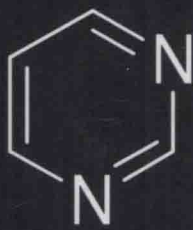
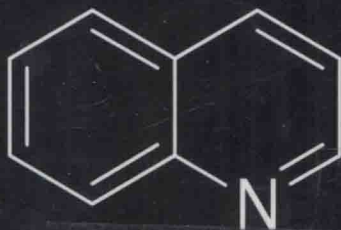
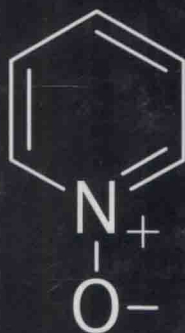
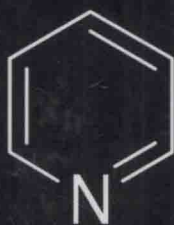
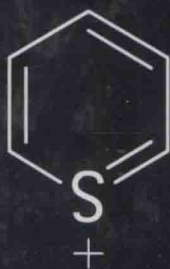


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Volume 101



Advances in
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VOLUME **101**

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MILESTONE OF 100 VOLUMES OF
ADVANCES IN HETEROCYCLIC
CHEMISTRY MARKED BY THE
PUBLICATION OF VOLUMES 99, 100,
AND 101 AS A CELEBRATORY SET

It is hard to believe that it is now 50 years since I conceived the concept of periodical volumes of these "Advances" that would record progress in Heterocyclic Chemistry. In 1960, heterocyclic chemistry was slowly emerging from the dark ages; chemists still depicted purines by the archaic structural designation introduced (was it by Emil Fischer?) 50 years before that. Together with Jeanne Lagowski I had published in 1959 a modern text on heterocyclic chemistry, the first that treated this subject in terms of structure and mechanism and attempted to logically cover significant methods of preparation and reactions of heterocyclic compounds as a whole, all in terms of reactivity.

The first two volumes of *Advances* contained extensive chapters on the tautomerism of various classes of heterocycles. Despite the great influence the precise structure of heterocyclic compounds has on chemical and biological properties (we only have to remember base pairing of nucleotides to illustrate this), at that time the literature was replete with incorrectly depicted tautomers. The basis for the position of tautomeric equilibria was usually completely misunderstood. Although great progress has been made in the last 50 years, there still exist holdouts even among otherwise reputable chemists who persist in depicting 2-pyridone as "2-hydroxypyridine" which is a very minor component of the tautomeric equilibrium under almost all conditions.

Over the years *Advances in Heterocyclic Chemistry* has indeed monitored many of the advances in the subject: the series is now boosted by "Comprehensive Heterocyclic Chemistry" of which the first edition was published in 1984 in 8 volumes, followed by the second edition in 1996 in 11 volumes and the third in 2008 in 15 volumes. Heterocyclic chemistry

has now taken its place as one of the major branches (by several criteria the most important) of Organic Chemistry.

Chemistry has rapidly become the universal language of molecular interactions; it has essentially taken over biochemistry and is rapidly gaining dominance in zoology, botany, physiology and indeed in many branches of medicine.

Chemical structural formulae are quite basic to this progress and have enabled us to rationalize many natural phenomenon and countless reactions both simple and exotic discovered in the laboratory.

Now we have reached the milestone of 100 volumes of the series. In place of a single volume we are offering the three volume set 99, 100 and 101 which contain a fascinating variety of reviews covering exciting topics in heterocyclic chemistry.

Alan R. Katritzky
Gainesville, Florida

PREFACE TO VOLUME 101

The final volume celebrating the attainment of the century for AHC contains five chapters contributed by heterocyclic chemists from six countries.

Soler, Moorefield, and Newkome (U. Akron, Akron, OH, USA) start with a fascinating account of the Senior Author's work on the construction of hexameric macromolecular architectures in organic chemistry. Patil, Kavthe, and Yamamoto (I.I.C.T., Hyderabad, India, and Tohoku U., Japan) summarize metal catalyzed cyclizations of alkynes bearing a heteroatom attached to a substituent which migrates during the annulation.

The chemistry of the 28 possible isomeric biindolyl structures is covered by Black and Kumar (UNSW, Sydney, Australia), while R.C.F. Jones (Loughborough U., Loughborough, UK) has reviewed his own and others' research on annulation reactions of 2-imidazoline. The volume closes with an upto date account of the chemistry of the Dimroth Rearrangement contributed by E.S.H. El Ashry, S. Nadeem, M.R. Shah, and Y.E. Kilany of Alexandria U. in Egypt.

