the midst of your diagrams and equations'

Albert Einstein, speech at the California Institute of Technology, February 16, 1931

The boundary separating pure and mission-oriented research in the calixarene field is frequently fuzzy. While a utilitarian goal is not always explicitly stated in publications dealing with the calixarenes, it is generally implied that the research will, in one way or another, be useful. And, to an increasing extent, hopes for practrical applications *are* being clearly stated as the motivation for the particular research being described. Thus, much of the work presented in the previous chapters of this book provides the basis for the applied aspects of calixarene chemistry which are discussed in this chapter (for a review, see ref. 13j).

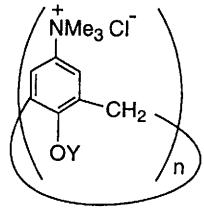
7.1 Calixarenes as Catalysts

The goal of designing calixarene-based catalysts has its roots at least as far back as the early 1970s when this book's author entered the field. In the 1980s a few examples of calixarene-catalyzed processes appeared, and a few more have been added in recent years. However, this remains the least well developed facet of calixarene chemistry and continues to pose an interesting intellectual and synthetic challenge to organic chemists.

The hydration of 1-benzyl-1,4-dihydronicotinamide catalyzed by $\mathbf{6}^{SO_3H}$ [772] and *p*-carboxycalix[*n*]arenes,[773] discussed in the previous volume (see ref. 1, pp.

[772] Shinkai, S.; Mori, S.; Koreishi, H.; Tsubaki, T.; Manabe, O. *J. Am. Chem. Soc.* **1986**, 108, 2409.
[773] Gutsche, C. D.; Alam, I. *Tetrahedron* **1988**, 44, 4689.

193–196), is the major example of a calixarene-catalyzed *addition* reaction. Most of the more recent examples are *hydrolysis* reactions such as the hydrolysis of 2,4-dinitrophenyl phosphate, which is catalyzed to a modest degree by calixarenes carrying *p*-trimethylammonium groups,[774] and by the base-induced hydrolysis of *p*-nitrophenyl dodecanoate,[775] which is dramatically catalyzed *ca.* 10^5-fold more effectively by **289** ($n = 6$; Y = Me or Oct) than by **289** ($n = 4$; Y = Me). The catalysis in the second example is partly the result of a deshielding effect but allegedly more the result of a host–guest interaction. Curiously, the hydrolysis of phenyl benzoates in $CHCl_3/MeOH/H_2O$–Na_2CO_3 is inhibited by *p-tert*-butylcalix[*n*]arenes, with $\mathbf{8}^{t\text{-Bu}}$ being the most effective inhibitor.[776] Modest regioselectivity in the ring-opening hydrolysis of cytidine-2′,3′-cyclic phosphate has been induced by *p*-sulfonatocalix[*n*]arenes, the largest value being a 3′/2′ cleavage ratio of 3.5 with $\mathbf{4}^{SO_3H}$ (as compared with a 1.5 ratio in the absence of a calixarene).[777] The most impressive hydrolysis catalyst to date[778] involves the calix[4]arene **273g**, which forms a complex containing a pair of Zn^{2+} ions. In the presence of this complex the rate at which $MeCH(OH)CH_2OPO_2C_6H_4NO_2$ undergoes conversion to a cyclic phosphate with extrusion of *p*-nitrophenol in neutral solution at 25 °C is increased by a factor of 2.3×10^4.

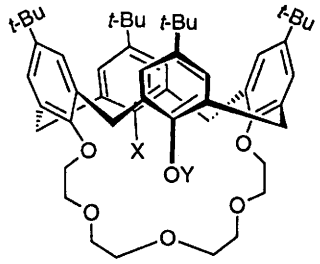


289

Several examples of selective 'olysis' reactions of calixarenes involve intramolecular catalytic phenomena. In the conversion of the diester **116** to the monoester **119** with imidazole in a $CHCl_3$/MeCN solution, the kinetics of the process suggest that two or more imidazoles are involved, one acting as a base to form a calixarene oxyanion and another acting as the nucleophlic receptor for the departing 3,5-dinitrobenzoyl moiety.[250] In what might be called 'pseudo intramolecular catalysis' the tetraesters **264** (R = *t*-Bu; R′ = alkyl; $n = 4$) in $CHCl_3$ or benzene solution undergo trifluoroacetic acid-catalyzed hydrolysis of a single ester moiety to yield the corresponding triester monoacids **268** ($Y^{1\text{-}3} = CH_2CO_2R'$; $Y^4 = CH_2CO_2H$).[622,779] The reaction is thought to be initiated by reversible complexation of H_3O^+ inside the cavity followed by attack of H_2O outside the cavity. In the presence of Na^+ (but not K^+), however,

[774] Shinkai, S.; Shirahama, Y.; Tsubaki, T.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1859.
[775] Shinkai, S.; Shirahama, Y.; Tsubaki, T.; Manabe, O. *J. Am. Chem. Soc.* **1989**, 111, 5477.
[776] Chawla, H. M.; Pathak, M. *Bull. Soc. Chim. Fr.* **1991**, 128, 232.
[777] Komiyama, M.; Isaka, K.; Shinkai, S. *Chem. Lett.* **1991**, 937.
[778] Molenveld, P.; Kapsabelis, S.; Engbersen. J. F. J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1997**, 119, 2948.
[779] Böhmer, V.; Vogt, W.; Harris, S. J.; Leonard, R. G.; Collins, E. M; Deasy, M.; McKervey, M. A.; Owens, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 431.

the reaction is curtailed as a result of preemption of the cavity site by the Na^+. Hydrolysis also fails to occur in dioxane or aqueous dioxane, solvents that are better solvaters of H_3O^+ than $CHCl_3$ or benzene. The termination of hydrolysis after the excision of a single ROH group is attributed to a change in conformation (supported by an X-ray crystal structure of the monoacid; see p. 155) and the consequent lower affinity of the cavity for complexation with the hydronium ion. Selective monohydrolysis has also been observed in several other cases including the diester diketone **268h**, although the analogous diester diamide **268i** is resistant to hydrolysis under these conditions. Still another example of intramolecular catalysis is seen in the base-induced hydrolysis of the monobenzoate esters of calix[4]arenes, which are viewed as 'partial models of the active site of an acyl intermediate in the mechanism of a proteolytic enzyme possessing an oxyanion pocket', the goal being to elucidate the role of the hydrogen-bonded network.[102] The hydrolysis rates of calixarenes bearing variously *p*-substituted benzoyl moieties show a negative Hammett ρ reaction constant, leading to the conclusion that the reaction involves an attack of OH^- on the mono- and dianions of the calixarene. The enhanced rates compared with the monomeric analogs are ascribed to intramolecular hydrogen bonding involving the un-ionized phenolic groups.



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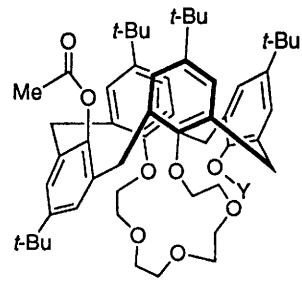
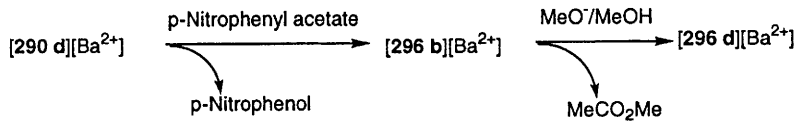
a) X = OH; Y = COMe
b) X = O⁻; Y = COMe
c) X = OH; Y = H
d) X = O⁻; Y = H



291 **a)** Y = COMe
b) Y = H

In another interesting example of pseudo intramolecular catalysis, the half-time for the methanolysis of the calixarene monoacetate **290a** with Me_4N^+ OMe^- in MeOH at 25 °C is reduced from 34 weeks to 8 seconds by the addition of Ba^{2+}.[348] The reactive species is thought to be the Ba^{2+} complex of the calixarene monoanion **290b** in which Ba^{2+} coordinates intramolecularly with the acyl carbonyl group to activate it toward attack by MeO^- to produce **290c**. Advantage is taken of this phenomenon in the preparation of the monoacetate of the partial cone conformer **291b** by partial hydrolysis of the diacetate **291a** using Me_4NOMe and $BaBr_2$ in MeOH.[349] Advantage is also taken in the design of a nucleophilic catalyst with transacylase activity. Using *p*-nitrophenyl acetate as

the substrate, Ungaro and coworkers[780] showed that its methanolysis to *p*-nitrophenol and methyl acetate in MeCN–MeOH solution with R_3N buffer is catalyzed by the Ba^{2+} complex of **290d** in a two-step process that involves the Ba^{2+} complex of **290b** as the intermediate. The kinetics are commensurate with the formation of an intermediate, and the presence of **290a** in a quenched reaction mixture was established by HPLC analysis. The overall reaction, represented below, is a true catalytic process, although the turnover number of 5.5×10^{-3} min^{-1} (*i.e.* 8 per day) is very small.



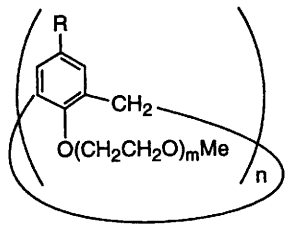
Nomura and coworkers have studied the phase transfer catalytic capability of the hexa(3,6,9-trioxadecyl) ether of $\mathbf{6}^{t\text{-Bu}}$ (**292a**) in several reaction systems, including (*a*) $ArOM + ArCH_2Br \rightarrow ArCH_2OAr$;[781] (*b*) $RCO_2M + p\text{-}O_2NC_6H_4CH_2Br \rightarrow RCO_2CH_2C_6H_4NO_2$;[338] (*c*) $R_2C{=}CR_2 + [{:}CCl_2] \rightarrow$ dichlorocyclopropanes;[782] (*d*) $RCH{=}CH_2$ or $RC{\equiv}CH$ or $RCH_2OH + KMnO_4 \rightarrow RCO_2H$.[783] Under certain conditions the effectiveness of the calixarene is generally equal to or greater than that of the tetraalkylammonium salts or 18-crown-6 compounds. Thus, reactions (*a*), (*b*), and (*d*) are catalyzed in CH_2Cl_2 solution but not in benzene solution, and a small amount of H_2O facilitates the reactions (except for the oxidation of $RC{\equiv}CH$). Rate studies of reactions (*b*) and (*c*) indicate that Michaelis–Menten kinetics are followed, from which the conclusion is drawn that the reactions occur within the cavity of the calixarene. The critical necessity for a 3,6,9-trioxadecyl chain in the calixarene ether has been questioned, however, for **292b** proves to be a somewhat more effective catalyst in reaction (*b*) than its trioxadecyl ether counterpart.[271]

An example of a catalytic phenomenon in which the phenolic OH groups play a part is the 'autoaccelerative' diazo coupling between calix[4]arene and arenediazonium compounds in which the tetra-*p*-substituted calixarene is almost the exclusive product even when starting material still remains.[784] Phenolic substrates are reported to be regioselectively hydroxylated with H_2O_2 in the presence of a cerium(IV)–calix[8]arene complex.[785]

A reaction involving what might be called 'proximity catalysis' is that of the hydroxymethylcalix[4]arene **180i** with toluene in the presence of toluenesulfonic acid. The product is a mixture of tolylmethylcalix[4]arenes in an *ortho/meta/*

[780] Cacciapaglia, R.; Casnati, A.; Mandolini, L.; Ungaro, R. *J. Am. Chem. Soc.* **1992**, 114, 10956.
[781] Tanaguchi, H.; Nomura, E. *Chem. Lett.*, **1988**, 1773; Nomura, E.; Taniguchi, H.; Kawaguchli, K.; Otsuji, Y. *Chem. Lett.* **1991**, 2167; Taniguchi, H.; Otsuji, Y.; Nomura, E. *Bull. Chem. Soc. Jpn.* **1995**, 68, 3563.
[782] Nomura, E.; Taniguchi, H.; Otsuji, Y. *Bull. Chem. Soc. Jpn.* **1994**, 67, 792.
[783] Nomura, E.; Taniguchi, H.; Otsuji, Y. *Bull. Chem. Soc. Jpn.* **1994**, 67, 309.
[784] Shinkai, S.; Araki, K.; Shibata, J.; Tsugawa, D.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3333.
[785] Chawla, H. M.; Hooda, U.; Singh, V. *J. Chem. Soc., Chem. Commun.* **1994**, 617.

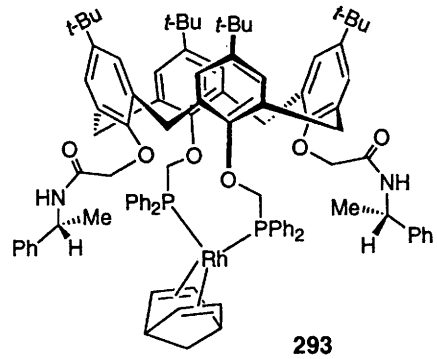
para ratio of 78/13/9, attributed to the methyl-group-in-the-cavity orientation of the toluene molecule.[786]



292

a) R = *t*-Bu; m = 3; n = 6

b) R = *t*-Oct; m = 1; n = 4



293

The rhodium complex **293** of a calix[4]arene carrying diphenylphosphinomethoxy groups on the lower rim catalyzes the hydroformylation of styrene to 2-phenylpropanal and 3-phenylpropanal in a 95:5 ratio.[787] The rate, however, is lower than that usually observed with rhodium–diphosphane complexes and is postulated to possibly be the result of the 'semi-encapsulated' character of the metal atom in the complex.

7.2 Ion Separations[788]

The first patent explicitly describing a calixarene for a practical application was issued in 1984 and described the use of $\mathbf{8}^{t\text{-Bu}}$ for the recovery of cesium from nuclear wastes. Several papers relating to the complexation of cesium by modified calixarenes have since appeared (see Chapter 6), including one specifically directed to the problem of nuclear wastes which discusses the efficacy of **208** [X = $(OCH_2CH_2)_2OArO(CH_2CH_2O)_2$ with Ar = 1,2-phenylene or 2,3-naphthylene] in supported liquid membranes.[789] The intriguing prospect of recovering uranium from sea water,[459c,461,630a,b] discussed in the previous volume (see ref. 1, pp. 173, 190–191), continues to command attention, *e.g.* through the use of flotation techniques.[790] A polymer-supported calix[4]arene[791] selectively extracts Fe^{3+} from an aqueous solution also containing Cu^{2+} Ni^{2+}, and Co^{2+}.

[786] Struck, O.; van Duynhoven, J. P. M.; Verboom, W.; Harkema, S.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1996**, 1517.

[787] Loeber, C.; Wieser, C.; Matt, D.; De Cian, A.; Fischer, J.; Toupet, L. *Bull. Soc. Chim. Fr.* **1995**, 132, 166.

[788] For brief review, see Perrin, R. 'New Separation Chemistry Techniques for Radioactive Waste and Other Specific Applications'; Elsevier Applied Science: London; **1991**, p. 125.

[789] Hill, C.; Dozol, J.-F.; Lamare, V.; Rouquette, H.; Eymard, S.; Tournois, B.; Vicens, J.; Asfari, Z.; Bressot, C.; Ungaro, R.; Casnati, A. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 399.

[790] Koide, Y.; Terasaki, H.; Sato, H.; Shosenji, H.; Yamada, K. *Bull. Chem. Soc. Jpn.* **1996**, 69, 785.

[791] Deligöz, H.; Tavasli, M.; Yilmaz, M. *J. Polymer Sci., Part A* **1994**, 32, 2961; Deligöz, H.; Yilmaz, M. *Reactive Functional Polymers* **1996**, 31, 81.

The Hg^{2+} complex of a calix[4]arene carrying thioamide groups on the lower rim has been incorporated into a membrane that shows anion selectivity.[792]

Calixarene **264** (R = $CH_2CH{=}CH_2$; R′ = Et; $n = 4$) has been covalently attached to silica *via* the allyl groups to provide a column material suitable for separation of alkali cations by HPLC, using conductivity detection.[793] Similarly, calix[4]arenecrown compounds **130a** (R = H and $CH_2CH{=}CH_2$; $Y^{1,2}$ = *n*-Pr) have been affixed to silica gel and used for chromatographic separation of Cs^+ and K^+ from alkali metal ions.[794]

7.3 Molecular Separations

7.3.1 Separations *via* Chromatographic Columns and Crystallization

Relatively few molecular separations have been studied from the utilitarian standpoint. One of these, the purification of fullerenes *via* $\mathbf{8}^{t\text{-Bu}}$, is discussed on p. 170. In a reciprocal experiment the separation of $\mathbf{4}^{t\text{-Bu}}$, $\mathbf{6}^{t\text{-Bu}}$, and $\mathbf{8}^{t\text{-Bu}}$ with a column using a chemically-bonded C_{60} silica stationary phase has been reported.[795] Chromatographic selectivity has been achieved[796] for amino acid esters and alkali metal cations on silica-bonded calix[4]arene tetraesters, the structure of which has been explored by ^{13}C and ^{29}Si-CP-MAS NMR.[797] Silica-bonded calixarenes have also been used as packing materials for HPLC columns that are capable of separating disubstituted aromatics, peptides, and nucleosides.[798] The HPLC separation of phenols using $\mathbf{6}^{SO_3H}$ as a constituent of the eluent has been described.[799]

Xylenes have been separated by extractive crystallization using $\mathbf{4}^{i\text{-Pr}}$,[800] and the removal of trihalomethanes from chlorinated water with $\mathbf{6}^{t\text{-Bu}}$ has been reported.[801]

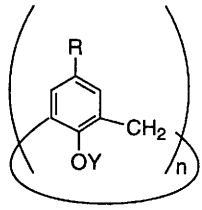
p-Sulfonatocalix[6]arene has been used as an additive in capillary electrophoretic separations of chlorophenols, benzenediols, and toluidines.[802] *p*-Carboxyethylcalix[4–8]arenes have been investigated for their ability to effect

[792] Wrobleviski, W.; Malinowska, E.; Brzózka, Z. *Electroanalysis* **1996**, 8, 75.
[793] Glennon, J. D.; O'Connor, K.; Srijaranaj; S.; Manley, K.; Harris, S. J.; McKervey, M. A. *Anal. Lett.* **1993**, 26, 153; Glennon, J. D.; Horne, E.; Hall, K.; Cocker, D.; Kuhn, A.; Harris, S. J.; McKervey, M. A. *J. Chromatogr. A* **1996**, 731, 47.
[794] Arena, G.; Casnati, A.; Contino, A.; Mirone, L.; Sciotto, D.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1996**, 2277.
[795] Saito, Y.; Ohta, H.; Terasaki, H.; Katoh, Y.; Nagashima, H.; Jinno, H.; Itoh, K.; Trengove, R. D.; Harrowfield, J. M.; Li, S. F. Y. *J. High Resolut. Chromatogr.* **1996**, 19, 475.
[796] Glennon, J. D.; Horne, E.; O'Conner, K.; Kearney, G. A.; Harris, S. J.; McKervey, M. A. *Anal. Proc.* **1994**, 31, 33.
[797] Brindle, R.; Albert, K.; Harris, S. J.; Tröltzsch, C.; Horne, E.; Glennon, J. D. *J. Chromatogr. A* **1996**, 731, 41.
[798] Friebe, S.; Gebauer, S.; Krauss, G. J.; Goermar, G.; Krueger J. *J. Chromotogr. Sci.* **1995**, 33, 281.
[799] Park, J. H.; Lee, Y. K.; Cheong, H. Y.; Jang, M. D. *Chromatographia* **1993**, 37, 221.
[800] Vicens, J.; Armah, A. E.; Fujii, S.; Tomita, K.-I. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1991**, 10, 159.
[801] Barbara, S.; Tamke, R. L.; Wainwright, K. P. *Chem. Ind. (London)* **1990**, 804.
[802] Shohat, D.; Grushka, E. *Anal. Chem.* **1994**, 66, 747.

separations of polyaromatic hydrocarbons *via* capillary electrokinetic chromatography.[803]

7.3.2 Separations *via* Interfaces

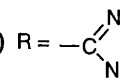
In the late 1980s, Regen and coworkers initiated a program aimed at the separation of small gaseous molecules. It involved the preparation of organic thin films ('perforated monolayers or multilayers') possessing well defined and adjustable pore structures.[804] After initial disappointments, they eventually found that a multilayered film as thin as 80 Å prepared by UV-induced polymerization of **294a** ($n = 6$) on a poly[(1-trimethylsilyl)-1-propyne] support affords a molecular sieve that allows the passage of He and N_2 but not the larger SF_6.[315] However, in a subsequent study of monolayers prepared from **294b** ($n = 4$) (internal dia 2.0 Å), **294b** ($n = 5$) (internal dia 3.6 Å), and **294b** ($n = 6$) (internal dia 4.8 Å) with a mixture of He (kinetic dia 2.6 Å) and SF_6 (kinetic dia 5.5 Å) as the permeant it was revealed that the passage of the gases through the films occurs by diffusion between the neighboring molecules rather than through the pores of the calixarenes.[805] Nevertheless, with a film prepared from **294c** ($n = 6$) in which the cohesiveness between molecules is promoted by hydrogen bonding, a Ne/N_2 flux ratio as high as 150 was measured.[806] What is described as 'extraordinary cohesiveness at the air–water interface' is observed with monolayers prepared from the hexadecyl ether of the boronic acid **294d**.[807]



294

a) R = $CONHCH_2CH_2SSCH_3$; Y = C_8H_{17}

b) R = $CONMe_2$; Y = C_8H_{17}

c) R =  ; Y = C_8H_{17}

d) R = $CH_2CH_2CH_2B(OH)_2$; Y = $C_{16}H_{33}$

Separations of molecules by membranes play a crucial role in biological systems, and they are proving to have important industrial applications as well. Therefore, considerable attention, particularly by Reinhoudt and coworkers,[808] is being devoted to the use of calixarenes as the carrier molecules in liquid membranes. An early demonstration showed, for example, that selective transport of K^+ can be achieved through a supported liquid membrane (SLM) containing the calix[4]arene-crown-5 (**130a**; R = *t*-Bu; $n = 3$).[646] A more recent

[803] Sun, S.; Sepaniak, M. J.; Wang, J.-S.; Gutsche, C. D. *Anal. Chem.* **1997**, 69, 344.
[804] Markowitz, M. A.; Bielski, R.; Regen, S. L. *J. Am. Chem. Soc.* **1988**, 110, 7545; Markowitz, M. A.; Janout, V.; Castner, D. G.; Regen, S. L. *ibid.* **1989**, 111, 8192.
[805] Dedek, P.; Webber, A. S.; Janout, V.; Hendel, R. A.; Regen, S. L. *Langmuir* **1994**, 10, 3943.
[806] Lee, W.; Hendel, R. A.; Dedek, P.; Janout, V.; Regen, S. L. *J. Am. Chem. Soc.* **1995**, 117, 6793.
[807] Hendel, R. A.; Janout, V.; Lee, W.; Regen, S. L. *Langmuir* **1996**, 12, 5745.
[808] For reviews, see van Straaten-Nijenhuis, W. F.; de Jong, F.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1993**, 112, 317; Visser, H. C.; Reinhoudt, D. N.; de Jong, F. *Chem. Soc. Rev.* **1994**, 23, 75.

example[809] makes use of calix[4]arene-biscrowns **131a** and **131b** in SLMs for selective cesium extraction (*vide supra*). Another study focuses on the attachment of a 2-nitrophenyl octyl ether moiety to calix[4]arenes and calix[4]arenecrowns to improve the compatibility of these carriers with the membrane solvents, providing membranes that are stable for long periods of time and at elevated temperatures.[810] Selective transport of Na^+ through very thin (*ca.* 30 Å) phospholipid bilayer membranes with **264b** as the carrier has recently been achieved.[811] The intercalation of *p*-trimethylammoniumcalix[4]arene by Cu(II)-montmorillonite provides another example of a potentially useful material for chromatographic application.[812]

7.4 Calixarenes as Sensors

(for reviews, see refs. 813–817)

The design of sensors to monitor the activity of chemical and biochemical species in various environments is an important and growing field of science that requires the interaction of a variety of disciplines, from solution chemistry to solid state electronics. For constructing a chemically-based sensor the task is first to design a system that is sensitive specifically to the species being monitored and then to devise a way for transducing the chemical response, which is at the molecular level, to an electrical or optical signal at the macroscopically observable and measurable level. Calixarenes have been employed in such devices in a variety of interesting ways.

