Aromaticity as a Cornerstone of Heterocyclic Chemistry

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Contents

1. Introduction 2777
1.1. The Importance of Heterocyclic Chemistry 2777
1.1.1. In Biochemistry and Life Processes 2777
1.1.2. In Society 2779
1.1.3. As a Fundamental Science 2780
1.2. Structure as the Basis for Behavior 2780
1.2.1. Physical Properties 2782
1.2.2. Chemical Reactivity 2782
1.2.3. Aromaticity and Tautomerism 2782
1.2.4. Biological and Technological Properties 2784
1.3. Aromaticity as a Guide to Behavior 2785
1.3.1. Above All in Determining Stability 2785
1.3.2. In the Rationalization of Chemical Reactivity 2785
1.3.3. In Determining Physical Properties 2785
2. Aromaticity as an Enduring and Developing Concept 2785
2.1. Brief Historical Overview 2785
2.2. Controversial Issues in Aromaticity 2786
2.3. Qualitative and Quantitative Aspects of Aromaticity 2787
2.3.1. Aromatic versus Non-aromatic in Heterocycles and Carbocycles 2787
2.3.2. Characteristic Criteria for Aromaticity 2787
2.3.3. Quantitative Measures of Heteroaromaticity 2787
3. The Extent and Classification of Heteroaromatic Compounds 2788
3.1. The Available Building Blocks 2788
3.1.1. Neutral and Charged Heteroatoms 2788
3.1.2. Exocyclic Double Bonds: C═W Groups, Betaine, and Zwitterionic Structures 2790
3.2. Known and Potential Monocyclic Three-Membered Heterocyclic Rings 2792
3.3. Known and Potential Monocyclic Four-Membered Heterocyclic Rings 2793
3.4. Known and Potential Heteroaromatic Five-Membered Rings 2793
3.5. Known and Potential Monocyclic Six-Membered Rings 2799
3.6. Known and Potential Monocyclic Seven-Membered-Ring Heteroaromatics 2804
3.7. Known and Potential Monocyclic Eight-Membered-Ring Heteroaromatics 2804
3.8. Known and Potential Monocyclic Nine-Membered and Larger Rings 2805
3.9. Bicyclic and Polycyclic Hetarenes 2805
3.10. Heterobicyclic Systems with Zero-Atom Bridges 2807
3.11. Cyclazines and Related Annulenes 2807
4. General Conclusion 2808
5. References 2808

1. Introduction

This review is based on the following premises: (i) that heterocyclic chemistry is a key to the understanding of life processes and to our efforts to improve the quality of life for humankind;[1] (ii) that chemical structure is the basis of understanding physical, chemical, biological, and technical properties;[2] and (iii) that the aromaticity concept is a cornerstone to rationalize and understand the structure and thus the behavior of heterocyclic compounds.[3,4]

Among approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic, and approximately half are heteroaromatic. Scheme 1 depicts some important monocyclic heteroaromatic compounds with one or more heteroatoms and five- and six-membered rings.

1.1. The Importance of Heterocyclic Chemistry

1.1.1. In Biochemistry and Life Processes

Heterocycles play a major part in biochemical processes.[1] The side groups of the most typical and essential constituents of living cells, DNA and RNA, are based on pyrimidine [cytosine (**1**), uracil (**2**), and thymine (**3**)] and purine [adenine (**4**) and guanine (**5**)] bases (Scheme 2), which are all aromatic heterocycles. Hydrolyses of DNA and RNA produce five

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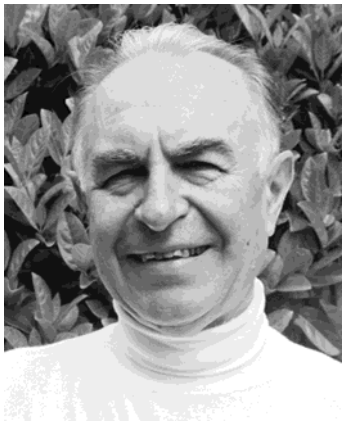
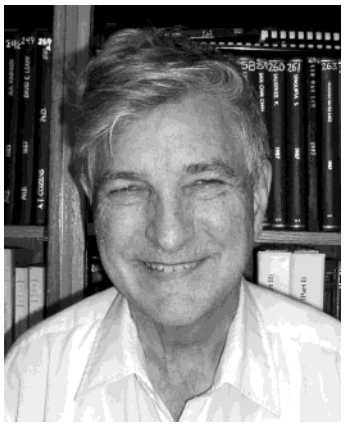


Alexandru T. Balaban, born in Timişoara, Romania, in 1931, is a professor at Texas A&M University at Galveston. Between 1956 and 1999, he taught organic chemistry at the Bucharest Polytechnic University, except for the period 1966–1969, when he was a Senior Research Officer at the Chemistry Section of the International Atomic Energy Agency in Vienna. He has held additional positions as Head of the Laboratory of Isotopically Labeled Compounds at the Bucharest Institute of Atomic Physics (1966–1974) and Vice-President of the Romanian Academy (1995–1998). His chemical research fields include new syntheses of aromatic heterocycles (pyrylium salts, oxazoles, indolizines) and stable nitrogen free radicals (including *N*-nitroso-nitroxides that can act as nitric oxide donors); catalytic automerization of phenanthrene and other polycyclic aromatic hydrocarbons; electronic and steric components of secondary isotope effects; and chemical applications of graph theory (reaction graphs, enumeration of valence isomers of annulenes and their derivatives, topological indices including the "Balaban index" *J* used in drug design, QSAR and QSPR studies, and theoretical invariants for fullerenes). Purely graph-theoretical results derived from reaction graphs are the unique trivalent cage with girth 11, and the first of the three possible trivalent cages with girth 10. His friendship with Alan Katritzky started more than 40 years ago, when the two collaborated on several papers and developed in parallel several ideas: one is discussed in the present paper; others are the merostabilization of free radicals (push–pull, or capto-dative effect) and the cleavage of polyarylpyridinium cations by nucleophiles. Daniela Oniciu and her husband are among his graduate students that have at present research or academic positions in the United States. He has authored or edited 17 books, over 50 chapters in books edited by others, and over 600 papers published in peer-reviewed journals. He is a member of the Romanian Academy and of the American-Romanian Academy, and an Honorary Member of the Hungarian Academy of Sciences. Among his awards is the 1994 Skolnik Award of the Division of Chemical Information of the American Chemical Society.