Alan R. Katritzky
Gainesville, Florida

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CHAPTER 1

Hexameric Macrocyclic Architectures in Heterocyclic Chemistry

Monica Soler,^a Charles N. Moorefield^b and George R. Newkome^{a,b}

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1. INTRODUCTION

Peter Stang once noted (97JA4777) that “In nature the hexagon represents the most common pattern throughout biological morphology from the simple diatoms to the bee honeycomb” after reading a treatise by Geoffrey Ozin (97ACR17) describing his investigations into the morphosynthesis of hierarchical inorganic structures, such as that of the radiolaria. The ubiquitous occurrence of the hexagonal motif in nature coupled with Peter Pearce’s postulate (78MI1) that “structure in nature is a strategy for design” provides insight and reason to the plethora of diverse hexagonal architectures formed throughout synthetic chemistry. As well, the burgeoning arena of Supramolecular Chemistry, pioneered by Jean-Marie Lehn (78PAC871, 88AGE89, 95MI1), expands the platform for access to self-assembled macrocycles based on the attractive interactions between select metal ions and structurally compatible heterocyclic ligands. Transcending consideration of covalent versus non-covalent bonding, supramolecular chemistry considers building blocks instilled with angles, coordination sites, and affinities that drive their assembly to architectures with utilities and designs not accessed from the starting materials alone. Conjointment of the supramolecular regime with directed and convergent synthetic protocols has facilitated new routes to macrocyclic structures.

In a seminal review of the field of self-assembly of architectures mediated by transition metals Stang et al. (00CRV853) discussed and delineated design strategies or models developed over the years by such notable scientists as Saalfrank (97AGE2482), Lehn (99CEJ102, 99CEJ113), Raymond (99ACR975) [“Symmetry Interaction” Model], Verkade (83JA2494), Fujita (98CSR417), and Stang (97ACR502, 98JCD1707) [“Molecular Library Model”].

The Symmetry Interaction model considers the geometric relationships between ligand coordination sites and metal centers by defining chelate or coordinate vectors, based on the directional orientation of the ligand-binding sites. For example, a bidentate bipyridine ligand coordinated to a metal possesses a vector pointing toward the metal that bisects the chelating group. The Molecular Library model considers the directionality and geometry of multibranching, monodentate ligands and their ramifications on the geometry of the desired molecular architecture. For example, rod-like building blocks with incorporated angles of 90° and end-group coordination sites would generate a tetragonal shape in the presence of a connecting metal that is capable of sustaining 90° coordination.

Herein, we present a brief overview of the current literature dedicated to hexameric macrocyclic architectures predicated on heterocyclic chemistry. We summarize the salient synthetic features of ring construction whereby the participating heterocyclic building blocks, or subunits,

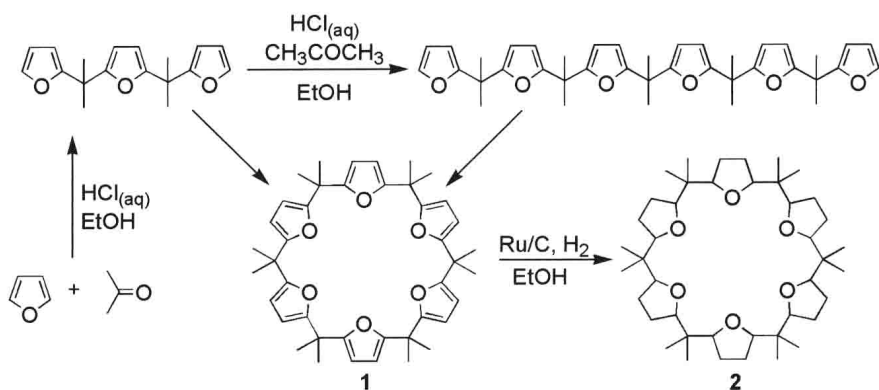
possessing at least one heteroatom, such as nitrogen, oxygen, or sulfur, with the recognition that such a broad subject will necessitate a limitation in scope.

Excluding the "Introduction," this review is organized based on the building blocks used for macrocycle construction into three sections: five-membered heterocyclic subunits, such as furan, furanose, or pyrrole; six-membered heterocyclic subunits, such as pyridine, bipyridine, phenanthroline, or glucopyranose; and miscellaneous subunits comprising, for example, a combination of five- and six-membered heterocyclic subunits or larger than six-membered ring subunits. We have sought to include as many pertinent new and classical examples as possible and will endeavor to include examples that have been missed in future manuscripts.