7.4.1 Ion- and Molecule-selective Electrodes

Electrodes selective for H^+ (*i.e.* pH meters) have been known for many years. Electrodes selective for other ions, however, are a more recent arrival, their entrance due in large part to the work of Simon and coworkers.[818] Because of the medical importance of such sensors, particularly for blood analysis, the alkali and alkaline earth cations have been given major attention in developing these electrodes, the first calixarene-based ion selective electrode[819] being designed for Na^+. McKervey and Diamond and their coworkers have been especially active in this field and have devised ion selective electrodes for Na^+ using compounds

[809] Asfari, Z.; Bressot, C.; Vicens, J.; Hill, C.; Dozol, J.-F.; Rouquette, H.; Eymard, S.; Lamare, V.; Tournois, B. *Anal. Chem.* **1995**, 67, 3133.
[810] Visser, H. C.; Vink, R.; Snellink-Ruel, B. H. M.; Kokhuis, S. B. M.; Harkema, S.; de Jong, F.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1995**, 114, 285.
[811] Jin, T.; Kinjo, M.; Koyama, T.; Kobayashi, Y.; Hirata, H. *Langmuir* **1996**, 12, 2684.
[812] Kijima, T.; Ohe, K.; Shinkai, S.; Nagasaki, T. *Bull. Chem. Soc. Jpn.* **1992**, 65, 2510; Kijma, T.; Kato, Y.; Ohe, K.; Machida, M.; Matsushita, Y.; Matsui, T. *Bull. Chem. Soc. Jpn.* **1994**, 67, 2125.
[813] Forster, R. J.; Cadogan, A.; Diaz, M. T.; Diamond, D.; Harris, S. J.; McKervey, M. A. *Sens. Actuators B* **1991**, 4, 325.
[814] Diamond, D. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 149.
[815] Diamond, D.; McKervey, M. A. *Chem. Soc. Rev.* **1996**, 25, 15.
[816] Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1996**, 115, 109.
[817] De Silva, A. P.; McCoy, C. P, *Chem. Ind. (London)* **1994**, 995.
[818] For a review, see Widner, H. M. *Anal. Methods Instrum.* **1993**, 1, 3.
[819] Diamond, D. *Anal. Chem. Symp. Ser.* **1986**, 25, 155; Diamond, D.; Svehla, G. *Trends Anal. Chem.* **1987**, 6, 46.

such as the tetraesters **264** (R = H or *t*-Bu; R′ = alkyl; $n = 4$),[820,821] and the analogous triesters.[822] Particularly effective are the methoxymethyl ester **264** (R = *t*-Bu, R′ = CH_2CH_2OMe; $n = 4$)[823] and the partial cone conformer of the calix[4]crown compound **270b** which shows a Na^+/K^+ selectivity[824] of 10^5. A Na^+ selective electrode especially useful for protein solutions is a calix[4]monoquinone bridged A,C with a crown ether moiety.[532] An anomalously high potential response is reported for the proton-dissociable ionophore **268e**.[825] Ion selective electrodes based on the *t*-butoxycarbonylmethyl ether of bisoxatetrahomocalix[4]arene[826] and *p-tert*-butylcalix[4]arene-crown-5[827] are selective for K^+; electrodes based on the ethoxycarbonylmethyl ether of $\mathbf{6}^{t\text{-Bu}}$[828] and the diisopropyl ether of calix[4]arene-crown-6 in the 1,3-alternate conformation[829] are selective for Cs^+; and electrodes based on the diphenylphosphorylethyl ether of $\mathbf{4}^{t\text{-Bu}}$ are selective for Ca^{2+}.[830]

Ion selective electrodes for a variety of cations other than the alkali metal cations have also been designed.[831] Calix[4]arenes carrying four $OCH_2CO_2CHN(CH_2)_3C{=}O$, $CH_2C(S)NEt_2$, or $CH_2CO_2CH_2CH_2SMe$ groups on the lower rim are useful for sensing Ag^+, Cu^{2+}, and Pb^{2+} cations,[832,833] the last of these compounds showing a log 1.16 selectivity in favor of Ag^+ over Na^+. A number of $OP(S)(OEt)_2$ substituted $\mathbf{6}^{t\text{-Bu}}$ compounds show selectivity for Pb^{2+} over Cd^{2+}, the best being the A,C-disubstituted compound.[834] By the use of $C_5H_5N^+CH_2CONHNH_2$ (Girards reagent) as the

[820] Diamond, D.; Svehla, G.; Seward, E. M.; McKervey, M. A. *Anal. Chim. Acta* **1988**, 204, 223; Cadogan, A.; Gao, Z.; Lewenstam, A.; Ivaska, A. *Anal. Chem.* **1992**, 64, 2496. Similar esters have also been studied by Kimura, K.; Matsuo, T.; Shono, T. *Chem. Lett.* **1988**, 615; Shibutani, Y.; Yoshinaga, H.; Yakabe, K.; Shono, T.; Tanaka, M. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, 19, 333. The particular efficacy of the esters has been affirmed by a study by Sakaki, T.; Takaaki, H.; Deng, G.; Kawabata, H.; Kawahara, Y.; Shinkai, S. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, 14, 285.

[821] O'Conner, K. M.; Cherry, M.; Svehla, G.; Harris, S. J.; McKervey, M. A. *Talanta* **1994**, 41, 1207.

[822] Grady, T.; Cadogan, A.; McKittrick, T.; Harris, S. J.; Diamond, D.; McKervey, M. A. *Anal. Chim. Acta* **1996**, 336, 1.

[823] Cadogan, A.; Diamond, D.; Smyth, M. R.; Deasy, M.; McKervey, M. A.; Seward, E. M.; Harris, S. J. *Analyst (London)* **1989**, 114, 1551; Diamond, D.; Svehla, G.; Seward, E. M.; McKervey, M. A. *Anal. Chim. Acta* **1988**, 204, 223; Cunningham, K.; Svehla, G.; Harris, S. J.; McKervey, M. A. *Anal. Proc.* **1991**, 28, 294.

[824] Yamamoto, H.; Shinkai, S. *Chem. Lett.* **1994**, 1115.

[825] Kimura, K.; Sakai, A.; Yokoyama, M. *Supramol. Chem.* **1996**, 7, 107.

[826] Cadogan, A.; Diamond, D.; Cremin, S.; McKervey, M. A.; Harris, S. J. *Anal. Proc.* **1991**, 28, 13.

[827] Brzozka, Z.; Lammerink, B.; Reinhoudt, D. N.; Ghidini, E.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1037.

[828] Cadogan, A.; Diamond, D.; Smyth, M. R.; Svehla, G.; McKervey, M. A.; Seward, E. M.; Harris, S. J. *Analyst (Cambridge)* **1990**, 115, 1207.

[829] Bocchi, C.; Careri, M.; Casnati, A.; Mori, G. *Anal. Chem.* **1995**, 67, 4234.

[830] McKittrick, T.; Diamond, D.; Marrs, D. J.; O'Hagan, P.; McKervey, M. A. *Talanta* **1996**, 43, 1145.

[831] For an extensive review of ISFETs for heavy metal ions, see Cobben, P. L. H. M., Ph.D. Thesis, Universiteit Twente, Enschede, The Netherlands, **1992**.

[832] O'Conner, K. M.; Svehla, G.; Harris, S. J.; McKervey, M. A. *Talanta* **1992**, 39, 1549; O'Conner, K. M.; Svehla, G.; Harris, S. J.; McKervey, M. A. *Anal. Proc.* **1993**, 30, 137.

[833] Malinowska, E.; Brzózka, Z.; Kasiura, K.; Egberink, R. J. M.; Reinhoudt, D. N. *Anal. Chim. Acta* **1994**, 298, 245.

[834] Wroblewski, W.; Brzózka, Z.; Janssen, R. G.; Verboom, W.; Reinhoudt, D. N. *New J. Chem.* **1996**, 20, 419.

cationic species, a formaldehyde-selective electrode has been designed.[835] Carbon paste electrodes have been prepared from a calixarene polymer and shown to be applicable to voltammetric methods of analysis.[836]

Anion selective electrodes are much less well-developed than their cation counterparts, the first calixarene-based entry into this field being a calix[4]arene carrying two cobalticinium groups on the upper rim which shows some ability to recognize adipate anions (see ref. 1, p. 135).[454]

Electrodes selective for a variety of molecules have been devised, one example being the esters **264b,d,f** which act as the host for the hydrazone generated *in situ* from heptanal and Girards reagent-P. It is claimed that as little as 3.4 μg of heptanal can be detected.[837] In comparable fashion, glucose can be determined with a calix[6]arene-containing ion sensitive electrode by *in situ* derivatization with lipophilic Girards-P reagent.[838] Other examples include the use of various calix[8]arenes for sensing ammonium and pyridinium surfactants[839,840] and the calix[6]arene **264** (R = H; R′ = $C_{10}H_{21}$; n = 6) for discriminating among primary amines carrying R groups of various shapes and sizes.[841] Carboxylic acids have been determined by *in situ* conversion to amines and subsequent detection with a calix[6]arene chromophore.[842]

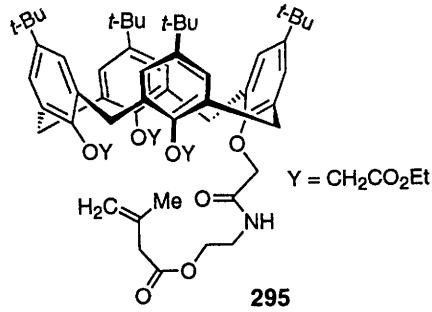
7.4.2 Field Effect Transistors

(for reviews, see refs. 816 and 843)

Field effect transistors (FETs) combine the ion selective electrode and solid state technologies and are referred to as CHEMFETs (chemically modified field effect transistors) and MEMFETs (membrane modified field effect transistors) or, more specifically, ISFETs (ion selective field effect transistors). They consist of a source region and a drain region embedded on a p-type silicon substrate and separated by a gate region, the conductance through which is sensitive to the surrounding environment.[844] Thus, the deposition on the gate region of a film containing an ion selective compound renders the conductance between the source and drain regions ion selective and allows this chemical response to be transduced into an electrical response. The various types of calixarenes that are effective for ion selective electrodes (*vide supra*) act in a comparable fashion in ISFETs, as first shown by Reinhoudt and coworkers[845] using the conformation-

[835] Chan, W. H.; Yuan, R. *Analyst (Cambridge)* **1995**, 120, 1055.
[836] Arrigan, D. W. M.; Svehla, G.; Harris, S. J.; McKervey, M. A. *Anal. Proc.* **1992**, 29, 27; *idem. Electroanalysis* **1994**, 6, 97.
[837] Chan, W. H.; Cai, P. X.; Gu, X. H. *Analyst (Cambridge)* **1994**, 119, 1853.
[838] Chan, W. H.; Wong-Leung, Y. L.; Lai, T. F.; Yuan, R. *Anal. Lett.* **1997**, 30, 45.
[839] Shvedene, N. V.; Shishkanova, T. V.; Pietnev, I. V.; Belchenko, N. V.; Kovalev, V. V.; Rozov, A. K.; Shokova, E. A. *Anal. Lett.* **1996**, 29, 843.
[840] Shvedene, N. V.; Nemilova, M. Y.; Kovalev, V. V.; Shokova, E. A.; Rozov, A. K.; Pletnev, I. V. *Sens. Actuators B* **1995**, 26–27, 372.
[841] Odashima, K.; Yagi, K.; Tohda, K.; Umezawa, Y. *Anal. Chem.* **1993**, 65, 1074.
[842] Lee, A. W. M.; Chan, W. H.; Lam, Y. S. *Analyst (Cambridge)* **1995**, 120, 2841.
[843] Reinhoudt, D. N. *Sens. Actuators B* **1992**, 6 179.
[844] For a good picture, see Chaabane, R. B.; Gamoudi, M.; Guillaud, G.; Jouve, C.; Lamartine, R.; Bouazizi, A.; Maaref, H. *Sens. Actuators B* **1996**, 31, 41.
[845] Sudhölter, E. J. R.; van der Waal, P. D.; Skowronska-Ptasinska, M.; van den Berg, A.; Bergveld, P; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1990**, 109, 222.

ally flexible dimethyl ether of calix[4]arene-crown-5 **130a** ($Y^{1,2}$ = Me; n = 3) and its conformationally fixed diethyl ether analog in the partial cone conformation[827] for K^+ determination. The di-*n*-propyl ether of calix[4]arene-crown-6 **130a** ($Y^{1,2}$ = Pr; n = 4) in the 1,3-alternate conformation is useful for Cs^+ determination.[846] Ion selective CHEMFETs for various other ions including Cu^{2+} with **129d**, Cd^{2+} with **129e**, and Pb^{2+} with **129f** (R = *t*-Bu) have been reported.[333] This same group of workers has found, however, that better results are obtained if the ionophore is covalently bound to the polysiloxane membrane that covers the gate region. This has been accomplished, for example, with the calix[4]arene **295** carrying a methacrylate group which allows it to be copolymerized with polysiloxane and tetraphenylborate.[847] A similar approach is reported by Kimura and coworkers[848] using calix[4]arenes carrying oligosiloxane moieties in silicone rubber membranes. A guanidinium-selective CHEMFET makes use of the calix[6]arene **275b** as the ionophore in a PVC membrane containing potassium tetrakis(4-chlorophenyl)borate which acts as a cation exchanger to extract preferentially the more lipophilic guanidinium cation into the membrane.[849]



295

7.4.3 Chromogenic and Fluorescent Sensors

Substances that change color or change fluorescence in response to a change in their environment are an integral part of nature and have been put to human use since antiquity, a modern example of long-standing being the application of indicator compounds to measure acidity and basicity. In recent years, increasing attention has been paid to such chromogenic molecules, and a number of calixarene-based systems have been studied. One of the simplest is $\mathbf{4}^{SO_3H}$ which

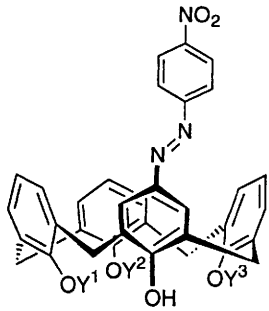
[846] Lugtenberg, R. J. W.; Brzózka, Z.; Casnati, A.; Ungaro, R.; Engbersen, J. F. J.; Reinhoudt, D. N. *Anal. Chim. Acta* **1995**, 310, 263.

[847] Brunik, J. A. J.; Lugtenberg, R. J. W.; Brzezka, Z.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Electroanal. Chem.* **1994**, 378, 185; Cacciapaglia, R. F.; van Doorn, A. R.; Mandolini, L.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1992**, 114, 2611.

[848] Kimura, K.; Matsuba, T.; Tsujimura, Y.; Yokoyama, M. *Anal. Chem.* **1992**, 64, 2508; Tsujimura, Y.; Yokoyama, M.; Kimura, K. *Electroanalysis* **1993**, 5, 893; Kimura, K.; Tsujimura, Y.; Yokoyama, M.; Yamada-oka, S. *Pure Appl. Chem.* **1995**, 67, 1085; Tsujimura, Y.; Yokayama, M.; Kimura, K. *Anal. Chem.* **1995**, 67, 2401.

[849] Kremer, F. J. B.; Chiosis, G.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans.* 2 **1994**, 677.

forms a colored complex with Ce^{3+} and, thus, is specific for this ion among the rare earths.[850] Other early examples employ the calix[4]arene **296a** carrying a *p*-nitrophenylazo chromophore which changes its absorption when the Li^+ complex forms,[851] and the *p*-quinoneimine **297** which undergoes a bathochromic shift upon complexation[852] with Na^+. A related example is **296b** in which the lower rim carries a crown-4 moiety and which shows a Na^+/K^+ selectivity of $> 10^{3.1}$, making it useful for optical sensing systems.[531] In fact, solutions of **296b** in soda-glass flasks rapidly turn deep green, which is the color of the Na^+ complex. Calixarenes carrying *p*-nitrophenylazo[853] or bridging phenylazo moieties[510,514a] on the upper rim have been prepared as chromogenic agents. 3-Hydroxy-4-nitrophenyl and 2-hydroxy-4-(*p*-nitrophenylazo)benzyl moieties have been attached to the lower rim of calix[4]arenes, providing sensors **298a** and **298b** in which the λ_{max} changes from *ca.* 350 and 380 nm in the absence of metal ions to *ca.* 430 nm[854] and 520 nm,[855] respectively, in the presence of Li^+ ions. Indoaniline-derived calixarenes **231** carrying CH_2CO_2Et ether groups,[536,856] show a bathochromic shift upon complexation with Ca^{2+}.



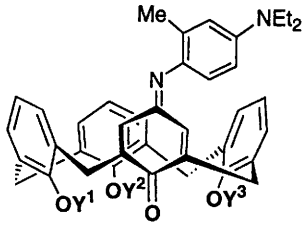
a) $Y^{1\text{-}3} = CH_2CO_2Et$

b) $Y^1, Y^3 = CH_2(CH_2OCH_2)_2CH_2$; $Y^2 = Et$

296

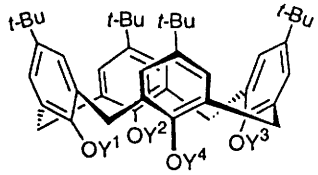
Ion sensitive detectors taking advantage of the great sensitivity of fluorescence have been made by affixing moieties such as anthracene,[857] pyrene,[858,859] and bithiazolyl[860] to the lower rim of calix[4]arenes. In the pyrene compound[858a] a *p*-nitrobenzyl group is also affixed to the lower rim to give **299**, providing a system in which the pyrene fluorescence is quenched in the absence of a metal ion

[850] Yoshida, I.; Yamamoto, N.; Sagara, F.; Ueno, K.; Ishii, D.; Shinkai, S. *Chem. Lett.* **1991**, 2105.
[851] Shimizu, H.; Iwamoto, K.; Fujimoto, K.; Shinkai, S. *Chem. Lett.* **1991**, 2147.
[852] Kubo, Y.; Hamaguchi, S.-i.; Kotani, K.; Yoshida, K. *Tetrahedron Lett.* **1991**, 32, 7419.
[853] Gordon, J. L. M.; Böhmer, V.; Vogt, W. *Tetrahedron Lett.* **1995**, 36, 2445.
[854] McCarrick, M.; Wu, B.; Harris, S. J.; Diamond, D.; Barrett, G.; McKervey, M. A. *J. Chem. Soc., Chem. Commun.* **1992**, 1287; *idem. J. Chem. Soc., Perkin Trans. 2* **1993**, 1963.
[855] McCarrick, M.; Harris, S. J.; Diamond, D. *Analyst (Cambridge)* **1993**, 118, 1127.
[856] Kubo, Y.; Hamaguchi, S.-i.; Niimi, A.; Yoshida, K.; Tokita, S. *J. Chem. Soc., Chem. Commun.* **1993**, 305.
[857] Pérez-Jiménez, C.; Harris, S. J.; Diamond, D. *J. Chem. Soc., Chem. Commun.* **1993**, 480; Pérez-Jiménez, C.; Harris, S. J.; Diamond, D. *J. Mater. Chem.* **1994**, 4, 145.
[858] (a) Aoki, I.; Sakaki, T.; Tsutsui, S.; Shinkai, S. *Tetrahedron Lett.* **1992**, 33, 89; (b) Aoki, I.; Sakaki, T.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* **1992**, 730.
[859] Jin, T.; Ichikawa, K.; Koyama, T. *J. Chem. Soc., Chem. Commun.* **1992**, 499.
[860] Pellet-Rostaing, S.; Regnouf-de-Vains, J.-B.; Lamartine, R. *Tetrahedron Lett.* **1996**, 37, 5889.