Daniela Carmen Oniciu received her M.S. in organic chemistry and chemical engineering from the University "Polytechnica" of Bucharest, Romania. After completing three years of industrial training, compulsory in the communist times, she worked as a senior scientist in medicinal chemistry (radioimmunochemistry) at the Institute of Endocrinology in Bucharest. Later on, as a Scientist at the Department of Organic Chemistry of the University "Polytechnica" of Bucharest, she received her Ph.D. in 1992, with a thesis focused on nitrogen-centered free radicals. Her postdoctoral experience was gained with Alan Katritzky at the University of Florida and Hiizu Iwamura at the University of Tokyo. In 1998, she joined the Alchem Laboratories, Inc. in Alachua, Florida, as Director of Chemistry, working in pharmaceutical research and development. Since February 2001, she is Director of Chemical R&D at Esperion Therapeutics, Inc. in Ann Arbor, Michigan. Her research interests encompass a broad area, among them heterocyclic chemistry, the chemistry of free radicals, and medicinal chemistry, with emphasis on pharmaceuticals to treat cardiovascular disease.

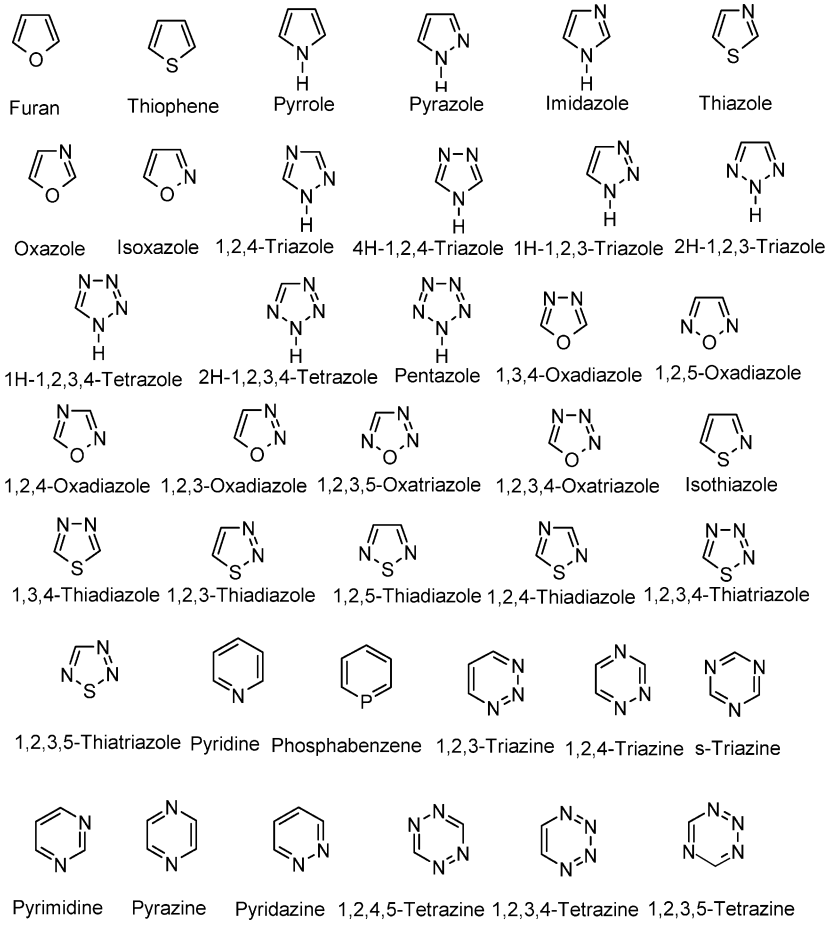


Alan Katritzky is Kenan Professor of Chemistry and Director of the Center for Heterocyclic Compounds at the University of Florida. He first met Sandy Balaban in August 1960 in Bucharest on his way back by car from a trip to Istanbul and ever since has admired Sandy as a scientist and valued him as a great friend. Thus, Katritzky considers it a particular pleasure to collaborate with him in this article. Equally, Daniela Oniciu has worked with both of them to great effect before starting her own highly successful professional career. Alan Katritzky has researched, taught, consulted, and published in heterocyclic chemistry for many years. In 2003, he became a foreign member of the Indian National Science Academy and of the Russian Academy of Science as well as receiving a Lifetime Achievement Award from the Indian Chemical Society and a Crystal Globe Award from the Scientific Partnership Foundation for outstanding contributions to science. He also received an honorary doctorate from the University of Timişoara in Romania.

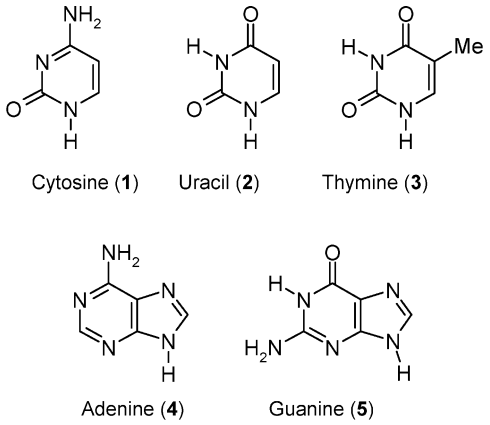
nucleosides, **6**−**10**, each being composed of an aromatic heterocyclic base, a phosphate, and a ribose moiety (Scheme 3); the latter two form the backbones of the polymer, and in the DNA's double helix the C-G and A-T base pairs form the rungs of the ladder. The aromaticity, hydrogen-bonding properties, and catalytic activity of the pyrimidine and purine bases of RNA may explain why they were formed in prebiotic conditions and gave rise to the "RNA world", which evolved later into life on Earth.[5a−e]

The essential amino acids tryptophan (**11**) and histidine (**12**) are aromatic heterocycles (Scheme 4). They participate along with other amino acids in protein constitution through amide linkages. Histamine, formed by decarboxylation of histidine, is a powerful vasodilator, is released in allergic responses, and stimulates acid secretion in the stomach, causing heartburn. Histidine receptor antagonists are among the top pharmaceuticals. Serotonin, formed from tryptophan, is an important neurotransmitter. L-Tyrosine is oxidized biologically to L-dihydroxyphenylalanine (L-DOPA); this affords dopamine by decarboxylation, and its production may be involved in schizophrenia (dopamine excess) or Parkinson's disease (dopamine deficit, treatable by administering L-DOPA). A practically infinite number of proteins can be synthesized from the 20 naturally occurring amino acids with the aid of DNA via translation into

Scheme 1. Monocyclic Aromatic Compounds



Scheme 2. Pyrimidine and Purine Bases



RNA messenger and transcription according to the universal genetic code.

Most coenzymes have aromatic heterocycles as major constituents. While enzymes possess purely protein structures, coenzymes incorporate non-amino acid moieties, most of them aromatic nitrogen heterocycles. Coenzymes are essential for the redox biochemical transformations, e.g., nicotinamide adenine dinucleotide (NAD, **13**) and flavin adenine dinucleotide (FAD, **14**) (Scheme 5). Both are hydrogen transporters through their tautomeric forms that allow hydrogen uptake at the termini of the quinonoid chain. Thiamine pyrophosphate (**15**) is a coenzyme that assists the decarboxylation of pyruvic acid, a very important biologic reaction (Scheme 6).