2. MACROCYCLES WITH FIVE-MEMBERED HETEROCYCLIC SUBUNITS

2.1 Furan, tetrahydrofuran, and thiophene

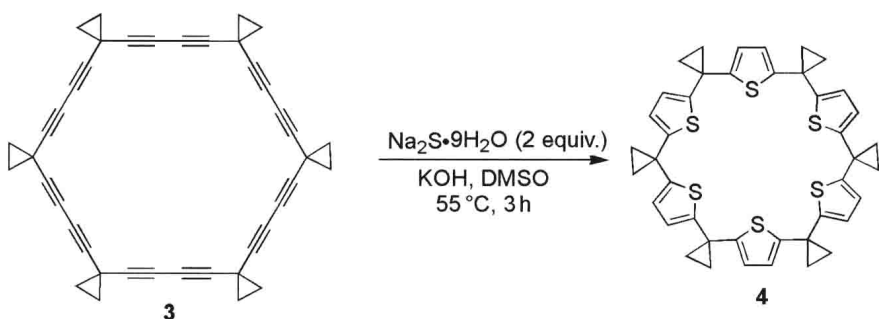
Hexameric macrocycles possessing subunits with oxygen have been reported, of which some of the earliest examples incorporated a series of 18-crown-6 ethers containing one-, two-, or three-furanyl subunits (74JA7159). In 1955, Wright et al. reported (55JOC1147) the first example of calix[6]furan **1**, comprising six furan rings joined by sp^3 -hybridized carbons. Such calix[6]furans possess a π -electron-rich cavity with a hydrophilic character similar to crown ethers, but with decreased electron-donating character compared with ethereal analogues (05AHC65). The calix[6]furan **1**, which contains methyl groups in the *meso*-positions, was synthesized following a two-step procedure involving the formation of a three-furan linear oligomer by an acid-catalyzed condensation of furan and acetone. Once the linear trimer was isolated, cyclization was achieved by reaction with acetone in the presence of hydrochloric acid affording (9%) the heterocycle **1** along with linear oligomers (Scheme 1). Kobuke et al. (76JA7414) modified the procedure for **1** by bubbling hydrogen chloride gas into a solution of acetone and linear hexamer to afford **1** in 52% yield. Other modified procedures include the addition of concentrated HCl, acetone, and linear hexamer in ethanol containing Li^+ or Cs^+ ions or no metal, which afforded **1** in ~50% yields (85JCS(P1)973), or slow addition of linear trimer and acetone to a diluted EtOH/HCl mixture with 25% yield (96TL4593). Musau et al. reported (93CC1029, 94JCS(P1)2881) the synthesis of the calix[6]furan with unsubstituted methylene bridges, by cyclization of the corresponding linear hexamer using dimethoxymethane, in the presence of $BF_3 \cdot Et_2O$, as the catalyst; however, the desired hexamer was isolated in ~1% yield. Kobuke et al.



Scheme 1

(76JA7414) also reported the tetrahydrofuran analogue (Scheme 1) by the hydrogenation of the furan units of **1** using ruthenium/carbon under high pressure conditions to generate an isomeric mixture of the hexamer **2**, which was shown to extract cesium, ammonium, and silver ions from an aqueous to an organic phase. Finally, a larger hexameric macrocycle containing six furan rings joined via acetylene bridges was also reported (69AJC1951).

Three examples of hexameric macrocycles containing thiophene rings have been reported. Meijere et al. described (95AGE781) the novel macrocycle **4**, composed of six thiophene rings linked *via* spirocyclopropane bridges. Reaction of polyalkyne **3** with Na₂S under basic conditions afforded within an hour **4**, which was isolated by recrystallization in chloroform in 59% yield (Scheme 2). The crystal structure (Figure 1) showed a chair-like conformation, in which three sulfur atoms are above and three below the plane of the macrocycle.