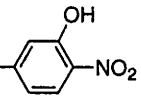


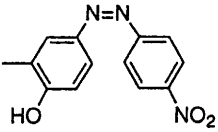
Y = CH_2CO_2Et

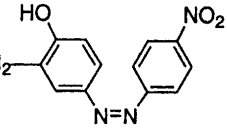
297

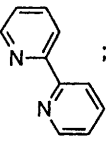


298

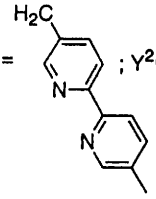
a) $Y^{1-3} = CH_2CO_2Et$; $Y^4 = CH_2CO_2CH_2$ 

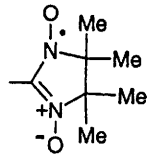
b) $Y^{1-3} = CH_2CO_2Et$; $Y^4 = CH_2CO_2CH_2$ 

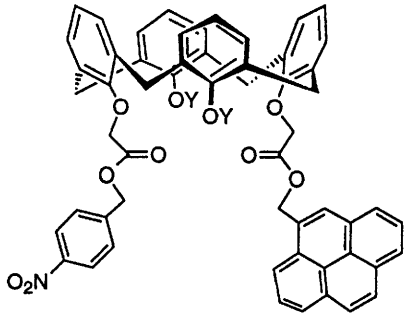
c) $Y^{1-4} = CH_2CH_2CO_2CH_2$ 

d) $Y^1 =$ 

; $Y^{2-4} = H$

e) $Y^{1,3} =$ 

; $Y^{2,4} =$ 



299

but active in its presence. Employing the fluorescence properties of Ru^{2+}, a pH sensor has been devised from calix[4]arene **298d** which forms a complex with Ru^{2+} in which the fluorescence becomes a function of whether the calixarene is in the phenol or phenolate form.[861]

In addition to ions, molecules have also been the target of calixarene-based chromogenic and fluorescent sensors. A particularly intriguing example is the chiral calixarene **300** which experiences a 148 nm bathochromic shift upon complexation with butyl amines (*t*-Bu ≫ *s*-Bu > *i*-Bu > *n*-Bu) and which produces different colored complexes **301** with the *R* and *S* enantiomers of 1-phenylethylamine.[549] Another compound capable of discriminating between enantiomers of 1-phenylethylamine and norephedrine on the basis of fluorescence quenching is a chiral calix[4]arene carrying (*S*)-di-2-naphthylprolinol moieties on the lower rim.[862] A sensor for acetylcholine (**302**) is based on the ability of this molecule to displace **303** from its complex with $\mathbf{6}^{SO_3H}$, **303** being nonfluorescent in the complex but fluorescent in the free state.[863] A change in fluorescence has also been used to detect a change in the extent of intramolecular hydrogen bonding in **304**, which goes from a 'closed form' to an 'open form' upon the addition of Na^+, the fluorescence of the guest molecule 7,8-dichloro-10-methyisoalloxazine being quenched only by the latter.[864] Test strips containing **298c** change from yellow to red in the presence of trimethylamine, providing a means for detecting this material in concentrations as low as 0.02 ppm.[865] The calix[6]arene **275c** carrying pyrenyl groups on the lower rim shows a decrease in fluorescence intensity upon complexation with guanidinium which is unaffected by the presence of butylammonium ions.[866]

7.4.4 Nonlinear Optical Compounds

Molecules exhibiting nonlinear optical (NLO) behavior are of interest for a variety of applications, including frequency doubling of laser light, electro-optical switching devices, and optical communication. Calixarene-derived compounds with this property[867] were introduced by Reinhoudt and coworkers with a variety of calix[4]arenes **305a–d** carrying nitro-containing moieties on the

[861] Grigg, R.; Holmes, J. M.; Jones, S. K.; Amilaprasadh Norbert, W. D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 185.

[862] Grady, T.; Harris, S. J.; Smyth, M. R.; Diamond, D. *Anal. Chem.* **1996**, 68, 3775.

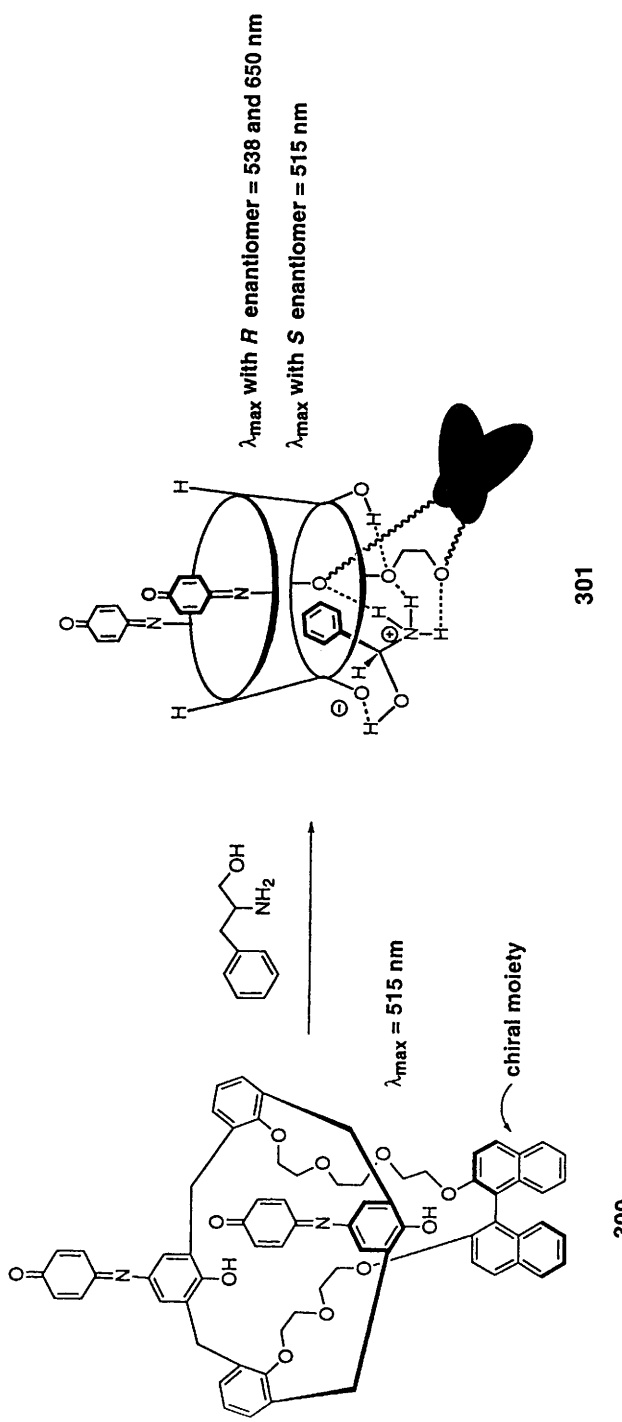
[863] Koh, K. N.; Araki, K.; Ikeda, A.; Otsuka, H.; Shinkai, S. *J. Am. Chem. Soc.* **1996**, 118, 755. A similar example using a calix[4]resorcarene is reported by Inouye, I.; Hashimoto, K.; Isagawa, K. *J. Am. Chem. Soc.* **1994**, 116, 5517. The binding of acetylcholine to *p*-sulfonatocalix[4 and 6]arenes has also been reported, with X-ray structures, by Lehn, J.-M.; Meric, R.; Vigneron, J.-P.; Cesario, M.; Guilhem, J.; Pascard, C.; Asfari, Z. *Supramol. Chem.* **1995**, 5, 97.

[864] Murakami, H.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1533; H.; Shinkai, S. *Tetrahedron Lett.* **1993**, 34, 4237.

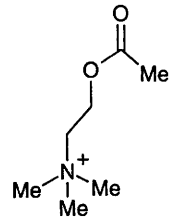
[865] McCarrick, M.; Harris, S. J.; Diamond, D. *J. Mater. Chem.* **1994**, 4, 217.

[866] Takeshita, M.; Shinkai, S. *Chem. Lett.* **1994**, 1349.

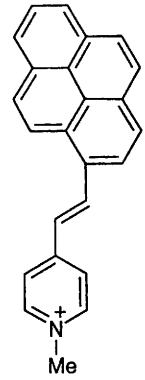
[867] For an evaluation of optical nonlinearities in calixarenes, see Morley, J. O.; Naji, M. *J. Phys. Chem. A* **1997**, 101, 2681.


λmax with R enantiomer = 538 and 650 nm
λmax with S enantiomer = 515 nm
301
λmax = 515 nm
chiral moiety
300

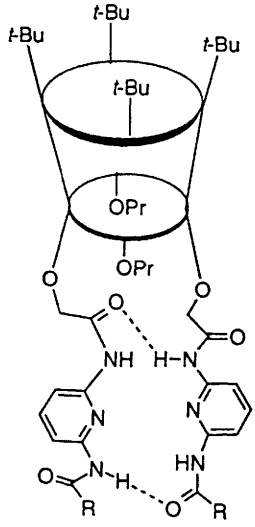
upper rim.[106,486,868] To study the macroscopic NLO properties of these materials, oriented thin films were prepared by spin-casting followed by poling by a strong DC electric field. For example, **305a** (Y = Pr), whose cone conformation possesses four nonconjugated D-π-A dipoles oriented in the same direction, forms a polymethacrylate film with the good optical properties and high stability suitable for wave guide fabrication. The closely-related compounds **305a** ($Y = C_{10}H_{21}-C_{18}H_{37}$) have been studied in Langmuir–Blodgett monolayers,[869] and **305a** (Y = Pr) deposited on Si_3N_4 or SiON has been tested as a

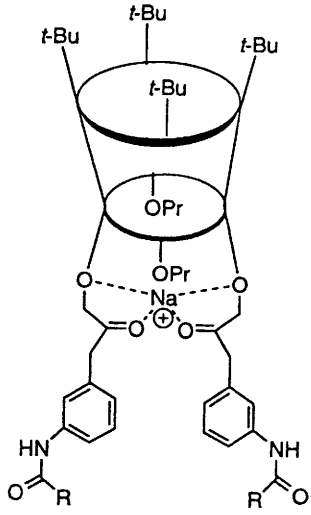


302



303





304

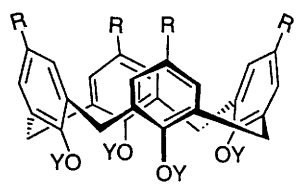
closed form

open form

[868] Heesink, G. J. T.; van Hulst, N. F.; Bölger, B.; Kelderman, E.; Engbersen, J. F. J.; Verboom, W.; Reinhoudt, D. N. *Appl. Phys. Lett.* **1993**, 62, 2015; Kelderman, E.; Heesink, G. J. T.; Derhaeg, L.; Verbiest, T.; Klaase, P. T. A.; Verboom, W.; Engbersen, J. F. J.; van Hulst, N. F.; Clays, K.; Persoons, A.; Reinhoudt, D. N. *Adv. Mater.* **1993**, 5, 925.

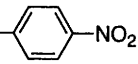
[869] Brake, M.; Böhmer, V.; Krämer, P.; Vogt, W.; Wortmann, R. *Supramol. Chem.* **1993**, 2, 65.

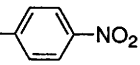
waveguide.[870] An even more tightly bound NLO monolayer is produced by the reaction of **305d** (Y = CH_2CH_2OEt) with a silica disk treated with $ClCH_2C_6H_4SiCl_3$ to produce **306**.[457]

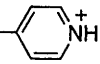


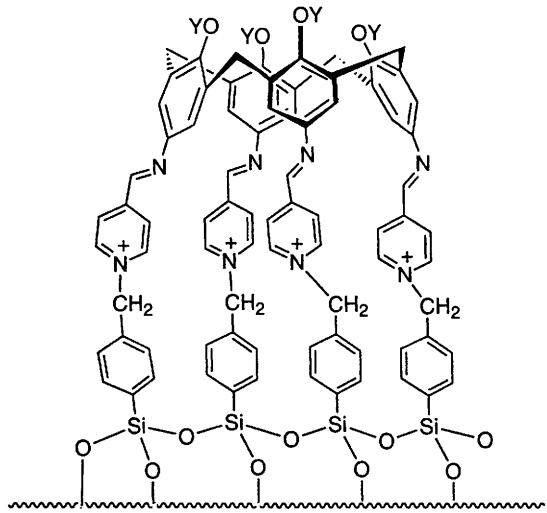
305

a) R = NO_2

b) R = CH=CH–  –NO_2

c) R = N=N–  –NO_2

d) R = CH=N– 



306

7.4.5 Other Sensors

Chemical sensors have been reported that are based on quartz micro balances or surface acoustic wave oscillators coated with the trimethylsilyl ethers of **4**$^{t\text{-Bu}}$ and **6**$^{t\text{-Bu}}$ and that are claimed to detect various solvent vapors in ppm amounts.[871]

7.5 Miscellaneous Applications

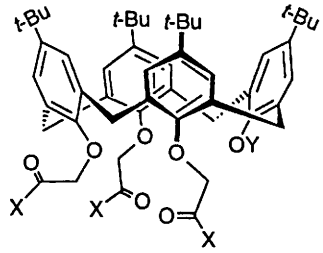
A Langmuir–Blodgett (LB) multilayered film showing a strong pyroelectric effect has been prepared using calix[8]arenes carrying amino groups [**269** (R = 1,1,3,3-tetramethylbutyl; Y = $CH_2CH_2CH_2NH_2$; n = 8)] and carboxyl

[870] Wörhoff, K.; Noordman, O. F. J.; Albers, H.; Lambeck, P. V.; van Hulst, N. F. *Optics Commun.* **1996**, 124, 493.

[871] Dickert, F. L.; Schuster, O. *Mikrochim. Acta* **1995**, 119, 55.

groups [**264** (R = 1,1,3,3-tetramethylbutyl; R′ = H; n = 8)] on their lower rims. The temperature dependent proton transfer between the carboxyl and amino groups, detected by FTIR, is thought to provide the mechanism for the pyroelectric effect.[872] Conducting mono- and multilayer LB films have been prepared from the calix[4]arene **264** (R = 1,1,3,3-tetramethylbutyl; R′ = H; n = 8) and Na^+TCNQ^-.[873] The change in permeability of oriented monolayers of **264b,f** induced by alkali cations has been studied,[874] the magnitude of the response falling in the order $Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$.

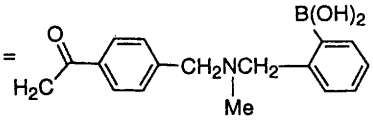
Taking note of the high luminescence quantum yield and long luminescence lifetime of the Tb^{3+} complex of **264b**,[618,875] along with the demonstration that one of the amide groups can be replaced by a sensitizer group such as phenacyl (**307a**),[876] Reinhoudt and coworkers have designed a time-resolved immunoassay system based on the delayed luminescence properties of the Tb^{3+} and Eu^{3+} complexes of **307b** (Ar = naphthalene, phenanthrene, and triphenylene).[877] The triphenylene 'antenna' proves most effective, sensitizing the luminescence of both the Tb^{3+} and Eu^{3+} complexes and allowing the use of excitation wavelengths up to 350 nm. Attachment of a boronic acid-containing moiety to the lower rim to give **307c** provides a compound for which the luminescence of the Tb^{3+} complex is sensitive to the presence of saccharides.[878] A study of energy-transfer processes in Tb(III) and other lanthanide dinuclear complexes of $\mathbf{8}^{t\text{-Bu}}$ shows them to be dipole–dipole in character.[879] In a somewhat different vein, *p*-carboxymethyl and carboxyethyl calixarenes have been shown to form thin films on porous silicon to provide systems that demonstrate selectivity with regard to the photoluminescence quenching by Cu^{2+} or amines.[880]



a) X = NR_2; Y = $CH_2COC_6H_5$

b) X = OH; Y = $CH_2CONHCH_2Ar$

c) X = NEt_2; Y =



307

[872] Richardson, T.; Greenwood, M. B.; Davis, F.; Stirling, C. J. M. *Langmuir* **1995**, 11, 4623.
[873] McArdle, C. B.; Harris, S. J.; Guthrie, J.; Casey, V. *Key Eng. Mater.* **1992**, 72–74, 359.
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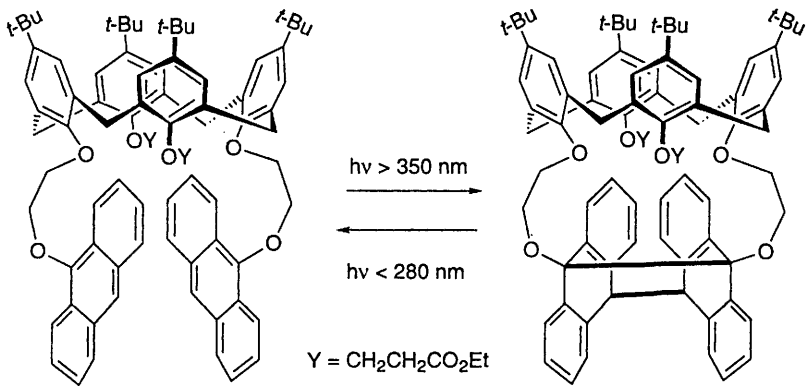
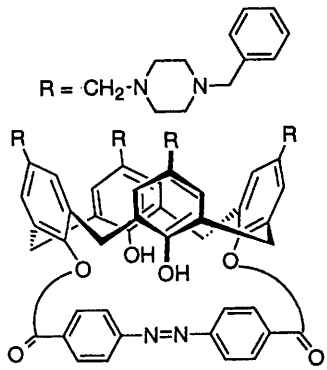
Molecules capable of reversibly switching between two distinct states are currently receiving considerable attention.[881] Photoresponsive molecules, for example, are of interest for their potential uses in optical data storage systems, and calixarenes are among the substances investigated for this purpose. Shinkai and coworkers have shown that the calix[4]arene **308**, carrying a pair of anthracene moieties on the lower rim, undergoes intramolecular ring formation to **309** when irradiated with 350 nm light, and **309** reverts to **308** when irridiated with 280 nm light.[882] It is interesting to note that **309** shows a considerably higher affinity for ions than **308**, particlularly for Na^+ which supresses its thermal reversion to **308**. Another system taking advantage of a light-induced



308 **309**



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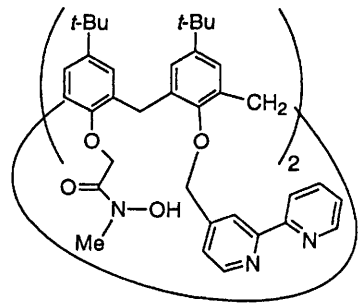

311

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transformation is **310** carrying an azobenzene moiety on the lower rim which is susceptible to *syn/anti* interconversion upon irradiation.[883] The *anti* isomer shows significantly higher binding capacity for the cations studied (Na^+, K^+, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Al^{3+}) than the *syn* isomer.

A calixarene-based redox switch **311** has been constructed by placing pairs of hydroxamate and bipyridyl moieties on the lower rim of a calix[4]arene to provide 'hard' and 'soft' binding sites, respectively.[884] In the presence of Fe^{3+} the 'hard' binding site comes into play, causing the bipyridyl groups to diverge. Conversely, when Fe^{3+} is reduced to Fe^{2+} the 'soft' binding site comes into play, causing the hydroxamate groups to diverge with a concomitant color change from orange to pink. Bipyridyl groups have also been used to modulate the through-space exchange interaction between nitroxo radicals attached to the bottom rim of calix[4]arene **298e**,[343] the magnitude depending on the presence or absence of Zn^{2+}. Another receptor containing both 'hard' and 'soft' metal ion binding sites is **131** in which one of the bridges is the oxygen-containing $CH_2(CH_2OCH_2)_4CH_2$ unit and the other is the nitrogen-containing $[CH_2CH_2OC_6H_4NHCH_2]_2CH$ unit.[885]

Calixarenes substituted in the *p*-positions with arylazomethine groups or arylazo groups carrying long alkyl chains may possess liquid crystal properties (for a short review, see ref. 12l). For example, **192** (Ar carrying *p*-octyl to *p*-hexadecyl groups),[488,886] and the tungsten–oxo complex of **285k** ($R^{1,2} = C_{10}H_{21}$)[754] are thermotropic, showing phase transitions attributed to the 'melting' first of the aliphatic chains and then the calix[4]arene bowl,[886] as schematically represented in Figure 7.1. The liquid crystalline state of the tungsten–oxo complex of **285k** (red in the solid state, yellow in solution) can be disrupted by the addition of DMF or pyridine, the guest molecules displacing the neighboring calixarene moieties in the columnar array (schematically represented by **287**).[754] Another construction of a calixarene-based liquid crystal system employs **192** (Ar = 4-pyridyl)[887] mixed with a benzoic acid carrying a long-chain alkoxy group in the *p*-position. Hydrogen bonding (or proton transfer and electrostatic binding) between the pyridyl and carboxyl groups yields a system structurally similar to those discussed above.