Some important vitamins, **16**−**20**, are constructed on an aromatic heterocyclic scaffold (Scheme 7).

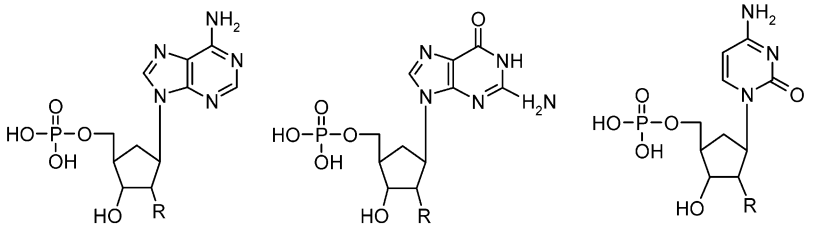
Porphyrins **21** are the backbone of major players in life cycles—cytochromes (Scheme 8). There are three types of cytochromes, classified by their color, or more precisely by their long-wavelength absorption band, as *a* (600 mn), *b* (563 nm), and *c* (550 nm). They are protein conjugates of a porphyrin complex with iron(II), which is a coenzyme called heme (**22**). In plants, porphyrins form a complex with magnesium-(II): chlorophylls *a* and *b* (**23**), vital in photosynthesis. Porphyrin derivatives are used in photodynamic therapy for dermatological diseases such as psoriasis, and for skin or subcutaneous cancer.[5c−e]

Numerous plant and animal hormones have aromatic heterocycles as a major component.

1.1.2. In Society

Observations of life in nature by primitive communities led humans to the discovery of many healing materials. Very many pharmaceutical products are mimics of natural products with biological activity, which include many heterocycles. In the fight against disease, some of the most significant advances have been and are being made by designing and testing new structures, many of which are heteroaromatic derivatives. The same is true for many pesticides. Antibiotics such as penicillins and cephalosporins, alkaloids such as vinblastine, ellipticine, morphine, and reserpine, and cardiac glycosides such as the class of digitalis are heterocyclic

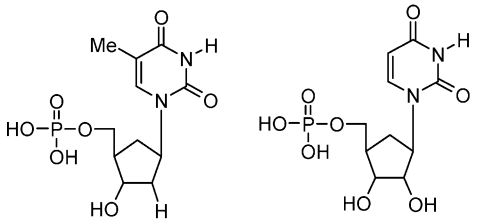
Scheme 3. Nucleosides



6 a: Adenylic acid (R = OH)
b: Deoxyadenylic acid (R = H)

7 a: Guanylic acid (R = OH)
b: Deoxyguanylic acid (R = H)

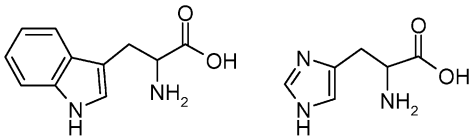
8 a: Cytidylic acid (R = OH)
b: Deoxycytidylic acid (R = H)



9: Deoxythymidylic acid

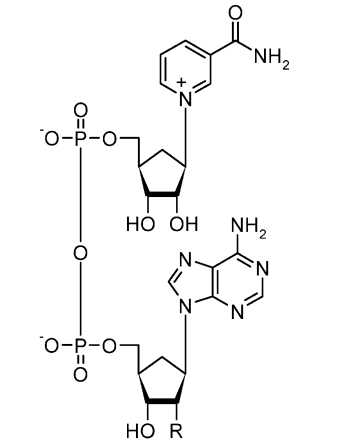
10: Uridylic acid

Scheme 4. Heteroaromatic Natural Amino Acids

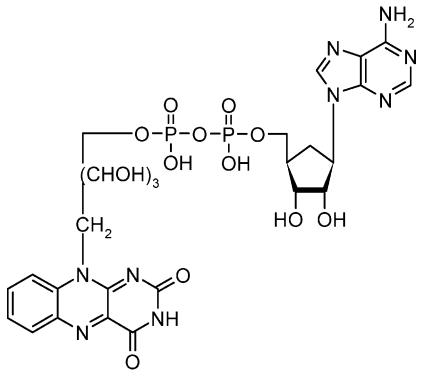


Tryptophan (**11**) Histidine (**12**)

Scheme 5. Coenzymes: Examples



13: Nicotinamide adenine dinucleotide (R = OH); Nicotinamide adenine dinucleotide phosphate(R = OPO_3H_2)



14: Flavin adenine dinucleotide (FAD)

natural products of significance for human and animal health. Inspired by them, pharmaceutical researchers have constantly designed and produced better pharmaceuticals for a better living. In the same light, pesticides, insecticides, rodenticides, and weed killers followed natural models, and a significant part of such biologically active compounds are heterocycles.

Modern life and civilization opened the way to other important practical applications of heterocycles, for example dyestuffs, copolymers, solvents, photographic sensitizers and developers, and in the rubber industry antioxidants and vulcanization accelerators. Some of the sturdiest polymers, such as Kevlar, have aromatic rings. Melamines (2,4,6-triamino-substituted *s*-triazines) are monomers with numerous applications as both homopolymers and copolymers. Scheme 9 shows a few examples of compounds with various applications in our daily life, having in common the same building block, the aromatic *s*-triazine.

A book on the importance of heterocycles in biochemistry and everyday life has been published.[1]

1.1.3. As a Fundamental Science

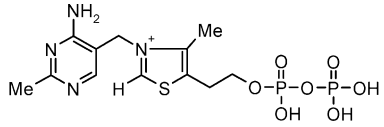
Apart from all the above reasons underlying the importance of heterocyclic chemistry as an applied science, it has much fascination as a subject for study in its own right.[5f]

Heterocyclic chemistry is an inexhaustible resource of novel compounds. Almost unlimited combinations of carbon, hydrogen, and heteroatoms can be designed, making available compounds with the most diverse physical, chemical, and biological properties. Heterocycles provide the main source of new aromatic compounds.