Scheme 2

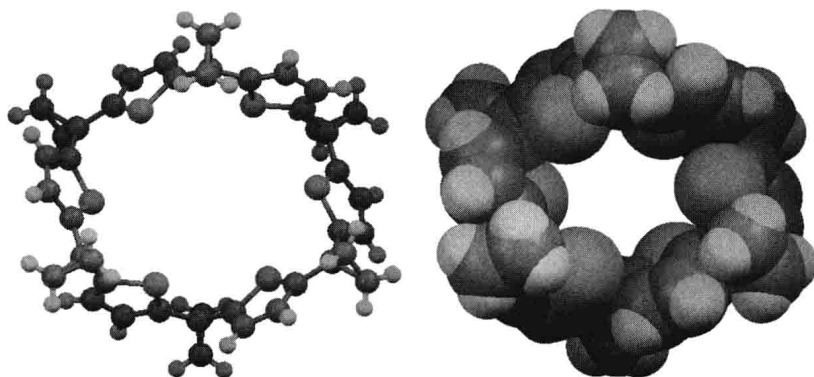
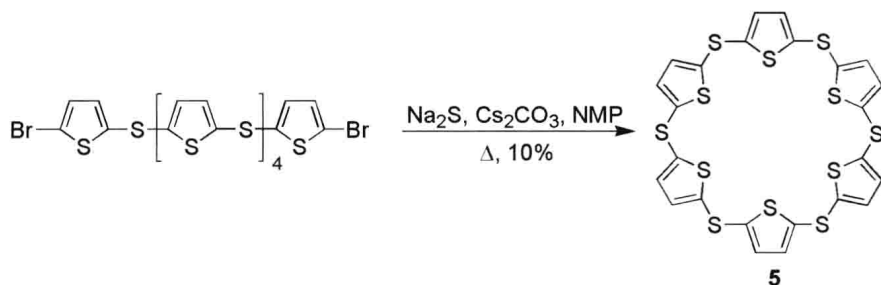


Figure 1 X-ray crystal structure of **4** (95AGE781) (Reproduced by permission from Wiley-VCH).

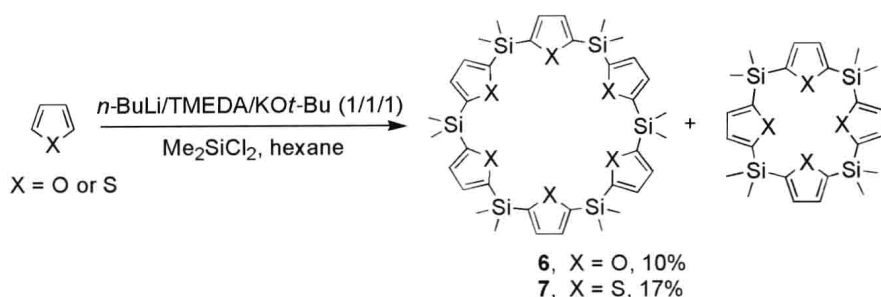
Ishii et al. (97CL897, 98BCJ2695) synthesized a sulfur-bridged thiophene macrocycle **5**. Several different conditions were examined for the preparation of **5** from different oligomers; the best results were obtained (~10%) by heating dibromo oligo(thio-2,5-thienylene) containing six thiophene rings with Na_2S in NMP in the presence of Cs_2CO_3 (Scheme 3). Conditions such as CuI -catalyzed or non-catalyzed reactions also gave the desired product, albeit in slightly lower yields. Sulfur-bridged calixarene-like molecules could function as hosts to soft and heavy metal ion guests.

Another example of a cyclohexathiophene was reported by Kauffmann et al. (75AGE713), composed of six thiophene subunits bound together through the 2,2'- and 3,3'-positions. It was isolated as a by-product in 4% yield, not completely purified, from the reaction designed to obtain cyclotetrathiophene.

Jones et al. (95AGE661) reported the synthesis of silicon-bridged heterocycles containing furan or thiophene subunits. Furan and thiophene were deprotonated at the 2- and 5-positions in hexane, to generate



Scheme 3



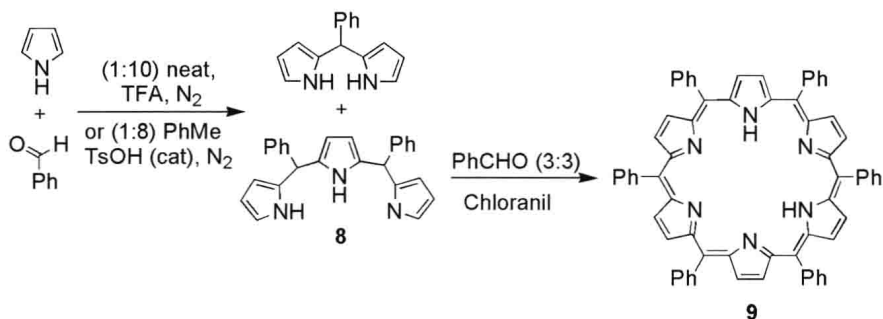
Scheme 4

the organolithium intermediates, followed by slow addition of Me_2SiCl_2 to afford the cyclic hexamer **6** or **7** (Scheme 4), respectively, along with their corresponding cyclic tetramers. Macrocycles comprising other ring sizes were detected in trace amounts by mass spectrometry.