The closely-related phenomenon of gelation has been observed with calixarenes.[888] Particularly effective are calixarenes carrying long-chain *p*-acyl groups such as *p*-dodecanoylcalix[8]arene,[889] which form gels with a variety of solvents, including benzene, toluene, CCl_4, CS_2, hexane, decane, cyclohexane, isopropanol, butanol, and hexanol; but not, however, with $CHCl_3$, CH_2Cl_2, acetone, methanol, or ethanol. The three-dimensional self association network giving rise to the gel, observable as a pattern by using a microscope with crossed

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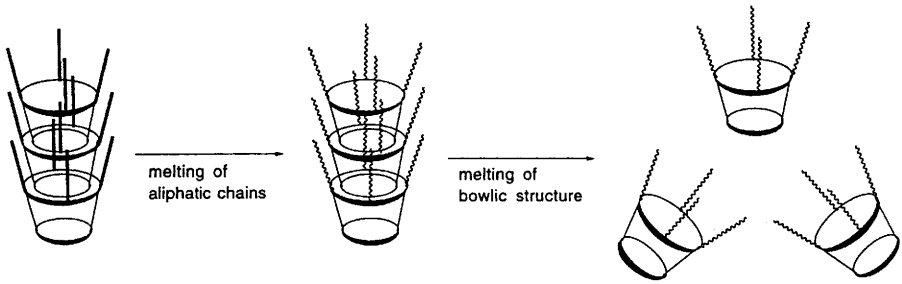

Figure 7.1 *Melting of a calixarene liquid crystal*

Nicol prisms, is attributed to intermolecular hydrogen bonding between the phenolic and carbonyl groups along with moderate affinity for the solvent.

The hexaacetate of **6**^{Me} has been tested as a high resolution negative resist for electron beam lithography, showing sufficient resolution to be useful for nanoscale device processing.[890] Quantum confined cadmium sulfide clusters are stabilized by the Mannich base calixarenes **195** (R = Me, Bu, cyclohexyl).[146,891]

Floriani and coworkers[892] have used the lower rim of calix[4]arenes as a platform for coordination with metals such as tungsten and zirconium to provide a convenient means for studying their chemistry, for example as illustrated by the conversion of **312** to **313**, **314**, and **315**.[893] McKervey and coworkers have used the lower rim as a platform for synthesizing a dendrimer, attaching a replicative moiety derived from the 3,5-dihydroxybenzyl residues to yield **316** (R = CO_2Me or CO_2H).[894] An approach to calixarene-based dendrimers has also been published by Shinkai and coworkers,[895] who have succeeded in synthesizing the oligomer **317**. The antibiotic vancomycin causes cell lysis by binding to the cell wall mucopeptide precursors terminating in the sequence D-alanyl-D-alanine. The calixarene-based vancomycin mimic **318** containing alanyl residues shows qualitatively similar though quantitatively somewhat inferior antimicrobial action against Gram-positive organisms.[896] In 1955, Sir John Cornforth and coworkers explored the possibilities of using the Zinke cyclooligomers, later to be named calixarenes, as tuberculostatic agents (see ref. 1, pp. 15–16). The

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[893] Also see Giannini, L.; Solari, E.; Zanotti-Gerosa, A.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 753 for the formation of metal–metal bonds between tungsten calixarenes.

[894] Ferguson, G.; Gallagher, J. F.; McKervey, M. A.; Madigan, E. *J. Chem. Soc., Perkin Trans. 1* **1996**, 599; also see Jacob, S.; Majoros, I.; Kennedy, J. P. *Polym. Mater. Sci. Eng.* **1997**, 77, 185.

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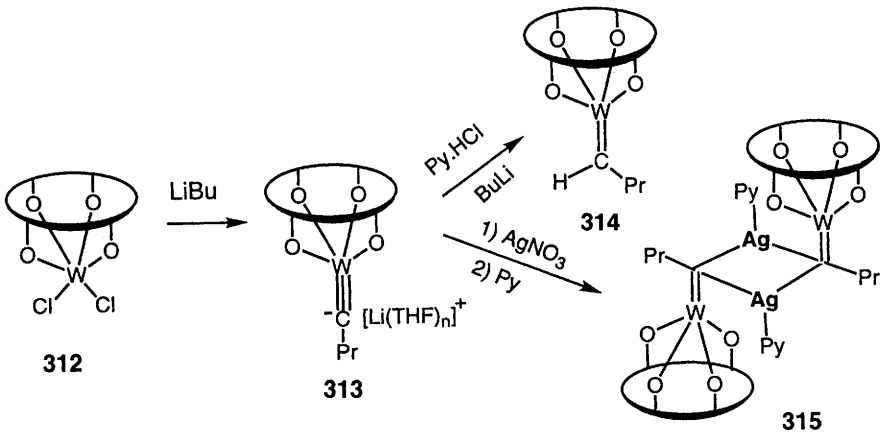
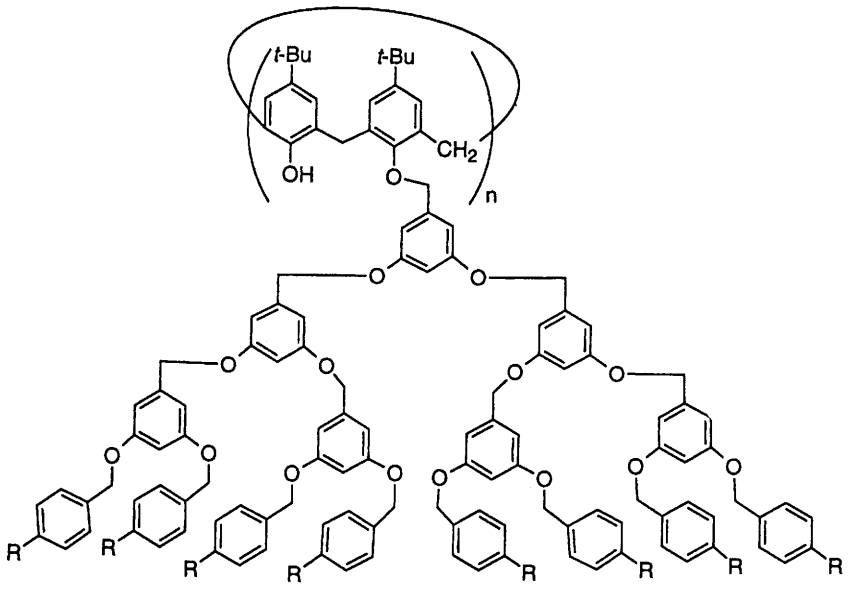
oxyalkylated derivatives were called Macrocyclons and did, indeed, show some promise. A recent study by D'Arcy Hart, one of the co-authors of this early publication, has reawakened interest in these compounds by showing that *in vivo* inhibition of *Mycobacterium tuberculosis* can be induced inside microphages by a calixarene carrying short polyethyleneoxy chains on the lower rim.[897]





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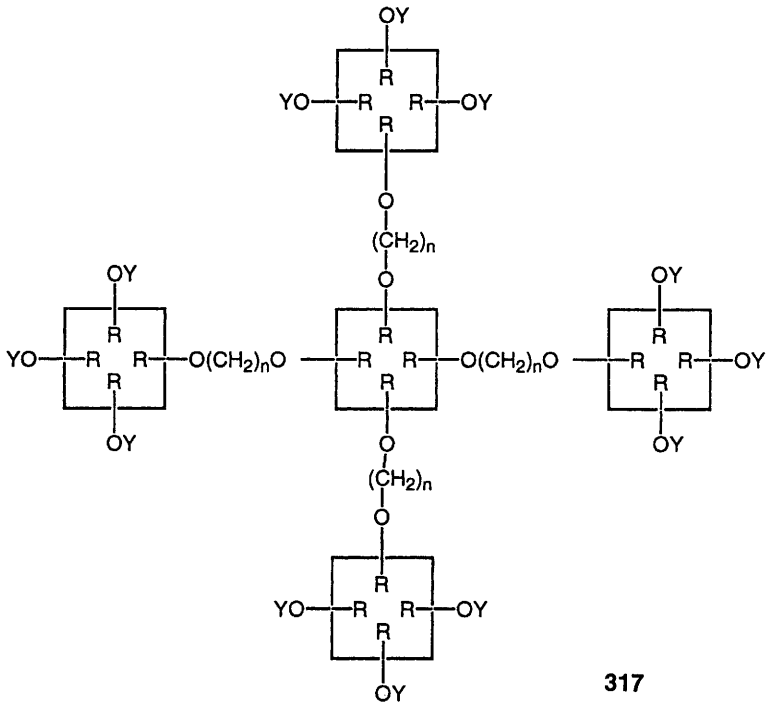
[897] D'Arcy Hart, P.; Armstrong, J. A.; Brodaty, E. *Infect. Immun.* **1996**, 1491.



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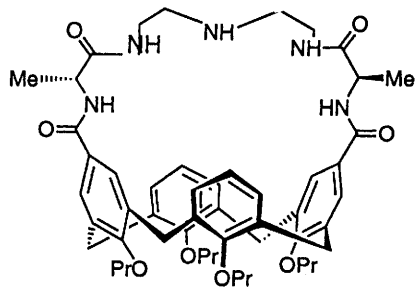

318

7.6 Patent Literature

Well over 100 patents have been issued for a variety of practical applications of calixarene-based molecules. Many of these, not surprisingly, involve the chemistry that is discussed in this book, especially the use of calixarenes in systems in which selective ion complexation plays the central role. A number, however, deal with quite different sorts of applications including, *inter alia*, the use of calixarenes as adhesion promoters,[898] electrophotographic photoreceptors,[899]

[898] Leonard, R. G.; Harris, S. J. *U.S. Pat.* US 4,695,615, Sept. 1987.
[899] Maeda, S, *Jpn. Kokai Tokkyo Koho* JP 05,323,632, May 1992.

photographic toners,[900] hair dyes,[901] diesel fuel additives,[902] curing agents,[903] antistatic agents,[904] antioxidants,[905] stabilizers,[906] temperature sensing devices,[907] pressure sensitive recording material,[908] flame proofing compounds,[909] safety glass compositions,[910] optical recording materials,[911] and antibacterial agents.[912]

7.7 Concluding Remarks

In the quotation at the end of the previous volume (see ref. 1, p. 204), Tennyson's Ulysses says that 'all experience is an arch wherethrough gleams that untravelled world whose margin fades for ever and for ever when I move'. In the quotation at the beginning of the present volume, Clarence Day says that 'books . . . sail further than Ulysses even dreamed of'. *Calixarenes Revisited* has strived to provide an updated and reasonably detailed chart of the oceans through which sails our Ulysses of chemistry, the calixarenes. It has painted pictures of the important ports of call that have been visited, it has enumerated the various techniques for making safe passages, and it has limned the vast reserve of minutiae that make a voyage interesting and memorable. To what undreamed of places with ever fading margins our voyage next will take us remains an intriguing question. As William Shakespeare's Antonio says in the *Tempest*, 'Whereof what's past is prologue, what to come In yours and my discharge'.

[900] Kuramoto, S.; Orihara, M.; Hagiwara, T. *Jpn. Kokai Tokkyo Koho* JP 04,295,862, March 1991; Yasuno, M.; Kobayashi, M. *Jpn. Kokai Tokkyo Koho* JP 05,127,426, Nov. 1991; Yamanaka, S.; Sukata, K.; Sugawara, S. *Eur. Pat. Appl.* EP 514,867, Nov. 1992; Iwasa, K.; Mukushiro, O.; Matsura, J. *Jpn. Kokai Tokkyo Koho* JP 07,234,547, Sept. 1995; Ueda, L. H. *Jpn. Kokai Tokkyo Koho* JP 05,119,534, May 1993; Isawa, K.; Mukushiro, O.; Matsura, J. *Jpn. Kokai Tokkyo Koho* JP 07,234,544, Sept. 1995; Hagiwara, T.; Kuramoto, S.; Kawasaki, K. *Jpn. Kokai Tokkyo Koho* JP 05,216,278, Feb. 1992; Yamanaka, S-i.; Sukata, K. *Eur. Pat. Appl.* EP 712,049, Nov. 1994; Tomita, M.; Asahina, Y.; Sasaki, F.; Kondo, F.; Mochizuki, C.; Iwamoto, Y.; Minamitani, T. *Jpn. Kokai Tokkyo Koho* JP 05,341,577, Dec. 1993; Takahashi, T.; Nagatsu, T.; Tanaka, K. *Jpn. Kokai Tokkyo Koho* JP 07,295,299, Apr. 1994.

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Author Index

Abidi, R., 99, 149, 161
Abraham, H., 55, 112
Acho, J. A., 97(2), 148
Ackerman, R. G., 26
Adams, M. J., 60
Adeobga, F., 60
Ágai, B., 117
Agawa, T., 57, 149
Agrawal, Y. K., 157
Ahn, S., 172
Ailmaier, G., 146
Akabori, S., 75
Akao, K, 73, 96, 121
Alam, I., 4, 47, 65, 76, 116, 149, 185, 205, 208
Albers, H., 201
Albert, K., 190
Aleksiuk, E., 61
Aleksiuk, O., 52, 65(2), 103(2), 133(2), 134(2), 174
Alfieri, C., 51, 89, 179
Almi, M., 113
Al-Rawi, J. M. A., 172
Alvarado, E., 142
Amilaprasadh Norbert, W. D. J., 198
Ammon, H. L., 55
Amoretti, G., 169
Ando, I., 39
Andreetti, G. D., 16, 34, 44, 51(2), 58, 60(2), 61(2), 75, 87, 88, 89, 150, 169, 170
Andreu, C., 178
Ankoné, M. J. K., 93
Antony, J. H., 39
Aoki, I., 196(2)
Aoki, M., 204(2)
Araki, K., 11(2), 34(3), 37, 53(2), 64(2), 65, 67, 70, 73(2), 74, 82, 84, 85, 89, 101, 109, 110, 111, 121, 125, 136, 141, 143, 147, 157, 161, 162, 164, 172, 173, 175, 178, 188, 198, 204
Arduini, A., 4, 15, 49, 52, 60, 75, 83, 84, 88, 90, 96, 105(2), 106(3), 112, 113, 114, 119, 120(2), 154, 177
Arena, G., 34, 175, 190
Arimori, S., 178, 183(2)
Arimura, T., 22, 23, 32, 39(2), 65, 67, 98, 109(2), 110, 114, 125, 136, 137, 141, 147, 164, 175, 190
Armah, A. E., 51, 190
Armstrong, J. A., 206
Arnaud-Neu, F., 4, 5, 55, 58, 87(3), 89, 90, 99, 120, 148, 151, 152(3), 153, 154, 158(3), 161, 172
Arnecke, R., 58, 72(2)
Arrigan, D. W. M., 4, 194
Arumura, T., 157
Asada, M., 26
Asahina, Y., 208
Asfari, Z., 4(3), 11, 20, 24, 47, 51(2), 52, 55(2), 62, 69(2), 90(2), 93, 99, 108, 120, 125, 147, 155, 157(2), 161(3), 162, 189, 192, 198, 204
Ashram, M., 12
Assmus, R., 149
Astarloa, G., 38
Astier, J.-P., 47
Atwood, J. L., 5, 34, 35, 51, 53(2), 55, 58(2), 65, 117, 148(2), 150, 164(5), 165, 166(2), 169(2), 170(2), 171, 178, 181
Auai, B., 130

Bacchus, A., 60
Bachmann, J., 208
Baert, F., 52, 55, 69
Baeyer, A., 2,
Baglioni, P., 183(2)
Bailie, A. G., 14
Baker, M. V., 149
Balzani, V., 4, 154, 202
Bando, A., 208(2)
Barbara, S., 190
Barbour, L. J., 164, 169
Barnes, C. L., 35
Barrett, G., 58, 87, 145, 151, 152(2), 154, 155, 158, 183, 196
Barth, A., 47
Bassus, J., 104, 113
Battocolo, E., 86
Bauer, C. B., 164
Bauer, L. J., 41, 62, 66, 68, 171
Bavoux, C., 24, 135, 159
Bayard, F., 46, 47
Beer, P. D., 47, 57, 80, 90(2), 92, 99, 110(3), 119, 131, 153, 154(2), 159, 165, 166, 168, 170
Beerli, R., 178
Belchenko, N. V., 194
Belmore, K. A., 58
Bencze, Z., 24
Benedetti, E., 14
Berger, B., 19

Bergveld, P., 88, 194
Bernardo, A. R., 184
Berthalon, S., 105
Berti, D., 111
Biali, S. E., 16, 18, 39, 47, 52, 56, 61, 65(4), 83, 100(2), 102(2), 133(2), 134(3), 135, 174
Bielski, R., 191
Bienert, R., 52
Bigi, F., 15, 16
Bitter, I., 117, 130
Black, D. St. C., 27
Blackett, P. M., 4
Blanda, M. T., 478
Blank, H., 169
Blixt, J., 67, 150
Bocchi, C., 161, 193
Bocchi, V., 57, 58, 88
Bodewes, P. J., 52(2)
Boerrigter, H., 125
Böhmer, V., 2, 3, 5, 13(2), 16(2), 18(3), 19(2), 20(2), 22, 47(2), 51, 58(2), 72(2), 80, 93, 98(2), 104, 108, 109, 110, 138, 141, 149, 152, 155, 158, 172, 179, 186, 196, 200(2)
Bomer, J. G., 88
Bos, M., 90
Boschke, F. L., 5
Bott, S. G., 53, 55, 60, 61, 117, 148, 150, 164(3), 178, 181
Botta, B., 14
Botta, M., 14
Bottino, A., 136
Bottino, F., 4
Bouazizi, A., 194
Bourakhoudar, M., 47, 60
Bowyer, M. C., 27
Bradshaw, J. S., 164
Brake, M., 200
Branda, N., 178
Brandt, W., 47(2)
Brenn, J., 47(2), 134
Bressot, C., 47, 189, 192
Briard, P., 158
Brindle, R., 190
Brinks, E. A., 39
Brodaty, E., 206
Brodesser, G., 5, 23
Brouwer, E. B., 4, 169(3), 170
Brown, C. T., 98
Brown, P. R., 148
Brown, W. H., 26
Bruening, R. L., 164
Bruins, A. P., 164
Brunik, J. A. J., 83(2), 84, 163, 195
Brzózka, Z., 190, 193(2), 195
Bubenitschek, P., 27
Bugge, K.-E., 83, 92
Bühlmann, P., 184
Buitenhuis, E. G., 159
Bünzli, J.-C. G., 36, 202
Burgard, M., 157
Burkhalter, R. S., 166, 171
Burton, J. M., 52, 96, 97
Buschmann, H.-J., 23
Byrne, L. T., 52

Cabaleiro, M. C., 3, 147, 159, 171, 172
Caccamese, S., 32, 138
Cacciapaglia, R., 76, 89(2), 90, 172, 188, 195
Caciuffo, R., 169(2)
Cadogan, A., 192, 193(5)
Cai, P. X., 194
Cairns, T., 178
Calestani, G., 60, 75, 88
Cali, R., 34
Cameron, B. R., 97, 119
Cammann, K., 23
Campillo, N., 36
Canevet, C., 204
Cantoni, M., 120
Cao, D. H., 99
Cárdenas García, J. D., 147, 172
Careri, M., 193
Carlile, C. J., 169
Carramolino, M., 61, 105, 106
Carroll, P. J., 97, 145
Carter, D. M., 60
Casabianca, H., 22
Casal, A. R., 147
Caselli, A., 205
Casey, V., 202
Casnati, A., 4, 11, 47, 51, 57, 60, 61, 70, 76, 82, 83, 84, 86, 88, 89(5), 90, 106, 111, 113, 154(2), 160, 161, 167(2), 171, 175, 177, 183, 188, 190, 193, 195, 205
Castellano, R. K., 178
Castillo, R., 183
Castner, D. G., 191
Cerioni, G., 39
Cesario, M., 198
Chaabane, R. B., 194
Chachimbombo, C. L., 171
Chan, W. H., 194(4)
Chandler, R. R., 47, 205
Chang, C.-K., 88
Chang, S.-K., 88, 106, 149, 171(2), 172
Chastrette, F., 26(2)
Chaulk, S. G., 12, 110, 120, 121, 176, 186, 188
Chawla, H. M., 110, 122, 124(2), 175, 187, 188
Chen, K., 99
Chen. S.-I., 29
Chen, S.-l., 112
Chen, Y.-Y., 89, 90, 145
Chen, Z., 57, 90, 110, 131, 170
Cheong, H. Y., 190
Cherry, M., 193
Chessari, G., 91
Chew, W., 96
Chiesi-Villa, A., 81, 97(3), 148, 149, 158, 205(2)
Chin, L. Y., 13
Chiosis, G., 195
Cho, I., 88
Cho, K., 129
Choi, D., 149
Choi, Y. K., 80
Chrisstoffels, L. A. J., 125
Christensen, J. J., 5, 148
Chun, J. C., 80
Chung, T. D., 149

Clark, D. L., 34
Clays, K., 200
Clegg, W., 62
Cobben, P. L. H. M., 88, 193
Cocker, D., 190
Coddens, G., 169
Codding, P. W., 55
Coffer, J. L., 47, 202, 205
Cohen, S., 18, 103(2)
Cohen, Y., 174
Colebrook, L. D., 96
Coleman, A. W., 53, 55, 150, 164, 183
Collins, E. M., 51, 87(2), 186
Colombi, S., 171
Comelli, E., 57
Conn, M., 178
Conner, M., 49, 85, 88
Consoli, G. M. L., 4, 47, 80, 85, 86, 87, 96
Contino, A., 175, 190
Contreras, K., 60
Coppi, L., 105
Corazza, F., 97(2), 148
Cordero, M., 177
Cordova, E., 184
Corelli, F., 14
Cornforth, J. W., 2
Corry, D., 152, 158
Coruzzi, M., 58
Costisella, B., 27, 52
Craig, D. C., 27
Cram, D. J., 2(2), 26
Creaven, B. D., 152
Cremin, S. J., 87(2), 152, 158, 193
Crooks, R. M., 184
Cruz, R., 183
Cuevas, F., 61, 105
Cunningham, K., 193
Cunsolo, C., 85
Cunsolo, F., 4, 47, 80, 86, 87, 96
Czugler, M., 62