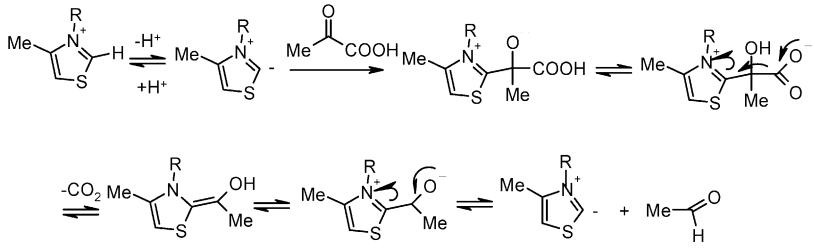
1.2. Structure as the Basis for Behavior

All properties, including physical, chemical, and biological, are encoded in the molecular and struc-

Scheme 6. Coenzymes: Thiamine Pyrophosphate and Its Role in the Decarboxylation of Pyruvic Acid

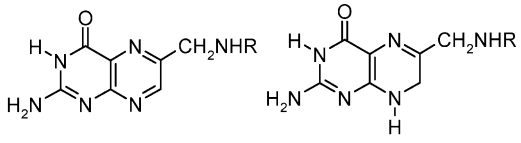


Thiamine pyrophosphate (**15**)

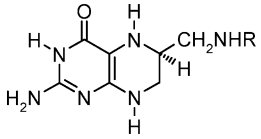


Assisted decarboxylation of pyruvic acid by thiamine pyrophosphate
(only the thiazole portion of the coenzyme is shown)

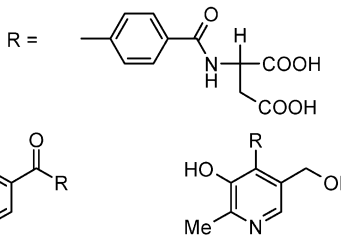
Scheme 7. A Few Vitamins



Folic acid (**16**) Didydrofolic acid (**17**)



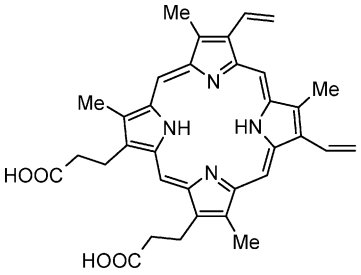
Tetrahydrofolic acid (**18**)



Vitamin B_5 (**19**)
Nicotinic acid (R = OH)
Nicotinamide ($R = NH_2$)

Vitamin B_6 (**20**)
Pyridoxine ($R = CH_2OH$)
Pyridoxal (R = CHO)
Pyridoxamine ($R = CH_2NH_2$)

Scheme 8. Porphyrins and Cytochromes



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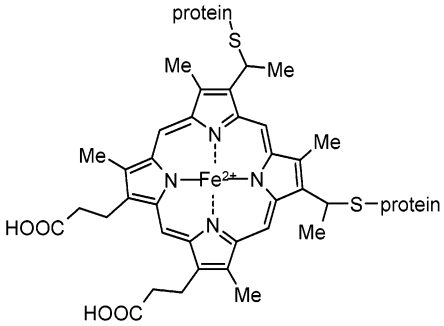

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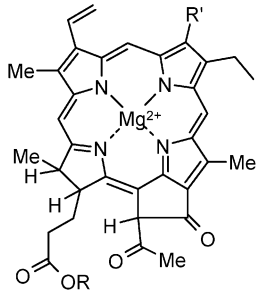
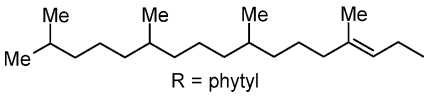


23

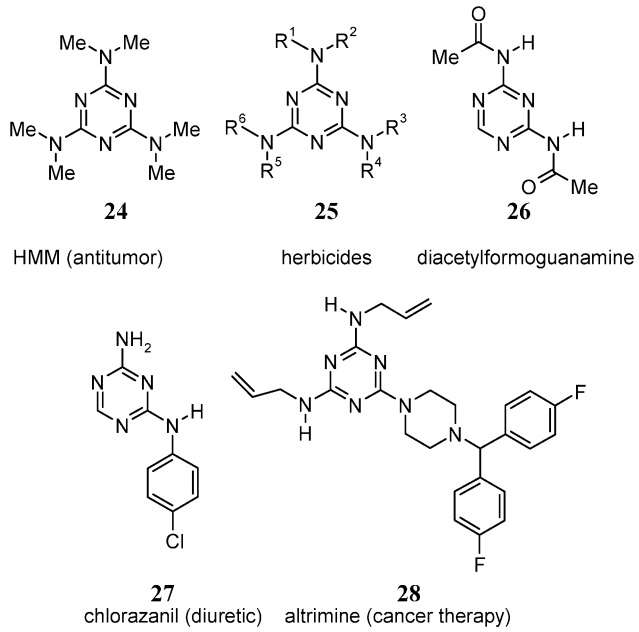
(a) R' = Me, R = phytyl
(b) R' = CHO, R = phytyl



R = phytyl

tural formulas of molecules. Critical structural features of molecules can be correlated by applying quantitative structure−property relationship (QSPR) techniques.[2] Chemists and physicists have adopted different ways to approach the quantitative evaluation of aromaticity. Chemists discuss the reactivity and quantify the heats of formation of a compound in order to draw comparisons with actual or hypothetical non-cyclically conjugated compounds. Physicists measure geometries or magnetic parameters of aromatic compounds and compare the results with the non-aromatic congeners. Lately, computational chemists have used sophisticated molecular calculations to extend and even replace experimental measurements. Quantitative structure−activity relationships are extensively used by medicinal chemists[5g,h] since the seminal work of Hansch and Leo.[5i]

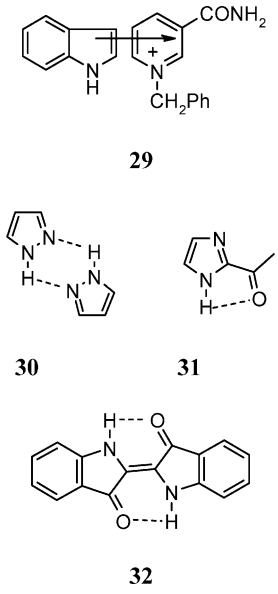
Scheme 9. *s*-Triazines and Their Applications



1.2.1. Physical Properties

Interactions between isolated (**29**, **30**) molecules determine colligative properties such as melting point, boiling point, vapor pressure, viscosity, etc. Nonbonding interactions include hydrogen-bonding, π-to-π interactions, and van der Waals forces (Scheme 10). The same types of interactions between different molecules determine solubility, micellar behavior, etc.[2] Intramolecular hydrogen-bonding is illustrated by 2-acetylimidazole (**31**) and indigo (**32**).

Scheme 10. Nonbonding Interactions in Heterocycles



Interactions with electromagnetic radiation determine the UV, IR, and NMR spectra, refractive index, etc. For such properties, conjugated systems, including aromatic systems, are particularly significant.

1.2.2. Chemical Reactivity

Stability, as measured by the tendency to undergo unimolecular reactions or to react with identical molecules, is determined by the electronic structure and orbital energies of a compound and relates to the HOMO−LUMO gap. Chemical reactivity, the reactivity toward other molecules, is determined by electronic interactions between two molecules and is quantitized by the difference in energy between the ground state and the transition complex formed by the two molecules.