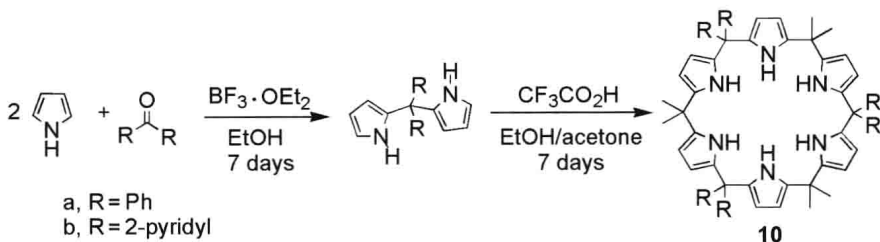
2.2 Pyrrole

Examples of hexameric macrocycles containing pyrrole rings reported in the literature (01CCR57, 08ACR265) include hexaphyrins or expanded porphyrins, calix[6]pyrroles, and cyclo[6]pyrroles.

Hexaphyrins are conjugated macrocycles composed of six pyrrole rings linked via sp^2 hybridized carbon atoms. The first example, *meso*-hexaphenylhexaphyrin (**9**), was prepared by Bruckner et al. (97CC1689) employing 5,10-diphenyltripyrane (**8**) (Scheme 5), which was isolated as a by-product from a reaction designed to generate 5-phenyldipyrromethane, by the condensation of pyrrole and benzaldehyde in the presence of an acid (94T11427, 94TL2455, 94TL6823). A 3+3-type condensation of trimer **8** with benzaldehyde, gave after oxidation and chromatography, the cyclic hexamer **5**. A similar example,



Scheme 5

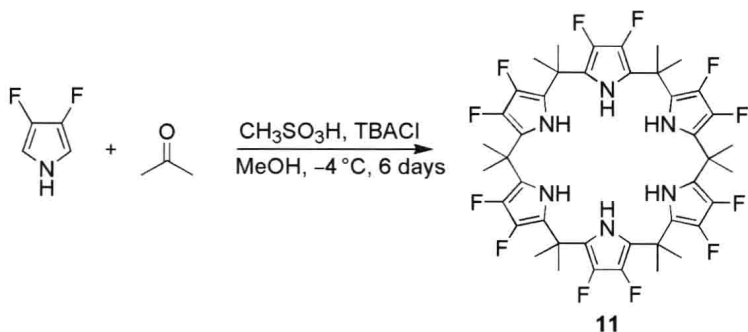
**Scheme 6**

meso-hexa(pentafluorophenyl)hexaphyrins, was reported by Cavaleiro et al. (99CC385) using a modification of the Rothmund synthesis (39JA2912).

Calix[6]pyrroles are nonconjugated macrocycles composed of six pyrrole rings linked via sp^3 hybridized carbon atoms. A simple and efficient route to calix[6]pyrrole (98AGE2475) involved an acid-catalyzed condensation of dipyrrolemethane with simple ketones that afforded polypyrrole **10** (Scheme 6). X-ray structure determination of **10** revealed that pyrrole units adopted a 1,3,5-alternate conformation in contrast to the more prevalent cone conformation found in calix[6]arenes.

Another example in this family was reported by Sessler et al. (05JOC5982), whereby the dodecafluorocalix[6]pyrrole **11** was constructed (20%) by the condensation of 3,4-difluoro-1H-pyrrole with acetone in the presence of methanesulfonic acid and tetrabutylammonium chloride (Scheme 7).

Calix[6]pyrroles have also been synthesized (00AGE1496) by the conversion of a calix[6]furan to form the dodecaketone **12** via a ring-opening process, as described by Williams and Le Goff (81JOC4143). Subsequent reduction of the olefinic bonds and reaction with ammonium acetate gave **13** in 42% yield (Scheme 8).

**Scheme 7**