Dahan, E., 16
Daitch, C. E., 24
D'Alessandro, F., 175
Dalla Cort, A., 172
Danil de Namor, A. F., 4, 147, 152, 159, 171, 172
D'Aprano, A., 147
D'Arcy Hart, P., 2, 206
Datta, S., 75
Davidson, M. G., 65
Davies, J. E. D., 5
Davis, F., 183, 202
Dawson, E. S., 164
de Apaza Sueros, N., 152
Dearden, D. V., 177
Deasy, M., 87(2), 186, 193
De Cain, A., 56(2), 89, 148, 158, 181, 198
De Cola, L., 4(2)
Decoret, C., 46, 47
Dedek, P, 85(2), 191
Dei, L, 183
De Iasi, G., 174
de Jong, F., 88, 89(3), 159, 160, 161, 174(2), 191, 192
Delaigue, X., 56(2), 104, 148, 181
de Lange, W. G. J., 96
de la Peña, A. M., 136
Deligöz, H., 109, 145, 189
Delle Monache, G., 14
de Mendoza, J., 18, 36, 39, 47, 55, 61(2), 70, 105, 106, 138, 173, 178
den Hartog, H. J. Jr., 163(2), 164
Deng, G., 193, 203
Dent, S. W., 90
de Paoli, D., 13
Derhaeg, L., 36, 114, 200
Dermody, D. L., 184
De Rosa, M. C., 14(2)
Derosa, T. F., 208
Desai, S. R., 100(2)
De Silva, A. P., 192
Detellier, C., 67, 150, 152
Deyama, K., 18, 28, 38
de Zeeuw, D., 163(2), 164
Dhawan, B., 2, 3, 24, 29, 51, 66
Diamond, D., 4, 192(4), 193(6), 196(3), 198(2)
Diaz, M. T., 192
Dickert, F. L., 50, 201
Dielman, C., 158
DiGiovanni, M. C., 14
Dijkstra, P. J., 83, 92
Di Modugno, E., 205
Dinoor, N., 83
Doamekpor, L. K., 13, 23, 30
Dodi, L., 84
Doelle, A., 39
Doerrer, L. H., 97
Domiano, L., 106, 154
Domiano, P., 61
Dondoni, A., 89, 115, 145
Dörrenbächer, R., 13
Dozol, J.-F., 89, 158(2), 161, 189, 192
Dradi, E., 51, 89
Drew, M. G. B., 47, 57, 80, 90(2), 110, 131, 153, 154(2), 159, 165, 166, 168, 180
Dubois, R. H., 58, 169
Duchamp, C., 32, 108
Duesler, E. N., 24, 25
Duplatra, G., 157
Duplâtre, G., 155
Durie, A, 108

Echavarren., A. M., 138
Echegoyen, L., 67, 149
Edamitsu, S., 136
Egberink, R. J. M., 88, 89, 108, 161, 193
Eglinton, G., 178
Ehlinger, N., 51, 169
Ehrhardt, D., 208(3)
El-Fadl, A. A., 89
Elguero, J., 36
Elsegood, M. R. J., 62
Engbersen, J. F. J., 4, 36, 49, 84, 114, 167(2), 168, 175, 184, 186, 195(3), 200(2)
Engler, E., 47
Enright, G. D., 4, 169(3), 170
Erxleben, A., 27
Estienne, J., 47

Ettahiri, A., 60
Eymard, S., 189, 192

Fabbi, M., 4, 49, 57, 90, 111, 205
Facey, G. A., 169
Fan, M., 84, 97(2)
Fanni, S., 89, 114, 120, 151, 152, 153
Fayet, J.-P., 36
Feltl, L., 3, 4, 147
Fenet, B., 159
Ferdani, R., 11
Ferguson, G., 1, 11, 13, 16, 18, 39, 47(2), 51(3), 52, 53, 58(3), 72(2), 88, 108, 151, 154, 155, 158, 205
Fijishima, H., 93
Fillaux, F., 169
Fischer, A., 52
Fischer, C., 159(3)
Fischer, E. W., 5
Fischer, J., 56(2), 56, 89, 148, 158, 181, 189
Fischer, S., 47
Flämig, G, 129
Fliege, T., 39
Floriani, C., 81, 97(3), 148, 149, 158
Fochi, M., 167(2)
Foina, D., 88
Forster, R. J., 192
Foti, M., 39, 47
Frampton, C. S., 169
Francescangeli, O., 169(2)
Franken, S. M., 70, 163
Fraternali, F., 149
French, D., 11
French, W. N., 26
Freriks, M., 61
Friebe, S., 190
Frings, M., 13
Froidevaux, P., 202
Fronczek, F. R., 66, 118
Fu, D.-K., 16
Fuchs, H. G., 208
Fujihira, M., 149
Fujii, S., 24, 51, 190
Fujimoto, K., 55(2), 75, 125, 156, 196
Fujio, K., 136
Fujita, J., 205(2)
Fujiwara, T., 51
Fujomoto, K, 157
Fukugaki, T., 165
Fukazawa, Y., 18(2), 38, 67, 170(2), 174
Furphy, B. M., 142, 147
Furukawa, J., 26

Gacs-Baitz, E., 14
Gagnon, J., 97
Gago, F., 173
Galán, A., 178
Gale, P. A., 27, 47, 57, 93, 119, 131, 170
Gallagher, J. F., 18, 39, 47(2), 51(2), 52, 53, 58, 72, 154, 155, 158, 205
Gamoudi, M., 194
Gao, Z., 193
Gapparov, H. L., 112
Gardiner, M. G., 55, 97, 148
Garrido Pardo, M. T., 4, 171, 172
Gauvrit, J. Y., 11
Gebauer, S., 190
Georghiou, P. E., 12
Georgiev, E. M., 4, 47, 55, 144
Geraci, C., 4, 86(2), 87, 90, 91(2), 92, 136
Gharnati, F., 47, 169
Ghidini, E., 60(2), 75, 83(2), 88, 89, 92, 154, 193
Ghiglione, C., 145
Giannini, L., 97(2), 149, 205(2)
Gibbs, C. G., 56, 104, 119, 149
Gibson, V. C., 62
Gil, E., 147
Girardini, R., 159
Giunta, L., 39, 47, 51, 138
Gleave, C. A., 116
Glennon, J. D., 33, 190(4)
Gloe, K., 23
Gloede, J., 52
Godinez, L. A, 184
Goermar, G, 190, 208
Gokel, G., 5, 175, 184(2)
Goldmann, H., 19, 20, 80, 152
Gómez-Kaifer, M., 67, 149
Gomez Orellana, I., 172
González, J. J., 138
Gordon, J. I., 175
Gordon, J. L. M., 196
Goren, Z., 47, 56
Görmar, G, 129, 171
Goto, K., 61(2), 73
Goto, M., 61, 156, 157
Goulden, A. J., 90, 110
Grady, T., 193, 198
Graf, E., 109, 148, 181
Graham, B. F., 30
Grandi, S., 106
Grandjean, D., 158
Grannas, M. J., 26
Graubaum, H., 28
Gravett, D. M., 145
Graviani, E, 120
Gray, G. M., 99
Graydon, A., 90, 110
Greenwood, M. B., 202
Grieve, A., 90, 110, 153, 154
Grigg, R., 198
Groenen, L. C., 4, 34, 38, 47(2), 51, 55, 56, 72, 82, 163
Grootenhius, P. D. J., 34(2), 47
Gross, H., 114
Grote Gansey, M. H. B., 112
Grün, A., 117, 130
Grushka, E., 190
Grüttner, C., 18, 109, 158
Grynszpan, F., 18, 52, 56, 61, 65(3), 83, 100, 103, 133(2), 135, 174
Gu, X. H., 194
Guardigli, M., 154, 159(3), 194, 202
Guastini, C., 81, 97, 148
Guelzim, A., 52, 55, 69
Guerra, L., 58, 87, 151, 152
Guilbaud, P., 47(3)

Guillaud, G., 194
Guillet, J. E., 145
Gulino, F. G., 175
Güther, R., 23
Guthrie, J., 202
Gütlich, P., 203
Gutsche, A. E., 62
Gutsche, C. D., 1, 2, 3, 4(2), 5, 11(3), 24, 28, 29(2), 39(2), 41, 43, 47, 55, 56, 58, 61, 62(2), 66, 67, 68, 74, 76(4), 80(2), 81, 87(2), 89, 90, 93, 96(2), 104(2), 117(2), 119, 120, 131, 135, 137, 149(3), 165, 171, 185, 191, 202, 205

Haas, J., 163(2), 164
Habata, Y., 75
Hagége, A., 157
Hagiwara, T., 208(2)
Hahn, F. E., 142
Haino, T., 18, 28, 170
Hajek, F., 148, 181
Halit, M., 60
Hall, K., 190
Ham, S.-h., 114
Hamada, F., 53(2), 65, 117, 164(3), 165, 169, 178, 204
Hamada, R., 181
Hamaguchi, S.-i., 90, 196(2)
Hamann, B. C., 180
Hampton, P. D., 24, 25
Han, S. Y., 171, 172(2)
Hancock, K. S. B., 166
Hanji, K., 26
Happel, G., 104
Harada, T., 37, 47(4), 73, 96
Haraguchi, M., 23
Harano, T., 18
Harkema, S., 47, 51, 52(2), 56, 57, 61, 71, 75, 83, 84, 92, 93, 105(5), 114, 125, 163(2), 175, 189, 192
Harriman, A. J., 89
Harris, S. J., 33, 51, 87(2), 145, 151, 152, 154, 155, 158, 186, 190(4), 192, 193(6), 194, 196(2), 198, 202, 207, 208
Harrowfield, J. M., 30, 52, 55(2), 56, 62(3), 142, 147, 149(3), 161, 169(2), 170, 190
Harvey, P. D., 97
Hasagawa, M., 13, 28
Hashimoto, K., 198
Hashimoto, N., 157
Hasse, W., 23
Hauptmann, S., 208(4)
Hauser, A., 203
Havlicek, J., 175
Hawkins, R. T., 148
Hazlewood, C., 110
He, G.-X., 50
Healy, M. de S., 26
Heath, J. A., 131
Heesink, G. J. T., 36, 200(2)
Heida, J. F., 47
Heitzsch, O., 23
Hendel, R. A., 191(3)
Hesek, D., 90, 110(3), 119, 165, 166
Heydenreich, M., 13
Hibino, K., 39
Higler, I., 176
Hill, C., 89, 189, 192
Hill, W., 149
Hillgeris, E. C., 27
Hillig, G., 47
Hinomoto, R., 60
Hirata, H., 192
Hirata, Y., 114
Hiroi, I., 208
Hisaichi, K., 125
Ho, D. S.-C., 149
Ho, K. H., 135
Ho, Z.-c., 112, 118
Hockless, D. C. R., 52
Hodacova, J., 110
Hoffmann, G., 2
Hofmeister, G. E., 142(2)
Hollis, R. L., 35
Holman, K. T., 166
Holmes, J. M., 198
Holt, E., 114
Hong, M., 83
Hong, M. S., 114
Hooda, U., 110, 188
Hope, H., 147
Hori, T., 28
Horie, S., 23
Horiguchi, K., 26
Horne, E., 190(3)
Horváth, G., 117
Horváth, M., 130
Hoskins, B. F., 26
Hoss, R., 23
Hosseini, M. W., 56(2), 104, 109, 148, 181
Hössinger, K., 2
Howard, J. A. K., 65
Hsu, M.-L., 2
Hu, Y., 118
Huang, Z.-T., 80, 89, 107, 112, 113, 114(2)
Huber-Patz, U., 15
Hubert, M., 181
Huc, I., 178
Huisman, B.-H., 184(2)
Hutchinson, S., 3
Hwang, H. S., 172
Hwang, K. L., 18, 114

Iammarino, M., 147
Ibragimov, B. T., 112
Ichikawa, K., 39, 196
Ihm, H., 106(2)
Ihringer, F., 36
Ikeda, A., 4, 37, 39, 47, 50, 96, 100, 113, 121(3), 125, 136, 150, 152, 162, 170, 175, 176, 198
Ikeda, H., 173
Iki, H., 56, 116, 141(2)
Imada, T., 158
Impellizzeri, G., 175
Inada, K., 143
Inazu, T., 25(2), 147
Inokuchi, F., 40, 73, 147(2), 177, 202
Inoue, K., 156(2), 157
Inouye, M., 198
in't Veld, P. J. A., 92
Iqbal, M., 3, 4, 29, 65, 76, 149
Irie, K., 17
Irngartinger, H., 15
Isagawa, K., 198
Isaka, K., 186, 208

Isernia, A., 159
Ishida, S.-I., 11, 39, 61
Ishii, D., 34, 196
Ishii, F., 23
Ishii, T., 75
Ishikawa, Y., 183
Isnin, R., 175
Israëli, Y., 152
Ito, K., 17, 27, 28
Itoh, K., 190
Ivaska, A., 193
Iwamoto, K., 11, 22, 32, 34, 37, 50, 53(2), 67, 75(2), 82, 84, 136, 137, 141, 196
Iwamoto, M., 50, 173
Iwamoto, Y., 208
Iwasa, K., 208
Iwasaki, Y., 11
Iwema Bakker, W. I., 4, 162, 163(4), 164
Izatt, R. M., 5, 148(3), 165
Izawa, S., 17

Jacob, S., 145, 205
Jacoby, D., 81, 158
Jacopozzi, P., 90
Jaime, C., 36, 39
Jakobi, R. A., 13, 109, 158
James, T. D., 106
Jang, M. D., 190
Jang, M. J., 172
Janout, V., 49, 85(2), 191(4)
Janssen, R. G., 38, 61(2), 70, 71, 73, 106, 110, 178, 193
Jauch, J., 21, 130
Jin, T., 39, 192, 196
Jinno, H., 190
Johnson, C. P., 35, 51, 164
Johnston, B., 152
Johnston, D. E., 2
Jones, C., 55, 148
Jones, P. G., 27, 52
Jones, S. K., 198
Jordon, J. G., 16
Jørgensen, M., 106, 116
Jouve, C., 194
Juneja, R. K., 34, 35, 51, 58(2), 166(2), 171, 181
Jung, K., 18
Jung, Y. E., 171(2)
Junk, P. C., 58, 148, 164, 169

Kai, Y., 57
Kaifer, A. E., 175, 184(2)
Kaitner, B., 39, 47, 87(2), 88
Kalchenko, O. I., 32
Kalchenko, V. I., 32, 138
Kamer, P. C. J., 96
Kamiyama, H., 28
Kämmerer, H., 5, 104
Kan, M., 153
Kanamathareddy, S., 39, 43, 81, 87, 96
Kanasugi, M., 208
Kanehisa, N., 57
Kang, M. H., 171, 172
Kang, S. K., 149(2)
Kang, Y. S., 172
Kanters, J. A., 55
Kappe, T., 2
Kapsabelis, S., 186
Kaptein, R., 19
Karaulov, A. I., 62
Karplus, M., 47
Kasai, N., 57
Kasai, Y., 23, 136
Kashyap, R., 39, 61, 66
Kasiura, K., 193
Kaspersen, F., M., 88, 156
Kato, Y., 178, 192
Katoh, Y., 190
Katritzky, A. R., 18
Kaufman, B. J., 208
Kaufmann, G., 90
Kawabata, H., 22, 32, 109, 112, 136, 141, 175, 177, 183, 193, 204(2)
Kawaguchi, H., 110, 112
Kawaguchi, K., 88, 188
Kawaguchi, M., 100
Kawahara, Y., 193, 203
Kawano, K., 164
Kawasaki, K., 208
Kearney, G. A., 190
Keefe, A. D., 80, 92, 99
Kelderman, E., 36, 114, 200(2)
Keller, N., 60(3), 62
Kennedy, J. P., 145, 205
Kentgens, A. P., 170
Kepert, D. L., 142
Khan, I. U., 25(2)
Khasnis, D. V., 52, 96(3), 97
Khomich, A. N., 112(2)
Khoo, K. S., 12
Khoo, S. B., 202
Khoo-Beattie, C., 163
Khrifi, S., 52, 55, 69
Kieffer, S., 148, 181
Kielkiewicz, J., 20
Kienzle, K., 164
Kiji, J.,11
Kijima, T., 56, 116, 144, 192
Kikuchi, T., 56, 116, 141(2)
Kikukawa, K., 39(2)
Kim, D., 117
Kim, D. S., 65, 83, 108, 130
Kim, H., 149
Kim, H.-J., 106
Kim, J. E., 22
Kim, J. M., 65, 83
Kim, T., 149, 172, 184
Kim, Y., 114
Kimura, K., 193(2), 195
King, A. M., 89
Kingston, J. E., 110
Kinjo, M., 192
Kinoshita, R., 18
Kintzinger, J.-P., 181
Kishi, K., 23
Kishida, S., 11
Klaase, P. T. A., 200
Klockow, D., 149
Knubley, R. J., 131, 168
Koay, L.-S., 175
Kobayashi, K., 31
Kobayashi, M. 208
Kobayashi, N., 93
Kobayashi, Y., 192
Kobuke, Y., 26
Koh, K., 178
Koh, K. N., 158, 162, 198, 204
Koide, Y., 189

Koizumi, K.-i., 23
Kojima, Y., 132
Kokhuis, S. B. M., 192
Kollman, P. A., 34, 47
Komiyama, M., 186
Komori, T., 116, 204(2), 208
Komoto, T., 39, 115, 104(2), 208
Kondo, F., 208
Kondo, Y., 204
König, B., 27
Konishi, H., 11, 31
Koo, H., 75
Kooijman, H., 96
Kook, S.-K., 83
Koreishi, H., 110, 157, 185
Kotani, K., 196
Koutsantonis, G. A., 97, 170
Kovalev, V. V., 11, 112(2), 194(2)
Koya, K., 105
Koyama, T., 192, 196
Kraft, D., 5, 58, 72(2), 93, 98, 109, 136, 158
Král, V., 27
Krämer, P., 200
Krauss, G. J., 190
Krawiec, M., 39, 56
Kremer, F. J. B., 195
Kretz, R., 2
Krueger, J., 190
Ku, M.-c., 79, 112, 118
Kubo, M., 136
Kubo, Y, 90, 132(2), 136, 196(2)
Kubota, M., 65
Kudelka, I., 65, 88
Kuhn, A., 190
Kumada, H., 28
Kumagai, H., 28
Kumar, N., 27(2)
Kumar, S., 28
Kung, T. C., 2
Kunitake, T., 183
Kuramoto, S., 208(2)
Kurosu, H., 39
Kwon, K. M., 18, 22
Kwon, S.-K., 88
Kyritsakas, N., 56(2)

Laali, K. K., 39, 177
Lai, T. F., 194
Lam, Y. S., 194
Lamare, V., 161, 189, 192
Lamartine, R., 4(2), 11, 24, 28, 30, 32, 81, 105, 108, 113, 116, 159(2), 194, 196(2)
Lamb, J. D., 148
Lamb, S., 65
Lambeck, P. V., 201
Lammerink, B., 193
Lan, B. T. T., 130
Lan, X., 18
Lance, M., 60(2), 62(2)
Lanfranchi, M., 16
Lanfredi, A. M. M., 57
Lang, H., 18
Lanteri, P., 11
Lara, F., 183
Larsen, M., 106, 116
Lattman, M., 52, 84, 96(3), 97(2)
Lauterbach, M., 47
Lawrence, S. M., 97, 148(2)
Leary, J. A., 142
Lecocq, S., 47, 51, 58, 62, 80, 108, 169
Lee, A. W. M., 194
Lee, C. W., 13
Lee, J. H., 172
Lee, J. W., 172
Lee, S. K., 149
Lee, W., 191(2)
Lee, Y. K., 190
Leeson, P. B., 47, 153, 159
Leggewie, E., 2
Lehmann, C.W., 65
Lehn, J.-M., 198, 202
Leize, E., 148, 181
Leonard, R. G., 155, 186, 207
Leonis, M., 3
Levine, J. A., 41, 66, 87, 104
Levine, M. L., 11
Lewenstam, A., 193
Lhoták, P., 100, 107, 122, 181, 205

Li, D.-Q., 110
Li, S. F. Y., 30, 190
Li, Z., 12(2)
Li, Z. J., 89
Liang, I.-M., 39
Liang, T.-M., 177
Libman, J., 204
Liemann, U. S. 93
Lim, C. H., 174
Lim, C. S., 12
Lin, L.-g., 55, 79, 80, 112(2), 118
Linnane, P., 4, 106
Linnemayr, K., 146
Lipkowitz, K. B., 47
Lipkowski, J., 32, 138
Lippard, S., 97(2)
Lippard, S. J., 148
Lippert, B., 27
Litwak, A. M., 65, 133
Liu, W.-c., 79, 112(2)
Llosa Tanco, M. A., 147
Lobouille, P. H. P., 173
Loeb, S. J., 119
Loeber, C., 55, 69, 89(2), 158(2), 189
Loh, C. L., 12
Lombardo, G. G., 34, 111
Longeray, R., 11
Lo Nostro, P., 183
López-Prados, J., 106
Lou, Y.-X., 113
Lough, A. J., 51, 87(3)
Lu, T., 175(2), 184(2)
Lu, X.-R., 89, 90
Lubitov, I. E., 11
Ludvig, R., 156
Ludwig, J. F., 14
Lugtenberg, R., 125, 161, 195(2)
Lüning, U., 73, 93, 95
Lutz, B. T. G., 38(2)
Lutze, G., 28
Luzikov, Y., 112
Lynch, V., 27, 93
Lyssenko, K., 159