Heterocycles with conjugated π-systems have a propensity to react by substitution, similarly to saturated hydrocarbons, rather than by addition, which is characteristic of most unsaturated hydrocarbons. This reflects the strong tendency to return to the initial electronic structure after a reaction. Electrophilic substitutions of heteroaromatic systems are the most common qualitative expression of their aromaticity. However, the presence of one or more electronegative heteroatoms disturbs the symmetry of aromatic rings: "pyridine-like" heteroatoms (=N—, $=N^+R-$, $=O^+-$, and $=S^+-$) decrease the availability of π-electrons and the tendency toward electrophilic substitution, allowing for addition and/or nucleophilic substitution in "π-deficient heteroatoms", as classified by Albert.[6a] By contrast, "pyrrole-like" heteroatoms (—NR—, —O—, and —S—) in the "π-excessive heteroatoms" induce the tendency toward electrophilic substitution (see Scheme 19). The quantitative expression of aromaticity in terms of chemical reactivity is difficult and is especially complicated by the interplay of thermodynamic and kinetic factors. Nevertheless, a number of chemical techniques have been applied which are discussed elsewhere.[6b]

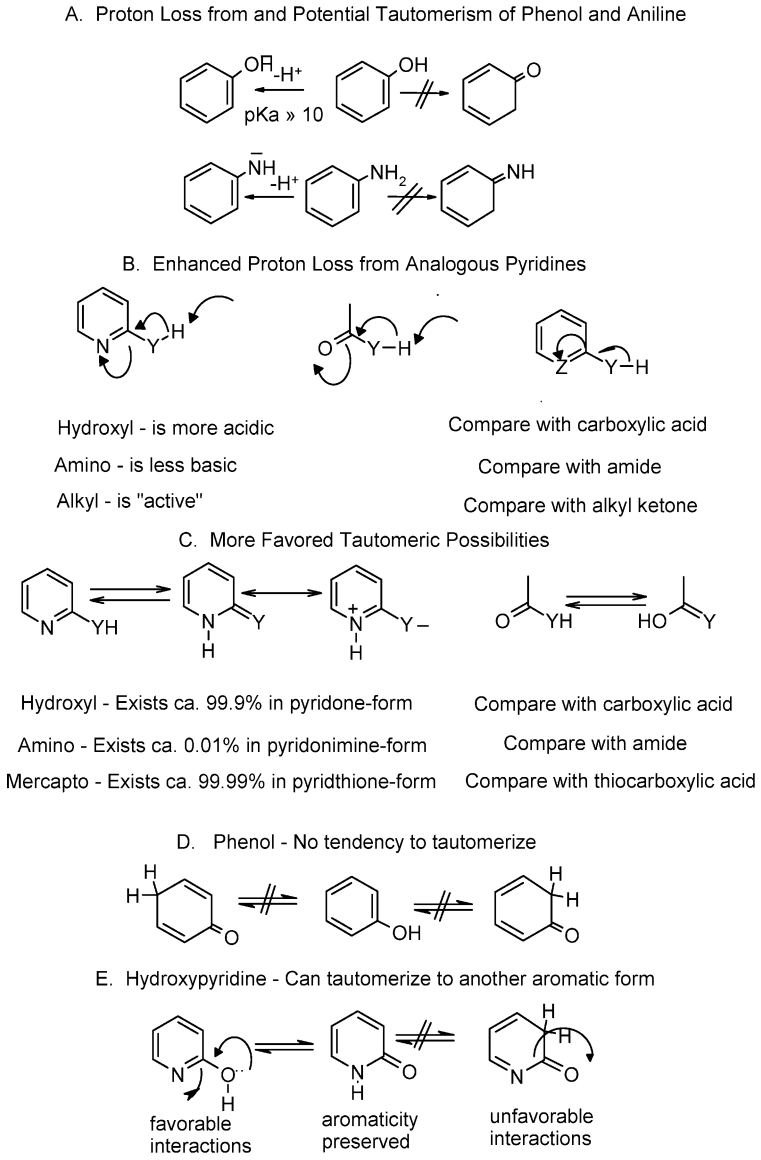
1.2.3. Aromaticity and Tautomerism

This topic has been extensively reviewed.[7] The degree of aromaticity of a ring has a profound influence on the properties of hydroxy substituents (and also of amino or mercapto substituents; see an earlier review[6b]). Phenol is weakly acidic, aniline much less so, and toluene almost not at all. Furthermore, there is no tendency for these benzenoid derivatives to tautomerize to their alternative tautomeric forms because of the loss of aromaticity that this would entail. The increased tendency toward proton loss from such substituents as OH, NH_2, and SH relative to their benzenoid congeners when situated α or γ to a pyridine-like nitrogen atom results in higher acidity and the possibility of tautomerism to an alternative form. These possibilities are outlined in Scheme 11, together with analogies to corresponding aliphatic compounds.

2-Hydroxypyridine could tautomerize in two fundamentally different ways: if the proton moves to the nitrogen, cyclic conjugation and hence aromaticity is preserved, whereas movement of the proton to a ring carbon is unfavorable; only the former process occurs and leads to the favored tautomeric form at equilibrium.

In 2-hydroxyfuran (Scheme 12), tautomerism always involves loss of aromatic stabilization, but the energy loss is far less here. Moreover, favorable interaction in the carbonyl tautomers offsets part of this loss, and the higher bond energy of the carbonyl group means that the carbonyl form is favored for

Scheme 11. Proton Loss and Tautomerism in Hydroxy, Amino, and Alkyl Pyridines

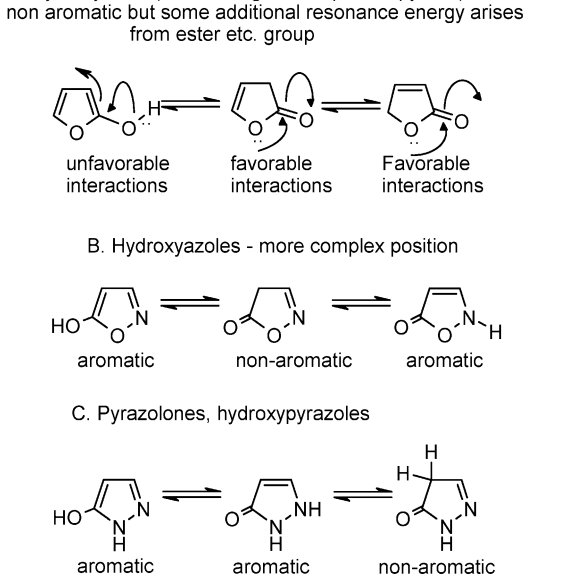


hydroxyfurans. The position in hydroxyazoles is more complex, and tautomerism to both aromatic and non-aromatic forms can occur, as shown in Scheme 12 for isoxazole and pyrazole derivatives. Exceptions to the expected pattern of tautomerism are found in compounds containing two directly linked nitrogen atoms. For instance, in substituted 1,2,4-triazines, tautomers containing an azo N=N group are disfavored, even when this means that an imino or methylene form becomes dominating (such as **33A** and **34A** in Scheme 13),[8] without completely canceling aromaticity.

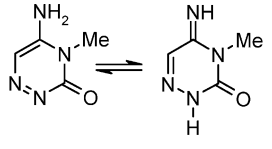
NMR study of the thione−thiol tautomerism of a 1,3,5-triazine derivative (Scheme 14) showed that the dithione structure **36** is the predominant tautomer in both solution and solid state, despite the apparently reduced aromaticity.[9]

In 2-(2′-hydroxyphenyl)benzimidazole (Scheme 15), the proton transfer between the keto **38B** and the enol **38A** forms in the ground state leads to a large difference in energy, which is explained by the stabilization brought in the enol form by the aromaticity of the six-membered ring.[10] Intramolecular

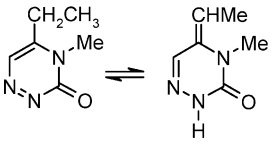
Scheme 12. Hydroxy Substituents: Reactivity Strongly Changed by Lower Aromaticity



Scheme 13. Unexpected Dominant Tautomeric Forms for Triazinones in Solution

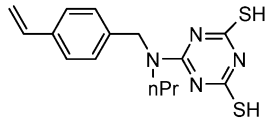


33A **33B**

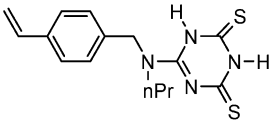


34A **34B**

Scheme 14. Thione−Thiol Tautomerization of a 1,3,5-Triazine Derivative in the Solid State



35



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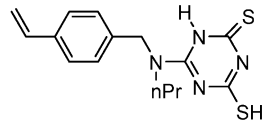
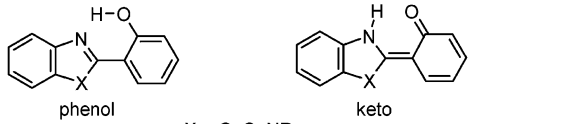
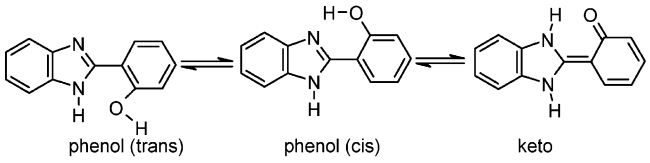


37

Scheme 15. Tautomerism and Hydrogen-Bonding



38A **38B**

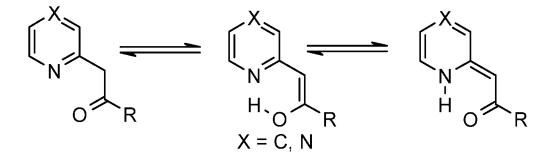


39A **39B** **39C**

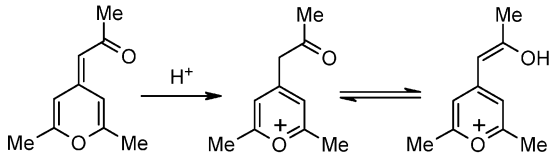
hydrogen-bonding favors this stabilization. Tautomerization via protonation/deprotonation or induced by Ar−Ar rotation makes possible the cis/trans phenol exchange, such as in **39A** and **39B**. Both the cation and the anion intermediates are stabilized by symmetrical delocalization.

Hydrogen-bonding can modify the aromatic character, and the role of solvents has been demonstrated by changes in the HOMA index caused by differences in the hydration of sodium and magnesium salts of

Scheme 16. Keto−Enol Tautomerism and Hydrogen-Bonding

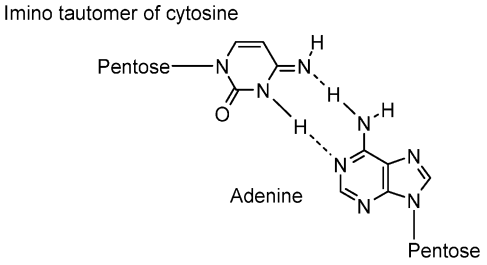


40A **40B** **40C**



41A **41B** **41C**

Scheme 17. Importance of Tautomerism in Mispairing of Nucleic Acid Bases



4-nitrosophenoxide anions.[11a−d] A comparison between the solvatochromy of aromatics, polyenes, and polymethines in various solvents led Dimroth and Reichardt to devise their pyridinium betaine that presents a huge solvatochormic effect according to the polarity of the solvent.[11e] Aromaticity in 6π-electron systems drives the tautomerism of six-membered-ring heterocycles (Scheme 16).[12] α-Heterocyclic ketones prevail as enamines **40B** in the case of pyrazines and as enaminones **40C** in the case of quinazolines and quinolines.

Protonation of vinylogous 4-pyrones **41A** yields a mixture of tautomers **41B** and **41C** in a ratio that is influenced by the solvent polarity.[13]

Tautomerism is responsible for genetic mistakes and for the whole concept of genetic evolution. As an example, cytosine in its imino form pairs with adenine and thus acts as a mimic of uracil. Cytosine normally pairs with adenine, but tautomerism leads to a mutation (Scheme 17).[1]

1.2.4. Biological and Technological Properties

Biological and technological properties are a combination of physical and chemical properties. The biological activity of a chemical relies mostly on its capability to bind reversibly to an active site, such as a receptor, and this is usually determined by physical interactions, especially hydrogen-bonding.[14] On the other hand, the biological activity of pesticides is determined by chemical reactions that block irreversibly vital centers of a parasite—insects, plants, fungi, or arachnids. Technological properties are a consequence of intermolecular interactions in matter that create bulk properties and make chemicals

useful in the daily life. In the same light, chemical interactions open routes to other materials.

1.3. Aromaticity as a Guide to Behavior

Many heteroaromatic compounds accord with the general characteristics of their carbocyclic analogues in being cyclic structures with significant resonance energies. Their electronic structures are in agreement with Hückel's $(4n + 2)$ π-electron rule, and the rings possess diamagnetic currents. They tend to react by substitution rather than addition. Bond orders and lengths tend to be intermediate between single and double.

Aromaticity relates fundamentally to chemical reactivity from both the thermodynamic and kinetic standpoints.[6b] From the experimental chemist's point of view, the energetic implications of aromaticity dominate. Whereas the geometric and magnetic effects of aromaticity are of undoubted theoretical interest, it is the energy differences between a molecule, its reaction products, and the transition state which leads to the reaction products that governs the stability and the reactivity of that molecule.[6b] From a practical standpoint, the concept of aromaticity is thus of critical importance, as follows.