Maaref, H., 194
Machida, M., 192
Macias, A., 175(2)

MacNicol, D., 5
Madigan, E., 51(2), 205
Maeda, K., 23
Maeda, S., 132, 136, 207
Maggi, R., 15, 16
Magrans, J. O., 39, 106, 173
Mague, J. T., 47, 55, 158
Mahjoubi, M., 34, 164
Majoros, I., 145, 205
Makishima, T., 23
Malinowska, E., 190, 193
Malone, J. F., 58, 158
Manabe, O., 64, 109(3), 110(3), 112(2), 114, 136, 157, 175, 185, 186(2), 188
Mandolini, L., 76, 89(2), 90, 172, 188, 195
Manet, I., 159(3)
Manfredi, G., 114
Mangiafico, T., 13, 76
Manley, K., 190
Mann, G., 208(3)
Manojlovic-Muir, L., 169
Mantovani, M., 49
Markovsky, L. N., 32, 138
Markowitz, M. A., 191(2)
Marques, E., 87(2)
Marra, A., 89, 115, 145
Marrs, D., 151, 152
Marrs, D. J., 158, 193
Marschollek, F., 18
Marsella, M. J., 145
Martin, J. P., 90
Martinez, M., 183
Maruyama, S., 90
Marzi, E., 16
Mascal, M., 107
Masci, B., 174
Masuda, T., 204
Mataka, S., 23
Matsuba, T., 39, 195
Matsuda, H., 11, 129
Matsuda, T., 34, 50, 53, 64(2), 65, 67, 75, 112, 113, 129, 136, 137, 141, 156(2), 173, 175, 183
Matsui, S., 205(2)
Matsui, T., 192
Matsumoto, H., 73, 106, 202(2)
Matsumoto, S., 125
Matsumoto, Y., 208
Matsumura, K., 18
Matsuo, T., 193
Matsura, J., 208(2)
Matsushita, Y., 192
Matsuzaki, T., 132
Matt, D., 55, 69, 89(2), 158(2), 189
Mauprivez, O., 158(2)
Mayzel, O., 174
McArdle, C. B., 202
McBranch, D., 110
McCarrick, M., 196(2), 198
McConnell, D. B., 27
McCoy, C. P., 192
McCoy, J. S., 5
McGregor, W., 52, 119, 151, 152
McGuffey, A. R., 60
McKervey, M. A., 4, 5, 33, 51(2), 52, 58, 87(3), 88, 90, 98(2), 145, 151(2), 152(6), 153, 154, 155, 158(2), 186, 190(3), 192(2), 193(6), 194, 196, 205
McKittrick, T., 193(2)
McLaughlin, M. L., 136
McMurry, J. E., 47
McNeil, J. D., 52
McSweeney, C. C., 33
Means, C. M., 164
Means, N. C., 164
Mecati, A., 154, 202
Meeda, K., 13
Meier, S., 23
Melone, S., 169(2)
Mercer-Chalmers, J. D., 89
Merhi, G., 183
Meric, R., 198
Mertens, W., 208
Meunier, S. J., 87
Meurs, H. G., 202
Miller, D. O., 12
Minami, H., 24
Minamitani, T.208
Minari, P., 4, 85, 88, 89, 90, 167
Mirone, L., 49, 190
Misiti, D., 14(2)
Mislin, G., 109
Mitchell, P. S. R.27
Miura, H., 25
Miyahara, Y., 147
Miyamoto, S., 47
Miyanari, S., 28
Miyano, S., 28
Mizuno, K., 93
Mnuk, P., 4, 147
Mocerino, M., 52, 55
Mochizuki, C., 208
Mogck, O., 108, 110, 179
Molenveld, P., 186
Molins, M. A., 47(2), 173
Monache, G. D., 14
Montavon, G., 155, 157
Moore, C. P., 89
Mora, R., 15
Moran, J. K., 47, 85, 96
Moran, M. B., 51(2), 154
Morgan, E. D., 2
Mori, G., 57, 193
Mori, S., 110, 185
Morikawa, O., 11, 31
Morishige, Y., 11
Morita, Y., 57, 149
Moriya, K., 28
Morley, J. O., 198
Morley, S. D., 164
Morozumi, T., 136(2)
Mortimer, R. J., 90
Morzherin, Y., 111
Motta, L., 135
Muddiman, D. C., 99
Muir, K., 150
Muir, K. W., 169
Mujrata, K., 204
Mukoyama, Y., 75
Mukushiro, O., 208(3)
Munch, J., 3
Munoz, L., 171
Munoz, M., 183
Murai, K., 165
Murakami, H., 22, 32, 34, 101, 141, 198(2)
Muramatsu, T., 136
Murase, T., 39(2)
Murata, K., 204

Musau, R. M., 26
Mussrabi, M., 24
Muthukrishnan, R., 3, 135
Muzet, N., 154

Nachtegaal, G. H., 170
Nagasaki, T., 39, 50, 67, 93, 125, 136, 156, 157(3), 158, 164(2), 175(2), 178, 183(2), 192
Nagashima, H., 190
Nagatsu, T., 208
Nagayama, S., 13, 30
Naji, M., 198
Nakamoto, Y., 11, 39, 61
Nakamura, I., 39
Nakamura, M., 90, 132
Nakamura, R., 89
Nakashima, K., 70, 73, 170(2), 203, 204
Nakashio, F., 156, 157
Nakayama, Y., 26
Nam, K. C., 4, 65, 80, 81, 83, 86, 108, 117(2), 130, 166
Namba, M., 184
Naumann, C., 90
Naven, R. T., 107
Nechifor, A. M., 89
Neda, I., 52
Nemilova, M. Y., 194
Neri, P., 4, 47(4), 51, 80, 85(2), 86(3), 87(2), 90, 91(2), 92, 96, 136
Neu, F., 152
Newkome, G. R., 118
Newland, R. J., 145
Ng, C. Y., 147
Ngammpaiboonsombut, O., 93
Ngayama, S., 23
Nicholls, G. A., 2
Nichols, P. J., 97, 170
Nicholson, G., 153
Nicoud, J.-F., 116
Niederl, J. B., 5
Nieger, M., 23
Nierlich, M., 60(2), 62(2), 161
Nierop, K. G. A., 39
Nieto, P. M., 18, 36, 39, 47, 61, 70, 105, 106, 138
Niimi, A., 196
Ninagawa, A., 11, 129
Nishihara, K., 208
Nishimura, J., 23, 136
Nishio, S., 73
Nishiyama, N., 55, 173
No, K., 3, 18(2), 22, 41, 51, 55, 66, 75, 83, 106, 114, 137, 172
Noack, H., 208
Nobori, T., 208
Noh, Y., 114
Noll, B., 208(3)
Nomura, E., 57, 60, 88, 165, 188(3), 205
Noordman, O. F. J., 201
Norberg, E., 11
Nowakowski, R., 32

Ochiai, Y., 205(2)
O'Conner, K. M., 4, 190(2), 193(2)
Odagaki, Y., 18
Odashima, K., 194, 202
Oehler, D., 47, 169
Oehler, O., 60
Oeser, T., 15
Ogata, M., 156
Ogden, M. I., 47, 62(3), 131, 147, 149(2), 153, 154(2), 159, 168
O'Hagan, P., 158, 193
Ohata, K., 31
Ohba, T., 17
Ohba, Y., 17(2), 27, 28(2)
Ohe, K., 192
Ohhara, N., 90
Ohnishi, Y., 11, 205(2)
Ohseto, F., 34, 47, 101, 106, 161
Ohta, H., 190
Ohto, K., 156, 157
Ohtsuchi, M., 51
Okada, Y., 23, 136
Okajima, T., 67
Okano, T., 11
Okazaki, R., 61(2), 73, 93
Olivier, A., 96
Olmstead, M. M., 147
Ori, A., 202
Ori, O., 160, 170
Orihara, M., 208
Orr, G. W., 34, 53(2), 58, 65, 117, 148, 164(3), 165, 169(2), 178, 181
Ortiz, A. R., 173
Osa, T., 93
Osano, Y. T., 132
Osawa, E., 47
Ostaszewski, R., 66, 163
O'Sullivan, P., 13
O'Toole, L., 183
Otsuji, Y., 88, 165, 188(3)
Otsuka, H., 4, 70, 73, 85, 89, 142, 157, 198
Otsuka, T., 55, 183
Ottens-Hildebrandt, S., 23
Owens, M., 51, 98(2), 154, 155, 186

Pacheco Tanaka, D. A., 4, 147, 171, 172
Padmakumar, R., 100
Paek, K., 106(2)
Paganuzzi, D., 52
Pagoria, P. F., 11
Pappalardo, S., 4, 18, 32, 39, 47(3), 51, 58(2), 72, 85, 90(2), 99, 138(2), 172, 175
Parini, C., 171
Parisi, M. F., 51, 90, 138, 172
Park, J. H., 190
Park, K. S., 86
Park, Y. J., 51, 55, 83
Parlevliet, F. J., 96
Pascard, C., 198
Pastorio, A., 15
Pathak, M., 186
Pathak, R., 144
Paul, D., 28
Paulus, E. F., 13, 16, 18, 19, 152, 179
Pawlak, J. S., 164
Pazur, J. H., 11
Peachey, B. J., 52
Pearl, G., 47

Pedersen, S. F., 142(2)
Pedone, C., 14
Pelizzi, N., 205
Pellet-Rostaing, S., 81, 196
Pellinghelli, M. A., 16
Peña, M. S., 136
Pepe, G., 47
Pérez-Adelmar, J.-A., 55
Pérez-Jiménez, C., 196
Peri, F., 16
Perrin, M., 4, 24, 47, 51, 58, 60(2), 62, 80, 108, 135, 159, 169(2)
Perrin, R., 4, 30, 34, 47, 51, 60, 108, 164, 169, 189
Persoons, A., 36, 114, 200
Petri, A., 208
Petringa, A., 90
Phelan, J. C., 47
Philipse, A. P., 89
Phillips, J., 51
Piattelli, M., 4, 47(2), 80, 85, 86(3), 87(2), 90, 91(2), 92, 96, 136
Pickard, S. T., 141
Pieroni, O. I., 147
Pietnev, I. V., 194
Pinazzotto, R. F., 47, 205
Pinkhassik, E., 175
Pipkorn, R., 15
Pirinccioglu, N., 34
Pirkle, W. H., 141
Pirozhenko, V. V., 138
Pitarch, M., 90
Platt, K. L., 22
Pletnev, I. V., 194
Plinta, H.-J., 52
Pochini, A., 4, 5, 11, 47, 49, 51(3), 52, 57, 58, 60(2), 61(3), 70, 75, 76, 82, 83, 84, 85, 87, 88(2), 89(2), 90(2), 96, 105, 106(4), 111, 112, 113, 114, 119, 120(2), 150, 154(2), 160, 161, 167, 170, 177, 183, 205
Poh, B.-L., 12, 13, 174(2), 175
Pons, M., 39, 47(2), 110, 173
Porta, C., 15, 16
Potts, K. T., 2
Power, P. P., 147
Prados, P., 18, 36, 39, 47, 55, 61(2), 70, 105, 106, 138, 173
Prager, M., 169(2)
Provencher, R., 97
Puddephatt, J., 87, 150, 169
Pulcha Salazar, L. E., 147
Pulpoka, B., 90(2), 204

Rajca, A., 100
Rajca, S., 100
Ramm, M., 52
Ramos, S., 183
Rao, G. N., 144
Rappoport, Z., 39
Raston, C. L., 55, 97, 148(2), 170(2)
Ratcliffe, C. I., 169(2)
Rathay, D., 104
Rauter, H., 27
Ray, K. B., 34
Raya, J., 181
Re, N., 205
Rebek, J. Jr., 178(4), 180
Reddy, P. A., 61, 67, 76, 131, 149
Redshaw, C., 62
Rees, R. J. W., 2
Regen, S. L., 49, 85(2), 88, 191(5)
Reggiani, M., 167
Regnouf de Vains, J. B., 32, 81, 105, 116, 135, 159(2), 196
Reichwein, A. M., 174(2)
Reichwein-Buitenhuis, E. G., 160
Reilly, S., 35
Reinhoudt, D. N., 2, 4(2), 5, 34(2), 36, 38(2), 39, 47(4), 49, 51, 52(2), 55, 56(2), 57, 61(2), 64, 70, 71, 72, 73, 75, 82, 83, 84, 88(3), 89(4), 90, 92, 93, 97, 98, 105(3), 106(3), 108, 109, 110, 111, 112, 114, 119, 125(3), 126(2), 156, 159, 160(2), 161, 162, 163(4), 164, 167(3), 175(2), 176(2), 178(2), 181, 184(2), 186, 189, 191, 192(2), 193(3), 194(2), 195(4), 200(2), 202
Ren, T., 97
Rest, A. J., 26
Reverberi, S., 87, 154
Rhim, S. K., 55
Richardson, T., 202
Richmond, W. R., 62, 149(3), 169(2), 170
Rieche, A., 114
Ripmeester, J. A., 4, 169(4), 170
Rissanen, K., 55
Rizzarelli, E., 34, 175
Rizzi, A., 106, 112
Rizzoli, C., 97(2), 149, 158, 205(2)
Robinson, K. D., 34, 51, 58(2), 65, 117, 148, 164(3), 169, 178
Robson, R., 26
Rocco, C., 47, 87
Rödel, M., 27
Rodriguez, A., 19, 152
Rodriguez, E., 60
Rodriguez, I., 30
Rodriguez, N. M., 147
Rogers, J. S., 4(2), 46, 56, 80, 164
Rokicki, G., 20
Rolfe, W. M., 208
Rooney, A., 152
Ross, C. R. II, 100
Ross, H., 73, 93, 95
Roundhill, D. M., 4, 5, 47, 55, 85, 96, 144, 154, 158
Rouquette, H., 89, 158(2), 189, 192
Roy, R., 87
Royer J., 22, 47
Rozov, A. K., 194(2)
Ruangpornvisuti, V., 93
Rudkevich, D. M., 89, 109, 111, 119, 156, 178, 184
Rudzinski, J. M., 47(2)

Ruël, B. H. M., 51, 82
Ruiz-Garcia, J., 183

Sabbatini, N., 154, 159(3), 202
Sagara, F., 34, 196
Saiki, T., 61(2), 73, 93
Saito, Y., 190
Sakai, A., 193
Sakaki, T., 70, 90, 131, 161, 177, 193, 196(2), 202, 203
Salomon, M., 147(2)
Samankumara Sandanayake, K. R. A., 89, 130
Sánchez, C., 18, 36, 39, 47, 55
Sánchez-Quesada, J., 173
Sannohe, H., 75
Sansom, P. I., 93
Sansone, F., 115, 205
Santini, A., 14
Santini, C. J., 52, 97
Sanyal, M., 157
Sarti, G., 159
Sartori, G., 15, 16
Saruwatari, Y., 13(2), 23
Sasaki, F., 208
Sasaki, S., 67
Sato, H., 189, 208
Sato, N., 202
Sato, Y., 28
Satoh, H., 109, 114, 136, 175
Satrallah, A., 22
Saunders, M. J., 118
Sawada, T., 23
Scharff, J.-P., 34, 164
Schätz, R., 15
Scheerder, J., 49, 167(2), 168
Scherrmann, M.-C., 89
Schiavone, S., 89
Schilling, G., 15
Schmid, E. R., 146
Schmitt, P., 99
Schmitz, J., 23
Schmutzler, R.52
Schneider, H.-J., 30
Schön, M., 18
Schouten, A., 55
Schulten, H.-R., 98
Schulz, M., 129, 171, 208(2)
Schulz, R. A., 147
Schulz, R. C., 5
Schurig, V., 21, 147
Schuster, O., 50, 201
Schwing-Weill, M.-J., 4, 5, 58, 87(3), 89, 151, 152(4), 153, 154, 158(3)
Schwinté, P., 87, 154
Sciotto, D., 34, 111, 175(2), 190
Scoponi, M., 145
Seangprasertkij-Magee, R., 90, 93, 120
Secchi, A., 49, 52, 96, 106, 119, 120
See, K. A., 4(2), 65, 66, 93(2)
Seiffarth, K., 129, 171, 208
Seki, Y., 11
Sepaniak, M. J., 191
Sessler, J. L., 27, 93, 98
Seward, E. M., 87(2), 88, 151(2), 193(3)
Sgamellotti, A., 205
Shaafstra, R., 90
Shade, M., 165
Shang, S., 97(2)
Shanzer, A., 204
Sharma, S. K., 74, 76(3), 83, 89, 117
Sheen, P. D., 99
Shevchenko, I., 96
Shi, Y. H., 88
Shibata, J., 112, 188
Shibutani, Y., 193
Shigematsu, S., 84
Shimizu, H., 136, 172, 196
Shimizu, K. D., 178, 180
Shin, J. M., 51, 83
Shinkai, S., 4(2), 5, 11, 22, 32, 34(4), 37, 39(3), 40, 47(5), 50, 53, 55(2), 56, 64(2), 65, 67(2), 70, 73(2), 74, 75, 82, 84, 85, 87, 89(2), 90, 93, 96, 100, 101, 106, 107, 109(2), 110(3), 112(2), 113, 114, 116(2), 120, 122(3), 125(4), 130, 131, 136(4), 137, 141(3), 142, 143, 147(2), 150, 152, 156(2), 157(2), 158, 161, 162(2), 164(2), 170(2), 172, 173, 175(3), 176, 177, 178(2), 181, 183(4), 185, 186(3), 188, 192, 193(2), 196(4), 198(4), 202(4), 203, 204(4), 205, 208(2)
Shinmyozu, T., 25
Shiomi, Y., 177
Shirahama, Y., 186(2)
Shiratsuchi, K., 156
Shishkanova, T. V., 194
Shobi, H., 208(2)
Shohat, D., 190
Shokova, E. A., 11, 112(2), 194(2)
Shono, T., 193(2)
Short, R., 183
Shosenji, H., 189
Shu, C.-m., 79, 112, 118
Shvedene, N. V., 194(2)
Sicuri, A. R., 4, 90, 106(3), 112, 114, 120(2)
Sidorov, V., 175
Siepen, A., 125
Sigel, G., 147
Sillescu, H., 5
Simon, N., 158(2)
Simonov, Y A., 138
Singh, H., 28
Singh, V., 110, 188
Sisido, K., 67, 125
Skelton, B. W., 52, 55(2), 142, 147, 148, 149(2), 169
Skowronska-Ptasinska, M., 194
Slawin, A. M. Z., 99
Small, A. C., 97(2)
Smirnov, S., 175
Smith, D. K., 110
Smith, J. M, 60, 61
Smith, P. H., 35
Smith R. D., 99
Smith, W. E., 114
Smithhisler, D. J., 100
Smyth, M. R., 193(2), 198

Snellink-Ruel, B. H. M. 175, 192
Sobolev, A. N., 55, 161, 169, 170
Soedarsono, J., 157
Solari, E., 97(2), 149, 205(2)
Solf, I., 208
Son, H., 172
Sone, T., 17(2), 27, 28(2), 109, 110
Song, B. M., 55, 171
Sonnenburg, R., 52
Souley, B., 11, 69, 161
Speier, G., 62
Spek, A. L., 96, 174
Spiering, A., 203
Springs, S. L., 98
Srijaranaj, S., 190
Srinivas, K., 122, 124(2), 175
Staffilani, M., 166
Stang, P. J., 99
Stanley, G. G., 56
Steed, J. W., 35, 164, 166(2), 171
Steemers, F. J., 202
Steinwender, E., 38, 55
Stephan, H., 23
Stevens, T. W., 88
Stewart, D., 3, 11(2), 29, 39, 58
Stezowski, J. J.100
Stibor, I., 175
Stirling, C. J. M., 183, 202
Stock, J. A., 2
Stokes, S. E., 110(3)
Struck, O., 125, 189
Struijk, H., 161
Sudhölter, E. J. R., 159, 194
Sudria, I. B. N., 170
Suenaga, H., 131
Suenaga, M., 25
Sueros Velarde, F. J., 4, 159, 171, 172
Suga, K., 149
Sugawa, Y., 28
Sugawara, M., 184, 202, 208
Sujeeth, P. K., 56, 87
Sukata, K., 208(2)
Sun, S., 191
Sunamoto, J., 109
Sung, R. L., 208(2)
Susuki, T., 89, 170
Sutherland, I. O., 89, 116
Suzuki, K., 24, 51
Suzuki, T., 121, 170
Svehla, G., 4, 192, 193(5), 194
Swager, T. M., 4, 16, 97, 145, 181(2)
Swanson, B., 110
Szemes, F., 90, 110, 165
Szöllösy, A., 117