1.3.1. Above All in Determining Stability

Aromatic molecules are highly conjugated but have stabilities greater than those shown by (i) noncyclic conjugated systems and (ii) cyclic but non-aromatic conjugated systems.

1.3.2. In the Rationalization of Chemical Reactivity

The concept of aromaticity is important in the rationalization of chemical reactivity and, by extension, in the understanding of biological properties and the prediction of technological behavior. In heteroaromatic chemistry, the degree of aromaticity is of particular importance in guiding our understanding of aromaticity.

1.3.3. In Determining Physical Properties

Energetic considerations again dominate in assessing the influence of aromaticity in determining physical properties. Although magnetic and geometrical attributes of aromaticity can play a role in the determination of physical properties, their interpretation is less straightforward.

2. Aromaticity as an Enduring and Developing Concept

2.1. Brief Historical Overview

A brief overview of the historical developments that led to the dichotomy between aliphatic and aromatic compounds delineates that the former are characterized by additivity for heats of formation and practically all other properties, whereas the situation for aromatic systems is less straightforward. Definitions, criteria, and properties of aromatic systems will be discussed. Notwithstanding controversies over aromaticity, this concept is still a cornerstone in organic chemistry and has been extended to inorganic compounds, e.g.: (i) for borazine, $B_3N_3H_6$, a simple analogue of benzene, a colorless liquid with normal boiling point 55 °C and lower stability than benzene (it decomposes slowly at room temperature and is hydrolyzed by hot water to ammonia and boric acid), first prepared by Stock;[15a] (ii) two- or three-dimensional aggregates of carbon[15b,c] or of boron,[15d] nitrogen,[15e] and carbon; and (iii) carbon nanotubes,[15f] a most promising new material.

In 1865−1866, in his *Treatise of Organic Chemistry*, A. Kekulé proposed the formula for benzene and introduced the term "aromatic" to denote the common structural character of hydrogen-poor aromatics in contrast to hydrogen-rich aliphatics.[16] One year later, E. Erlenmeyer defined aromaticity by reactivity and proposed the present-day formula for naphthalene.[17a] Shortly thereafter, W. Körner[17b] and J. Dewar[17c] proposed the pyridine formula. To overcome A. Ladenburg's objections to his formula,[17d] Kekulé advanced in 1872 his oscillating bond hypothesis. The almost perfect similarity between the physicochemical properties of benzene and thiophene (discovered by V. Meyer[17e,f] in 1883 as an impurity in benzene prepared from coal tar) brought attention to five-membered heterocyclic compounds whose centric formula was proposed by E. Bamberger in 1891−1893, in anticipation of E. C. Crocker[18a] and followed by Armit and R. Robinson's π-electron sextet (1925);[18b] the sextet theory was justified and generalized in 1931−1938 by Erich Hückel on a quantum-chemical basis.[18c]

Continuous cyclic conjugation was advocated as a necessary and sufficient condition by J. Thiele, but this was disproved by R. Willstätter's experimental evidence that cyclooctatetraene was not aromatic, and that cyclobutadiene resisted attempts at preparation by normal chemical approaches.[19a,b] Hückel's approach justified the supplementary $(4n+2)$ π-electron restriction [or in mathematical modulo 4 terms 2(mod 4)] in an m-membered ring composed of sp^2-hybridized atoms with $m \geq 3$ and n as a non-negative integer.[18c,19c,d] A triumphant success for Hückel's explanation of the stability of the cyclopentadienyl anion was his prediction for stability of the tropylium cation and related systems, and the fulfillment of this prediction by the discoveries of tropolone (M. J. S. Dewar,[20] Nozoe,[21] and Pietra[22]), tropylium (W. E. Doering[23]), and cyclopropenylium (R. Breslow[24]). However, until M. J. S. Dewar proposed[25−27] open-chain conjugated reference compounds (rather than Hückel's isolated double-bond systems), exaggerated stabilization energies were calculated using Hückel's theory. Other methods for obtaining resonance energies in aromatics are based on graph-theoretical approaches: conjugated circuit counts (Randic[28]), topological resonance energies (Hess and Schaad,[29] Aihara,[30] Trinajstic et al.[31]), and valence bond methods (Herndon[32]). The best methods for obtaining accurate estimates of resonance energies are based on isodesmic reactions (hypothetical reactions in which the number of bonds of each type, e.g., C−H, C−C, C=C, etc., is conserved but the relationships

among the bonds are altered) and a subclass of these reactions, called homodesmotic reactions (conserving also the numbers of carbon atoms in corresponding hybridization states and the number of hydrogen atoms joined to individual carbon atoms).[5f,33]

The instability of [10]annulene is caused by steric factors, as demonstrated by E. Vogel when he synthesized bridged [10]- and [14]annulenes with naphthalenic and anthracenic peripheries, respectively,[34] and by V. Boekelheide with bis- or tris-bridged [14]-annulenes with a pyrenic periphery.[35]

Heterocyclic systems have played an important role in this historical development. In addition to pyridine and thiophene mentioned earlier, a third heterocyclic system with one heteroatom played a crucial part: protonation and methylation of 4*H*-pyrone were found by J. N. Collie and T. Tickle in 1899 to occur at the exocyclic oxygen atom and not at the oxygen heteroatom, giving a first hint for the π-electron sextet theory based on the these arguments.[36] Therefore, F. Arndt, who proposed in 1924 a mesomeric structure for 4*H*-pyrone, should also be considered among the pioneers who contributed to the theory of the aromatic sextet.[37] These ideas were later refined by Linus Pauling, whose valence bond theory (and the electronegativity, resonance and hybridization concepts) led to results similar to Hückel's molecular orbital theory.[38]

Along with the historical events that were mentioned above, one should recall three instances when aromatic systems were detected experimentally but failed to be recognized as such in the absence of theoretical support. The first one involves a carbocyclic aromatic system, while the other two deal with heteroaromatics.

(1) G. Merling had obtained tropylium bromide in 1891 by brominating cycloheptatriene but could not guess its structure; tropylium was discovered when prepared again via the same route by W. E. Doering and L. H. Knox in 1957, i.e., 66 years later.[23]

(2) Noelting and Michel, as well as A. R. Hantzsch, had observed around 1900 that benzenediazonium cations evolved dinitrogen on treatment with azide anions, but only R. Huisgen and I. Ugi's kinetic reinvestigation of this reaction at low temperature revealed in 1956−1957 the formation of 1-phenylpentazole, and allowed later the isolation of stable arylpentazoles when the phenyl group had electron-donating substituents.[39]

(3) On treating diisobutene with acetic anhydride and anhydrous zinc chloride, A. C. Byrns and T. F. Doumani had isolated in 1943 a crystalline compound to which they had ascribed the structure of a zinc complex with a 1,3-diketone;[40] the correct pyrylium chlorozincate structure was established by A. T. Balaban et al.[41] in 1961, after extended investigation on the formation of pyrylium salts by alkene diacylation.[42] This formation again had remained undetected for many decades during which alkenes had been acylated but only the water-insoluble monoacylation products had been investigated, whereas the water-soluble pyrylium salts went into the sink with the Lewis or Brønsted acid catalysts that had been used in the acylation.