Tabatabai, M., 5, 16(2), 141, 152, 155
Tafi, A., 14
Tajiri, Y., 175
Takaaki, H., 193
Takahashi, T., 208
Takasu, I., 173
Takemura, H., 25(2)
Takeshita, M., 4, 73, 87, 89, 198
Takeuchi, M., 93
Talafuse, L. K., 60
Tallpov, S. A., 112
Tamke, R. L., 190
Tan, C. M., 12, 174(2)
Tan, F.-s., 79
Tanaguchi, H., 188
Tanaka, K., 208
Tanaka, M., 193
Tang, C.-P., 145
Tang, F.-s., 112(2)
Taniguchi, H., 57, 60, 88, 165, 188(3)
Tantikunwatthana, N., 93
Tarzia, G., 205
Tashiro, M., 13, 23, 105, 136
Taskeshita, M., 4
Taty-C, A., 22
Tavasli, M., 189
Tear, T., 110
Terasaki, H., 189, 190
Teshima, O., 125
Thibodeaux, S., 136
Thielman, M. J., 19
Thiemann, T., 23
Thompson, N., 158
Thondorf, I., 13, 18, 27, 47(2), 134, 179
Thoseby, M. R., 208
Thozet, A., 60(2), 159
Thuéry, P., 60(2), 62(2), 161
Timkom, J. M., 26
Timmerman, P., 2, 38, 51, 52, 57, 106(2), 125, 126, 176(2)
Ting, Y., 56(2), 111
Tisza, S., 62
Tobiason, F. L., 19
Tohda, K, 194
Töke, L., 117, 130
Tokita, S., 90(2), 132(2), 136, 196
Tokitoh, N., 61(2), 93
Tomita, K.-I., 24, 51(2), 190, 208
Tong, W., 24, 25
Torabi, A. A., 150
Tóth, G., 117
Toth, K., 130
Toupet, L., 189
Tournois, B., 189, 192
Trengove, R. D., 30, 190
Troev, K., 144
Tröltzsch, C., 190
Troxler, L., 47
Tsantrizos, Y. S., 96
Tsubaki, T., 109, 110(2), 185, 186(2)
Tsudera, T., 162
Tsugawa, D., 188
Tsuge, A., 23
Tsujimura, Y., 195
Tsutsui, S., 196, 204
Tsuzuki, H., 23, 47, 55, 56, 116, 152
Tuntulani, T., 93
Turek, P., 89
Tymoschenko, M., 178

Ueda, H., 208
Ueda, K., 110, 130, 131, 157
Ueda, N., 208(2)

Ueda, Y., 51
Ueno, K., 34, 196
Ugozzoli, F., 16, 34, 44, 47, 52, 57, 60(2), 61(2), 75, 83, 88, 89(3), 90, 112, 113, 119, 150, 154, 160, 161, 169, 170, 177
Ulrich, G., 89, 99, 159
Umezawa, Y., 184, 194, 202
Ungaro, R., 4, 5, 11, 34, 46, 47, 49, 51(4), 52, 57, 58, 60(2), 61(3), 70, 75, 76, 82, 83(2), 84, 85, 87, 88(3), 89(8), 90(2), 92, 96, 105(3), 106(4), 111, 112, 113, 114, 119, 120(2), 150, 154(3), 159(3), 160, 161, 167(2), 170, 175, 177, 183, 188, 189, 190, 193, 195, 202, 205(2)
Usui, S., 18, 28, 38

Valdez, C., 178
Valenzuela, M., 60
van Delzen, E. U. T., 184
van den Berg, A., 194
van der Maas, J. H., 38(2), 55
van der Tol, E., 156, 202
van der Waal, P. D., 194
van Dienst, E., 4, 175
van Doorn, A. R., 90, 174(2), 195
Van Dorsselaer, A., 148, 181
van Duynhoven, J. P. M., 49, 70, 71, 73, 89, 126(2), 168, 176, 181, 189
van Eerden, J., 90
van Essen, G., 52
Van Gelder, J. M., 134(2)
van Hoorn, W. P., 39, 47, 50, 64
van Hulst, N. F., 200(2), 201
van Hummel, G. J., 34, 52, 57, 61, 71, 105, 125
van Leeuwen, P. W. N. M., 96
van Loon, J.-D., 5, 47(2), 56, 72, 93, 98, 105(2), 110, 156, 178
van Straaten-Nijenhuis, W. F., 88, 159, 174(2), 191
van Veggel, F. C. J. M., 39, 47(2), 64, 73, 97, 126, 176, 184(2)
van Wageningen, A. M. A., 125, 126, 176
vanHulst, N. F., 36
Varnek, A., 47(3), 149, 161
Vecchio, G., 175
Veda, S., 28
Verbiest, T., 200
Verboom, W., 2, 4, 5, 36, 38, 39, 47(2), 49, 51, 52(2), 56(2), 57, 61(2), 70, 71, 72, 73, 75, 82, 84, 88(2), 89, 90, 93, 98, 105(3), 106(3), 108, 109, 110, 111, 112, 114, 119, 125(3), 126(2), 156, 163(3), 164, 174, 176(2), 178(2), 181, 189, 193, 200(2), 202
Verhoeven, J. W., 156, 170(2), 202
Vertut, M. C., 36
Vetrogon, V., 152
Vicens, J., 3, 4(2), 11, 20, 22, 24(2), 47, 51(2), 52, 55(2), 60, 69(2), 89, 90(3), 93, 99, 120, 125, 155, 157(2), 161(3), 162, 189, 190, 192, 204
Vicenti, M., 120
Vierengel, A., 155
Vigner, J.-D., 60(2), 62(2)
Vigneron, J.-P., 198
Vincent, R. L., 34, 164(2), 169
Vink, R., 192
Visotsky, M. A., 32, 138
Visser, H. C., 160, 191, 192
Vittal, J. J., 87
Vocanson, F., 4, 11, 24, 28, 30, 32
Vogt, W., 13(2), 16(2), 18, 19(2), 20(2), 22, 72(2), 80, 93, 98(2), 108, 109, 110, 136, 138, 141, 152(2), 155, 158, 179, 186, 196, 200
Vögtle, F., 5, 23, 125
von der Lieth, C.-W., 15
von Piekartz, I., 175
Vreekamp, R. H., 49, 52, 106, 178, 181
Vrielink, A., 55
Vuano, B. M., 147
Vural, U. S., 11

Wainwright, K. P., 190
Walker, A., 33, 58, 158
Wamme, N., 11
Wang, G.-Q., 80, 113, 114(2)
Wang, J.-S., 90, 191
Wang, J., 147, 172, 202
Warmuth, R., 107
Warner, I. M., 32, 136
Wasikiewicz, W., 20
Watson, W. B., 61
Watson, W. H., 39, 56, 66
Wear, T., 90, 110
Weatherhead, R. H., 34
Webber, A. S., 191
Weber, C., 15
Wechsler, S., 152
Wehling, B., 149
Weightman, J. S., 90
Weinelt, F., 30, 208
Weinelt, H., 208(3)
Weiss, J., 4, 99, 120, 125
Wendel, V., 112
Wenger, S., 4(2), 90(2)
Wesdemiotis, C., 177
Wever, L., 208
Whitaker, C. R., 55
White, A. H., 52, 55(2), 62(3), 142, 147, 148, 149(3), 169(2)
Whiting, A., 26
Widner, H. M., 192
Wieser, C., 89, 189
Wijmenga, S., 72, 163
Williams, A., 34
Williams, D. J., 99
Williams, G., 51, 153
Williams, R. M., 170(2)

Wilner, F. R., 142, 147
Wintner, E., 178
Wipff, G., 46, 47(4), 149(2), 154, 161
Wolff, A., 16, 18, 22, 138
Wolfgong, W. J., 60
Wong, M. S., 116
Wong, P. S. H., 177
Wong, W. M., 174
Wong-Leung, Y. L., 194
Wörhoff, K., 201
Wortmann, R., 200
Wright, G. F., 26
Wrobleviski, W., 190, 193
Wu, B., 196
Wu, C.-Y., 145
Wu, S.,25
Wyler, R., 178

Xie, D. J., 120, 165
Xu, B., 4, 16, 97, 181(2)
Xu, W., 87, 150, 169
Xu, X.,147

Yagi, K., 194, 202
Yakabe, K., 193
Yamada, A., 39(2)
Yamada, K., 28, 189
Yamada-oka, S., 195
Yamagata, Y., 24, 51
Yamamoto, H., 90, 106, 130, 131, 193
Yamamoto, N., 34, 196
Yamamoto, T., 157
Yamanaka, S.-i., 208(2)
Yamanobe, T., 39
Yamato, T., 13(3), 23, 30, 105, 156
Yamazaki, M., 67
Yanagi, A., 74, 137
Yanase, M., 170
Yang, H., 47, 205
Yang, L.-M., 113
Yang, S. J., 130
Yang, X., 110
Yang, Y. S., 80
Yano, M., 157
Yao, B., 104, 113
Yasumatsu, M., 13, 23, 30
Yasuno, M., 208
Yeh, M.-l., 79, 112
Yilmaz, M., 11, 109, 145, 189
Yokoyama, M., 193, 195
Yoon, D. I., 142
Yoon, T. H., 117
Yordanov, A. T., 4, 47, 158
Yoshida, I., 34, 196
Yoshida, K., 196(2)
Yoshikawa, K., 208
Yoshimura, K., 25, 67, 174
Yoshimura, M., 121, 170, 176
Yoshinaga, H., 193
Youk, J., 172
Yu, X. J., 177
Yuan, R., 194(2)
Yuan, T.-s., 112
Yuldashev, A. M., 112
Yun, J. W., 97

Zakrzewski, M., 169
Zanotti-Gerosa, A., 97(2), 149, 205(2)
Zeissel, R., 202
Zerr, P., 24
Zett, A., 125
Zetta, L., 18, 19, 22
Zhang, F. S., 17
Zhang, H., 52, 53(2), 84, 96, 97, 164(2)
Zhang, H. C., 96
Zhang, L., 175(2), 184(2), 202
Zhang, W.-C., 107
Zhang, Y., 32, 136
Zhang, Z., 18
Zhang, Z. H., 88
Zheng, Y.-S., 107, 112
Zhong, Z.-L., 89, 90, 145
Zhu, J., 85
Ziat, K., 87, 151, 152, 153
Ziegler, E., 2
Ziessel, R., 89, 99, 159
Zigeuner, G., 2
Zimmermann, J., 129
Zinke, A., 2
Zu, B.,97
Zwier, J. M., 170

Subject Index

Acid-catalyzed condensation, 14–16, 31
Acid strengths, 34–36
Acylation, 75–76, 79–80, 114
Adsorption, on metals, 184
Alkylating agents, 83–86, 90
Alkylation, 74–76, 82–87, 112
Alkyne coupling, 125
Allosteric effect, 165, 168, 177
Aminomethylation, 117
Anions, calixarene,
  bis-anion, 60
  calix[8]arene tetraanion, 91
  conformations, 65
  oxyanions, 65
  stabilization, 35
  X-ray structures, 65
Anion complexes, 165–167
Antimicrobial action, 205
Aromatic Solvent Induced Shift (ASIS), 174
Aroylation, 76, 80–83, 114
Arylation, 116
Arylsulfonates, 81
Asymmetric calixarenes (*see* Chiral calixarenes)
Atomic Force Microscopy (AFM), 184
Autoclave-induced reaction, 13
Azacalixarenes, 25–26

Baekeland, Leo, 4
Baeyer, Adolph von, 4, 27
Baeyer–Villiger oxidation, 130
Bases,
  $Ba(OH)_2$, 82, 84
  t-BuOK, 74, 78
  Cs_2CO_3, 74–75, 77–78, 85, 90–91, 126
  CsF, 82, 85
  CsOH, 23, 124
  EtOTl, 76
  K_2CO_3, 75, 77, 82, 84, 91, 117
  KH, 91
  LiOH, 23
  Me_3SiOK, 83, 86
  1-methylimidazole, 74
  Na_2CO_3, 75
  NaH, 74, 77–79, 82, 86, 90–91
Binding sites, hard and soft, 158, 204
Bis-calixarenes, 20–21, 98–99, 124, 161, 166
Borohydride reduction, 129
Bridged calixarenes (*see also* Bridging moieties), 19–20, 89–100, 119–129
  azacrowns, 90
  bis-calixarenes, 20–21, 98–99, 124, 166
  calixcarcerands, 125
  calixcrowns, 89–90, 159–160
  calixcryptands, 90
  calixsalophens, 90, 175
  calixspherands, 162–164
  calix[4]arene, A,B-bridged, 90
  calix[4]arene, doubly-bridged, 92
  calix[5]arene, 93
  calix[6]arene, 90, 93, 96
  calix[8]arene, 90, 96
  calix[8]arene crown, 90
  double cavity, 93
  doubly-bridged, 20, 24, 90
  intermolecular, 98–100, 124–129
  intermolecular *vs.* intramolecular, 125
  intramolecular, 89–97
  octacalixarene, 100
  quadruply-bridged, 20, 96
  tetracalixarene, 99
  triple attachment, 96
  tris-calixarene, 100
Bridging moieties,
  alkane, 19–20
  alkene, 90, 99
  alkyne, 125

Bridging moieties (*cont.*)
anhydride, 120, 122
anthrylene, 93, 96, 120
bipyridyl, 90, 99
bis-diazonium, 122
catechol, 122
chelates, 125
diacetylene, 96
diyne, 119
durylene, 93
hemispherand, 92, 162
intermolecular *vs.* intramolecular, 98
metallocenyl, 99
metals, 97
methylenedioxy, 93
oxygen, 20
phenanthrolene, 93
phenylene, 93, 119
phosphorus moieties, 96
phthaloyl, 72, 93, 96
polyoxyalkyl, 89–90, 96, 98
porphyrin, 119, 125
pyridinedicarbonyl, 95, 172
resorcinol, 122
Schiff base, 120
two-carbon, 120
Broken chain pathway, 68
Bromination, 106–107
p-tert-Butylcalix[4]arene,
acylation, 75–76, 79–80
alkali metal salts, 65
alkylation, 82–84
aroylation, 76, 80–83
de-*tert*-butylation, 104
deoxygenation, 100
deuterated, 29
ethers,
dibenzyl-A,C, 83
dimethyl-A,B, 84
dimethyl-A,C, 83
dipyridylmethyl-A,B, 84
monomethyl, 51, 82, 174
NMR spectrum,
computer-assisted, 64
temperature dependent, 72
tetraethyl, 53
conformational inversion, 67
tetramethyl, 53, 83–84
conformational inversion, 66–67
dealkylation, 83
nitration, 108
tetrapropyl, 75
tetra-*n*-propyl, charge transfer complex, 175
tetrapyridylmethyl, 89
trimethyl, 67, 84, 87
trimethylsilyl, 201
tripropyl, 76, 84
nitration, 107–110
oxidation, 130–134
pK_a value, 35
reactions (*see also* Functionalization, lower rim and upper rim),
with benzylamine, 29
with dimethylaminoarsine, 96
with dimethylaminophosphine, 96
with propyl bromide, 75
sulfonation, 110
synthesis,
from *p-tert*-butylcalix[8]arene, 29
fragment condensation, 17
one-step, 10–12
X-ray structure, 51
p-tert-Butylcalix[5]arene,
acylation, 80
bridged, 90, 93
esters, 69, 81, 85–86
ethers, 66, 69, 85
oxidation, 133
self-complexation, 58–59
synthesis, one-step, 11
X-ray structure, 59
p-tert-Butylcalix[6]arene,
acylation, 80
bridged-A,B, 93–96
conformation, 60
esters, 81
ethers, 85–86, 105
formation from hemicalixarenes, 30
mechanism of formation, 30
oxidation, 129–130, 133
pK_a value, 35
sulfonation, 110
X-ray structrure, 61
p-tert-Butylcalix[7]arene,
synthesis, one-step, 11
X-ray structure, 63
p-tert-Butylcalix[8]arene
bridged, 90–93

conformational inversion, 65–66
conversion to cyclic tetramer, 29
deuterated, 29
esters, 81
ethers, 86–87
oxidation, 133
pK_a value, 35
synthesis, one-step, 11
X-ray structure, 63

Cahn–Ingold–Prelog rules, 42
Calixarene anion (*see* Anions, calixarene)
Calixarene complexes (*see* Complexes of calixarenes)
Calixarene polymers, 144–145, 181
Calix[4,5,6,7,8]arenes, *p-tert*-butyl (*see* *p-tert*-Butylcalix[4,5,6,7,8]arenes)
Calix[4]arenes, 1, 7, 18, 50–58
Calix[5]arenes, 17–18, 27, 58
Calix[6]arenes, 18, 60–61
Calix[7]arenes, 61–62
Calix[8]arenes, 18, 28–29, 62
Calixcarcerand (*see also* Bridged Calixarenes), 125
Calix crater, 1–2
Calixcrowns (*see also* Bridged calixarenes), 89–90, 159–162
Calixcryptand (*see also* Bridged calixarenes), 90
Calix[3]indoles, 27
Calix[4]pyrroles, 27
Calixquinones, 130–132
complexation, 149
conformation, 57
electrochemistry, 149
rections, 132
synthesis, 130–132
X-ray structures, 57
Calixresorcarenes, 8, 31, 125, 130, 176–177, 184
Calixsalophens (*see also* Bridged calixarenes), 175
Calixspherands (*see also* Bridged calixarenes), 162–164
Calixthiols, 56, 103
Calorimetry, differential scanning, 169
Capillary electrokinetic chromatography, 191
Capillary zone electrophoresis, 32
Carcerands, 125
Carceroisomerism, 177
Catalysis, 185–189
acylase mimic, 187–188
autoaccelerative, 188
cyclic phosphate formation, 186
diazo coupling, 188
Hammett ρ constant, 187
hydration of dihydronicotinamide, 185–186
hydroformylation of styrene, 189
hydrolysis,
of dinitrophenyl phosphate, 186
of *p*-nitrophenyl acetate, 187–188
of *p*-nitrophenyl dodecanoate, 186
of *p*-nitrophenyl phosphate, 186
selective, of calixarene tetraester, 186–187
inhibition, hydrolysis of phenyl benzoate, 186
intramolecular, 186
methanolysis of calixarene monoacetate, 187
phase transfer, 188
proximity, 188–189
pseudo intramolecular, 154–155, 186–187
regioselective, ring opening of a cyclic phosphate, 186
turnover number, 188
Cation effects, 13, 23, 49, 65, 67, 74–75, 150, 152–156, 163
Cation–π interaction, 161
Cation transport, 149
CHEMFETs, (*see also* Sensors), 194
Chiral calixarenes, 20–22, 25, 135–143
calix[5–8]arenes, 142
via external attachment, 135
guest-induced asymmetry, 169
inherent chirality, 136–142
via meta substitution, 141
resolution, 32, 137
shift reagent, 37
substitution patterns, 136–142
synthesis, 20–22
via unsymmetrical upper rim bridges, 142
via upper and lower rim substitution patterns, 136–139
Chloromethylation, 112

Chromatography, 32–33
enantioselective, 32, 142
HPLC, 32–33, 142, 189–190
supercritical fluid, 33
Chromogenic sensors, 195
Chromotropic acid, 12
Circular dichroism, 147
Claisen rearrangement, 105, 118, 124
Columnar array, 181–182
Complexaton guests (*see* Guests for complexation)
Complexes of calixarenes,
calorimetric measurements, 152, 154
cation exchange, intramolecular, 162
cation oscillation, 162
charge transfer, 175
comparison of esters, ketones, amides and carboxylic acids, 155
comparison with crown ethers and cryptands, 153
effect of,
background electrolyte cation, 156
conformation, 151, 175
ring size, 153
solvent, 172, 176
p-substituent of calixarene, 151, 154, 172
symmetry, 152, 165
endo, 147–149, 174, 183
entropy- and enthalpy-driven, 152
exo, 149
extraction efficiency, 156, 164
gas phase, 177
kinetic stability, 164
solid state, 169–170, 173
solution state, comparison with solid state, 171–177
X-ray structures, 147–148
Computational studies, 46–50
calix[6]arenes, 63–64
comparison of methods, 47–49
complexes, 154, 170, 173
conformational composition, tetramethyl ether of $\mathbf{4}^{SO_3H}$, 67
conformational mobility, deoxycalixarenes, 56
conformations, 47–50
dipole moments, 50
free energy perturbation methods, 50
MM3-optimized conformations, 49
pK_a Values, 47
Conductivity, 147
Cone–cone interconversion, 19, 49, 68
Conformation, 41–78
annelated calixarenes, 51
1,2-alternate, 41, 47, 55–56, 72
1,2,3-alternate, 61, 73
1,2,4,5-alternate, 61–62
1,3-alternate, 41, 47, 55–56, 72
bis-roof, 56
boat, 51
bridged calixarenes, 49
calixarene-related compound, 68
calix[6]arenes, 60
calix[7]arenes, 61, 70
calix[8]arenes, 62, 70
calixquinones, 61
chair, 56
computational studies, 46–50
cone, 41, 46, 50–52, 63, 65, 70
determined by ^{13}C NMR, 39
distorted 1,2,3-alternate cone, 60
distorted cone, 46, 58, 60, 155
double partial cone, 60
doubly flattened partial cone, 55
effect of,
Ag^+ on NMR spectrum, 49
cation binding, 150
complexation, 151, 159
mono *O*-substitution, 70–71
solvent, 60, 66–67
p-substituents of aryl ring, 66–67, 70
energies, 47–50
fixed pseudo pleated loop, 96
flattened 1,2-alternate, 58
flattened cone, 51, 52, 73
hinged, 60
interrupted pleated loop, 37
mobility of calix[*n*]arenes, 63–66
mono-substituent effect, 70–71
NMR, temperature dependent, 49
nomenclature (*see* Conformational notation)
partial cone, 41, 46, 57, 60
partial flattened cone, 52–55
pinched, 60, 71
pinched cone, 49, 56–8, 66–67, 181
pinched cone wobble, 73
pinched cone interconversion, 49
pleated loop, 37, 46, 62–63, 65, 96

representations, 41, 44
Schönflies point symmetry designation, 45
solid state, 50–62
solution state, 63–66
twisted, 62
twisted double cone, 170
up/down orientation, 41
winged, 60, 64
winged cone, 64
Conformational interconversion, 63–68
bridged calix[4]arenes, 72
bridged calix[6]arenes, 72–73, 93
broken chain pathway, 68
calixarene ethers, 66
calixquinones, 67
cone–cone, 19, 49, 68
conformer distribution, 66–67
continuous chain pathway, 68
$\Delta G^{\ddagger}$ values, 49, 64–66, 70–71
$\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values, 64, 66–67
deoxycalixarenes, 65, 67
effect of,
cations, 65, 67
complexaton, 49
hydrogen bonding, 71
solvent, 65–67
steric factors, 70
m-substituents, 66
OR-substituents, 66
p-substituents, 65, 67
entropic control, 67
equilibrium mixture, tetramethyl ether of $\mathbf{4}^{t\text{-Bu}}$, 66–67
hydrogen bonding, 71
isokinetic temperature, 64
kinetics, 67
large calixarenes, 63–64
pathways, 68–69
tetraacetates, 76
Conformationally immobile calixarenes, 68–73
bridged structures, 72
conformatonal barriers, 71
dependence on OR and *p*-R groups, 69–70
ethers and esters, pathways for interconversion, 68–69
fully etherified and esterified calixarenes, 68–69
minimum structural requirements, 68–69
partial ethers and esters, 70
Conformational mobility (*see* Conformational interconversion)
Conformational notation, 41–46
Cahn–Ingold–Prelog rules, 42–43
dihedral angles, 44–46
reference aryl group, 42
up/down, 41
Continuous chain pathway, 68
Cornforth, Sir John, 2, 5, 41, 205
Crown ethers, 10, 90
Cryptands, 153, 156
Cryptocalix[6]arenes, 96
Crystal packing forces (*see* Conformation, solid state)
Cyanation, 106
Cyclodextrin calixarene, 175
Cyclodextrins, 10, 41, 125, 175
Cyclooligomers, 15, 26–27
Cycloveratrylene, 96

Dealkylation of calixarene ethers, 82–83
De-*tert*-butylation, 104–105
deMendoza rule, 39
Dendrimers, 205
Deoxycalixarenes, 100–104
conformational mobility, 60–61, 67
X-ray structure, 56
Dialkylation, 83
Diazo coupling, 112
Diels–Alder reaction, 134
Dihedral angles, 44–46
Dimers, 178
Dipole moments, 36–37
computational study, 37
effect on conformational equilibrium, 67
Disproportionation, 84
Dissymmetric calixarenes (*see* Chiral calixarenes)
Double cavity calixarenes, 93

Electrodes, ion- and molecule-selective, 192–194
Electrophilic substitution (*see also* Functionalization, upper rim), 105
Electrophoresis, 32

Enzyme mimics, 10
Esterification, 76–78, 79–81
  effect of,
    reaction conditions, 80
    p-substituent of calixarene, 80
  partial, 80
Etherification, 74–78, 82–89
  conformational outcome, 74–78
  effect of,
    base, 74, 77, 83–86, 91
    leaving group, 75
    pressure, 85
    reaction conditions, 84–85
    p-substituent of calixarene, 77, 85
  general rules, 78
  partial, 76, 83–84
  pathways, 76–77, 87
  synthesis, 82–86
    A,C,E-triether of calix[6]arenes, 85
    calix[8]arene ethers, 86
    distal diethers, 83
    monoethers, 82
    partially alkylated, 82–86
    pentaethers, 85
    by protection/deprotection, 84
    proximal diethers, 84
    tetraethers, 84
    triethers, 84
European consortium, 143

Faces of calixarenes, 8
Field effect transistors (*see* Sensors)
Flattened cone, 52
Fluorescent sensors, 195
Formylation, 114–116
Fragment condensation, 17–21
Free energy values (*see* $\Delta G^{\ddagger}$ values)
French, Dexter, 11
Friedel–Crafts reaction, reversibility, 18
Fries rearrangement, 114
Fullerenes, 89, 170, 176, 183
Functionalization, lower rim (*see also* Esterification and Etherification), 73–78, 79–103, 114
  acylation (*see also* Esterification), 75–76
  alkylation (*see also* Etherification), 74–76, 83–87
  aroylation, 80, 114
  replacement of OH, 100–103
    with H, 100, 103
    with NH_2, 101
    with SH, 103
Functionalization, selective, 143–144
Functionalization, upper rim, 104–126
  acylation, 105, 114–115
  via acyl intermediates, 115–116
  alkylation, 106, 112
  alkynylation, 107
  amination, 106
  aminomethylation, 117
  aroylation, 76, 80–91, 105, 114
  arylation, 76, 116
  boronation, 106
  bridging (*see also* Bridging moieties), 121–122, 125
  bromination, 106–107
  carbonation, 106
  chloromethylation, 113
  chlorosulfonation, 111
  Claisen rearrangement, 105, 118, 124
  cyanation, 106
  cyanomethylation, 117
  de-*tert*-butylation, 104
  diazo coupling, 112
  electrophilic substitution, 105
  formylation, 106, 114–116
  fragment condensation, 104
  Fries rearrangement, 114
  halogenation, 106
  hydroxlylation, 106
  iodination, 106
  lithiation, 106
  Mannich base intermediates, 117
  nitration, 107–109
  overview, 104
  sulfonation, 110
  vinylation, 107

$\Delta G^{\ddagger}$ values, 64, 66, 70–71
Gas phase complexation, 177
Gelation, 204
Girards reagent, 183–194
Gross method, 114–115
Growth curve, 5–6
Guests for complexation,
  anions, 165–167
  metal cations,
    aluminum, 61, 97, 148, 164, 204
    americium, 158

barium, 149, 153–154, 156, 188
cadmium, 158–159, 164, 193, 195
calcium, 153–154, 156, 158, 193, 196
cerium, 154, 196
cesium, 148–149, 151–153, 183, 193, 195, 202
chromium, 164
cobalt, 164–165, 189
copper, 156–159, 160, 162, 164–165, 189, 193, 195, 198, 202, 204
erbium, 156
europium, 147–148, 154, 156–159, 202
iron, 158, 164, 189, 204
irridium, 171
lanthanum, 62, 148, 156, 202
lead, 158–159, 193–195
lithium, 148–149, 152–153, 155, 202
luteceum, 148
magnesium, 153–154, 156
mercury, 56, 149, 159, 164–165
neodynium, 156
neptunium, 158
nickel, 156–157, 159, 164–165, 189, 204
niobium, 97, 148–149
palladium, 158, 164
platinum, 158
plutonium, 158
potassium, 148–153, 155, 159–160, 162, 164, 183, 190–191, 193, 196, 202, 204
praseodynium, 154
rhenium, 165
rhodium, 158, 171, 189
rubidium, 148–149, 150–154, 155, 160, 162–164, 183, 198, 202
ruthenium, 165, 198, 202
silicon, 148
silver, 49, 149–150, 154, 158, 162, 164–165, 193
sodium, 49, 65, 148–153, 155–156, 159–165, 183, 192–193, 196, 202–204
strontium, 148, 153–154, 156
tantalum, 97, 148
terbium, 157–159, 202
thorium, 62, 158
thulium, 148, 154
titanium, 147–148
tungsten, 97, 141
uranium, 74–75, 189
ytterbium, 154, 156, 164
zinc, 148, 157, 164, 204
zirconium, 97
molecular cations, 169, 171–174
adenine, protonated, 164
amino acids, 174, 190
ammonium, 171–172, 194
guanidinium, 172–173, 195–196, 198
pyridinium, 193–194
trimethyl-1-phenylammonium, 136, 172
molecules, 174–177
acetylcholine, 172
aliphatics, 169
amines, 169, 173, 198
aromatics, 169–170, 175, 180, 184
$Cr(CO)_3$, 116, 141, 171
fullerenes C_{60} and C_{70}, 170, 176
imidazole, 173
naphthalenesulfonates, 175
phenols, 174, 190
phosophatidylcholine, 173
polycyclic aromatics, 175
salts, 167–168
steroids, 176
sugars, 176–177
tetracyanoethylene (TCNE), 175
trihaolmethanes, 190
urea, 174

Halogenation, 106
Hayes and Hunter, 17
Head-to-tail bis-calixarenes, 20
Hemicalixarenes, 28–31
Historical perspective, 2–7
Hoffman rearrangement, 130
Holand, 176
Hosts for complexation,
bis-calixarenes, 161
calix–calixresorcarene, 184
calixcarcerands, 176
calixcrowns, 161–162, 168
calix dimers, 178–181
calixsalophens, 175
calixspherands, 162–164
calixthiols, 149
homooxacalixarenes, 174

Hosts for complexation (*cont.*)
lower rim-substituted calixarenes, 150–164
amides, 152
bipyridyl-bridged, 166–167
calixcrowns, 159, 166
carboxylic acids, 154
esters, 150
ethers, 150
ketones, 152
nitrogen-containing, 158
phosphorus and sulfur-containing, 158
pyridine-bridged, 172
upper rim-substituted calixarenes, 164–170
Hydroboration, 88
Hydrogen bonding,
array reversal, 71
calixarene dimers, 178–181
clockwise/anticlockwise, 64
conformation, effect of *p*-substituents, 49
directionality, 181
flip-flop *vs.* permanent, 50
host–guest interaction, 169, 172–173, 204
infrared stretching frequencies, 37
intermolecular, 40, 166, 173, 179–181
intermolecular *vs.* intramolecular, 181
intramolecular, 37–38, 49, 61, 63–64, 70, 82, 85
NMR proton shift values, 38
Hydroxyl group,
endo, 7, 8, 16, 19, 50–51
exo, 8, 12, 16, 18–19, 51
IR stretching frequencies, 37
NMR of bridged calixarenes, 49
NMR resonances, 38

Iconographic representations, 44
Infrared spectra, 37, 71, 171, 202
Iodination, 106
Ionophoric tube, 161–162
Ion-selective electrodes, 192–194
Ion separations, 189–190
Ipso nitration, 108
ISFETs (*see also* Sensors), 194

Kämmerer, Hermann, 5, 10, 17
Ketocalixarenes, 130
Kinetics of complexation, 22, 152
Koiland, 148, 181

Langmuir–Blodgett monolayers, 200
Large calixarenes, 14
Lawsson's reagent, 88
Linear oligomers, 14, 16, 26–27, 34, 178
Liquid crystals, 204
Liquid membrane, 174–175, 191–192
selective transport of amino acids, 172
transport of CsCl, 168
Lithiation, 106
Lithography, electron beam, 205
Lower rim, 8
Lower rim through the annulus pathway, 69
Luminescence, 159, 202

Macrocyclons, 206–208
Mainz group, 5
Major calixarenes, 11
Mannich base, 117
Mass spectra, 39–40, 146
Mechanism of calixarene formation, 28–31
base-induced reaction, 28
fragmentation–recombination, 29–30
hemicalixarenes, 28–30
molecular mitosis, 29
pseudocalixarenes, 30
thermodynamic control, 128
Melting points, 33
Metacyclophane, 1
Methoxy groups, conformational stabilization, 70
Micelles, 183
Mitsunobu reaction, 89
Moleclular complexes, 169
Molecular dynamics (*see* Computational studies)
Molecular mitosis, 29
Molecular separations, 190
Monobenzylation, 83
Mono ether effect, 70–71
Monolayers, 183–184, 200
adsorption on surfaces, 184
effect of cations, 183
Langmuir–Blodgett, 200
oriented, 200

perforated, 191
Mono-substituent effect, 70–71
Montmorillonite, 192
Multiple ansa compound, 125

Nanostructure, 126
Nano-tube, 125
Naphthalenediol disulfonate, 12
Naphthol-derived calixarenes, 12, 22
Narrow rim, 8
Negative resist, 205
Neutron scattering, 169
Newman–Kwart procedure, 103
Nitrocalixarenes, 109
Nitrogen bridges, 27
Nitroxo group, 89
NMR spectra, 37–39
  bridged calixarenes, 49
  ^{13}C NMR, 39, 174
  2D EXSY NMR, 72
  δ_{OH} values, 38
  NOE and NOESY, 149, 163
  ^{17}O NMR, 39
  pulsed gradient spin echo, 174
  relaxation times, 172
  solid state, 39, 169, 170, 174
  temperature dependent, 49
Nomenclature, 7–9
  abbreviated, 8–9
  calixresorcarene, 8
  colloquial, 8
  conformation, 41–45, 77
  lower rim, 8
  major calixarenes, 11
  minor calixarenes, 11
  narrow rim, 8
  substituents, arrangement, 9
  upper rim, 8
  wide rim, 8
Nonconvergent stepwise synthesis, 17
Nonlinear optical compounds, 198
Nuclear Overhauser (NOE) spectra, 149, 163

Octacalixarenes, 100
Octamethylcalix[4]arene, 16
Oligomers,
  aggregation, 70, 180
  linear, 8, 14, 16, 26–27, 34, 178
Organic clays, 164
Oxacalixarenes, 15, 24–25
Oxidation, 129–134
  aromatic ring, 130
  ketocalixarenes, 130
  methylene groups, 129
  quinones, 130
  spirodienones, 132
Oxyanions, 65
Oxyethylation, 88

Parma group, 5
Patent literature, 207–208
Pathways for alkylation, 77, 87
Perforated monolayer, 191
Petrolite, 7
Phase transfer extraction, 151
Phenol,
  p-benzyl, 11
  p-benzyloxy, 11
  bis-phenol, 12–13, 16, 20, 25–26
  p-*tert*-butyl, 11, 14
  o-chloromethyl, 118
  o-hydroxymethyl, 16
  p-(−)-menthyl, 21
  p-methyl (cresol), 11
  p-phenyl, 11
  trimethyl-1,3,5, 18
Phenol-derived calixarenes, 2, 7–8, 11
Phosphates, synthesis, 81
Phosphonates, synthesis, 81
π-Interaction, 150, 172–173, 177
pK_a values, 34–36, 47–50
  apparent, 36
  calculated, 50
  linear trimers, 35–36
  lower rim carboxylic acids, 154–155
  methyl ethers of $\mathbf{4}^{t\text{-Bu}}$, 36
  OH-depleted calixarenes, 36
  picrate titration, 36
  potentiometric titration, 34
  p-sulfonatocalixarenes, 35
  spectrophotometric titration, 34, 36
  water-insoluble calixarenes, 35
Platforms, molecular, 125, 205
Point symmetry, 45
Polymers, 144–145, 181
Porphyrins, 93, 125
Potentiometric titration, 34
Preorganization, 126, 156–157
Pseudocalixarenes, 30

Pseudo C_2 symmetry, 43
Purification of calixarenes, 32–33
Pyroelectric effect, 202

Quantum confined cadmium sulfide clusters, 205
Quinonemethide route, 117
Quinones, 58, 130–132, 142

Reagents,
  chlorine dioxide, 130
  thallium nitrate, 131
  thallium trifluoroacetate, 130
  trimethylphenylammonium tribromide, 133
  trimethylsilyl iodide, 82
Rearrangement, A,C-diester to A,B-diester, 80
Redox switch, 204
Reduction, calixarene framework, 135
Resorcarenes (*see* Calixresorcarenes)
Resorcinol-derived calixarenes, 2, 7–8, 31
Rotaxane, self-anchored, 73

Saint Louis group, 5
Salt complexes, 167–168
Schönflies point symmetry, 45
Selective functionalization, 143–144
Selective transport, 172, 191–192
Self assembly, 177–184, 204–205
  calixarene dimers, 178–180
  colloids, 184
  columnar array, 181–182
  dimeric assemblies, 177–180
  dimers, 178
  double rosette aggregate, 181
  effect of molecular shape, 182–183
  gel, 181, 204–205
  oligomers, 181–183
  polymers, 181
  solid state, crystal packing forces, 174
  vesicular arrays, 183
Self-complexation, 58
Sensors, 192–206
  chemically modified field effect transistors (CHEMFETs), 194
  chromogenic, 195–198
  field effect transistors (FETs), 194
  fluorescent, 195–198
  for,
    acetylcholine, 198
    amines, 198
    guanidinium, 198
    immunoassay systems, 202
    phenylethylamine, chiral recognition, 198
    saccharides, 202
  ion-selective electrodes, 192–193
  ion-selective field effect transistors (ISFETs), 194
  molecule-sensitive electrodes, 194
  quartz micro balance, 201
  surface acoustic wave oscillator, 201
Separation and purification of calixarenes, 32–35
Separations employing calixarenes, 32, 189–191
  capillary electrokinetic, 191
  at interfaces, small gas molecules, 191
  ions, 189
    cesium from nuclear wastes, 189
    uranium from sea water, 189
  molecules, 190
Shift reagent, 137, 141
Silacalixarenes, 27–28
Silicon-based calixarenes, 198
Silvanols, 118
Solid state complexes, 169
Solution state complexes, 171, 174
Spectra (*see also* Infrared spectra, NMR spectra, Ultraviolet spectra), 37–30
Spectrophotometric titration, 36
Spin label, 89
Spirodienones, 132–134
  reactions, 133
  stereochemistry, 142–143
  synthesis, 133
Structure representation, 7–8
Substituents,
  endo-hydroxyl, 19
  endo-rim, 8, 19
  exo-hydroxyl, 8, 18–19
Sulfonation, 110
Sulfonatocalixarenes, 35
Sulfur bridges, 27
Supercritical fluid chromatography, 33
Supported Liquid Membrane (SLM), 174–175, 191

Supramolecular assembly, 177–178, 204–205
Suzuki arylation, 116
Switching, 203–204
  photoresponsive molecules, 203
  redox switch, 204
  reversible, 203
Synthesis, calixarene-related compounds, 23–27
Synthesis of calixarenes, one-step, 10–16, 30–31
  acid-catalyzed, 14, 16, 31
  base-induced, 10–13
  cation effects, 13
  chiral, 20–22
  substituent effects, 13
Synthesis of calixarenes, stepwise, 10, 17–19, 104
  bridged, 19–20
  chiral, 20–22, 136–143
  convergent, 17–23, 100, 104
    2 + 1 + 1, 19
    2 + 2, 17, 23, 100
    3 + 1, 18, 22, 100
    3 + 2, 18
  organolithium methodology, 100

Tandem Claisen rearrangement, 124
Telomers, 145
Template effect, 126
Tetracalixarenes, 99
Thermodynamic studies, complexation, 172
Thin films, 191
Third sphere ligand, 148
Trimethoxytoluene-derived cyclooligomer, 15
Trioxane, 14
Triphenylmethane-derived cyclooligomer, 15
Tris-calixarene, 100
Tuberculostatic agents, 206
Tunneling, cations, 162

Ultraviolet spectra, 37
Upper rim, 8
Upper rim through the annulus pathway, 69
Upside-down representation, 8
Uracil-derived calixarene, 27
Uranophiles, 157, 164, 174–175, 189

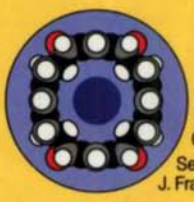
Valinomycin, 160
Vancomycin mimic, 205
Vesicular arrays, 183

Water soluble calixarenes, 110, 112–113, 118
Waveguide, 200–201
Wide rim, 8
Wittig reaction, 116
Wolff–Kishner reduction, 129, 134

X-ray crystallography, 33–34, 43–44
X- ray structures,
  1,2-alternate conformer, 54
  1,3-alternate conformer, 54
  4$^{t\text{-Bu}}$, A,B-dipyridyl-C-benzyl ether, 52
  4$^{t\text{-Bu}}$, A,C-dicyanomethyl ether, 52
  5$^{t\text{-Bu}}$, penta-*i*-propyl ether, 59
  5$^{t\text{-Bu}}$, self-complexed, 59
  6$^{t\text{-Bu}}$, 1,2,3-alternate conformer, 61
  6$^{t\text{-Bu}}$, pinched cone conformer, 61
  7$^{t\text{-Bu}}$, 63
  8$^{t\text{-Bu}}$, 63
  calixcrown, K^+ complex, 161
  calixspherand, K^+ complex, 163
  partial cone conformer, 54
  tetradeoxoy-**4**$^{t\text{-Bu}}$, 57

Yne-coupling, 122

Zinke, Alois, 2



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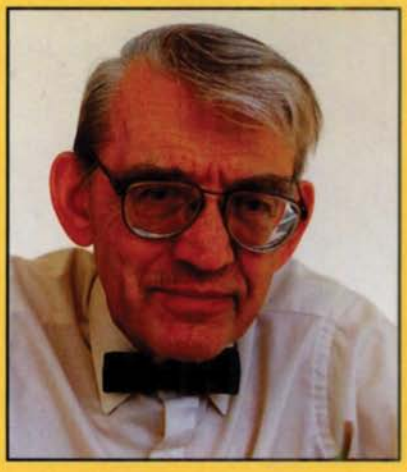
Supramolecular chemistry, in all its rich forms and varied facets, is still growing in stature, scope and potential. It is important that practitioners expose its challenges, rewards, fascination and excitement to as many fellow scientists as possible. The series 'Monographs in Supramolecular Chemistry' was created with these goals in mind and aims to popularize this branch of molecular science among the scientific community at large. It will prove invaluable to research scientists at varying stages of career development in both industry and academia.

In recent years there has been an explosive growth in the field of calixarene chemistry.



Calixarenes Revisited, a sequel to the 1989 publication *Calixarenes*, will bring researchers right up to date with current developments in this increasingly competitive area. Spanning the period 1989 to 1996, items are fully referenced and there is also an extensive bibliography.

Covering in depth the synthesis, characterization and properties, as well as conformation, reactions and complex formations of these 'baskets', **Calixarenes Revisited** is the most complete treatment of the subject available for researchers employing calixarenes in their work. It builds on the framework of the first volume, and can be used by readers already familiar with the field. For those with a less detailed background, it can be used in tandem with *Calixarenes* to provide a complete picture.

A practising chemist for 50 years, C. David Gutsche researched and taught at Washington University in St. Louis for many years, including a period as chairman of the department. As one of the earliest investigators dealing with these compounds, he is considered to be the major initiator of modern calixarene chemistry. On his retirement, Professor Gutsche became the Robert A. Welch Professor of Chemistry at Texas Christian University in Fort Worth.

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