2.2. Controversial Issues in Aromaticity

Aromaticity, defined as a structural feature, was used as a predictive tool for compounds that had not been prepared previously, whereas reactivity, bond length, or magnetic criteria had to await the isolation of a compound and its experimental investigation. Only recently has the development of quantum-chemical methods reached the point where one can predict with sufficient accuracy the magnetic properties, the bond lengths, and the reactivity patterns of aromatics. The multidimensional character and the definition and measurement of aromaticity generated confusion and conflicts.[43] A recent review discussed the multidimensional character of aromaticity and theoretical and experimental approaches to aromatic structures and their predictions, and references are indicated extensively.[6b]

As outlined in the historical overview, the concept of "aromatic character" confronted controversies from the start. More recently, it was even argued by Binsch and Heilbronner,[44] Labarre,[45a] and later again by Binsch[45b] that "aromaticity" was an obsolete concept which should be relegated to the physicochemical dustbin along with other nonexisting phenomena, such as the vital force, phlogiston, and the all-pervading ether. Like most other chemists, we believe, however, that the aromaticity concept (although fuzzy) is not only useful (like many other fundamental ideas of contemporary chemistry) but essential in any logical treatment of chemistry.

In agreement with Hückel's rule, cyclic delocalization of monocyclic systems with $4n+2$ π-electrons leads to all the attributes of aromatic stabilization, in contrast to systems with $4n$ electrons, which are anti-aromatic and destabilized. In carbocyclic chemistry, the typical aromatic compound is benzene with no ring strain, equal bond lengths, diatropic ring current, and a stabilizing delocalization energy of 21 kcal/mol;[5f,46] the typical anti-aromatic compound is cyclobutadiene, which is rectangular and is additionally destabilized by ring strain. A recent determination of its anti-aromatic destabilization energy (via photoacoustic calorimetry)[47] afforded a value of 55 kcal/mol; the ring strain energy adds a supplement of 32 kcal/mol. These values for $(CH)_6$ and $(CH)_4$ are based on homodesmotic reactions that preserve the numbers of C−C and C−H bonds and their local bonding environments. An equivalent statement is that, on a per-electron basis, the resonance stabilization energies are 3.5 kcal/mol for benzene and −14 kcal/mol for cyclobutadiene.[47]

The role of σ-electrons in the stabilization of aromatics has been repeatedly emphasized by Shaik and Hiberty[48] and has recently received experimental confirmation after a study of the effects of deuterium substitution of annulenes with internal hydrogens, such as the anti-aromatic [16]annulene and the aromatic [18]annulene.[49,50]

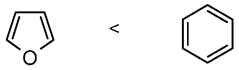
In a review, Gorelik[51] has shown that magnetic, structural, and energetic properties are determined by the electronic structure of cyclic conjugated systems, which are stabilized by a cyclic delocalization of electrons. Chemical reactivity cannot serve satisfactorily as a general criterion of aromaticity.

2.3. Qualitative and Quantitative Aspects of Aromaticity

2.3.1. Aromatic versus Non-aromatic in Heterocycles and Carbocycles

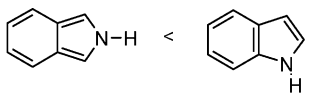
In carbocyclic chemistry, rather firm dividing lines usually exist between aromatic, non-aromatic, and anti-aromatic compounds, while in heterocyclic chemistry enormous variations in the extent of aromatic character are displayed.[52] Furthermore, there is an enormous number of potential heterocycles as compared to carbocycles, as will be detailed in section 3 of this review. The degree of aromaticity has classically been judged qualitatively in connection with the diene character of heterocycles manifested in Diels–Alder reactions or polymerizations. In this regard for instance, furan (**42**) is less aromatic than benzene (**43**), as is isoindole (**44**) compared to indole (**45**) (Scheme 18). Therefore, a quantitative aromaticity scale would be useful.

Scheme 18. Some Heterocycles Are More Aromatic Than Others



42 **43**

Furan less aromatic than benzene, and shows some diene character (Diels-Alder)



44 (isoindole) **45** (indole)

Pronounced diene character of isoindole

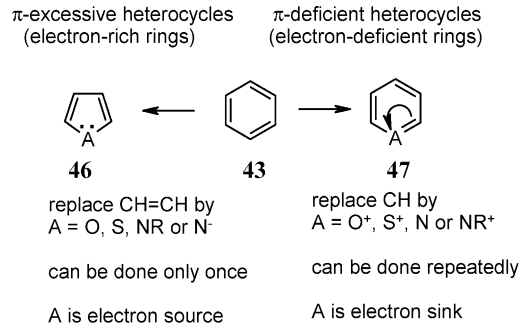
2.3.2. Characteristic Criteria for Aromaticity

Some qualitative and quantitative criteria are outlined below, and the topic has been recently reviewed in detail[6b] by two of the present authors. Examples are given extensively and original literature sources are indicated there.

- reactivity criteria: Predominance of substitution versus addition reactions; thermal stability; stabilizing ability for aryl- or heteroaryl-substituted free radicals, anions, or cations (such as carbenium, halonium, oxonium, diazonium cations);
- magnetic properties (exaltation and anisotropy of magnetic susceptibility, diatropic ring current, nucleus-independent chemical shifts (NICS) at a distance (angströms) from the molecular plane indicated in brackets (NICS(0) and NICS(1) values);[53]
- bond equalization (Jug), planarity (but see Cram's "bent and battered benzene rings" in cyclophanes, or fullerenes);
- resonance energy;
- prefixed aromaticity types (homo, bis/tris-homo, pseudo-, anti-, quasi-) and the criticisms thus engendered.

Qualitatively, heterocycles with five- and six-membered rings have been considered as modified benzenes, where a pair of carbon atoms (for five-membered systems) plus any number of carbon atoms is substituted with a heteroatom. Hence, most heterocycles could be classified as π-excessive (**46**) or π-deficient (**47**) (Scheme 19).[3,6] This approach is useful in assessing the aromatic properties of monocycles but lacks generalization.

Scheme 19. Heteroaromatic Compounds as Modified Benzenes



2.3.3. Quantitative Measures of Heteroaromaticity

Various methods to quantify the aromaticity of heterocycles and the interrelationship between different scales are controversial and have been covered in a recent article.[6b]

In heterocyclic chemistry, a quantitative evaluation of the aromatic character is a necessity as new heterocyclic systems are designed and synthesized and need to be evaluated in connection with property predictions. Three major approaches to the quantization of aromaticity exist:

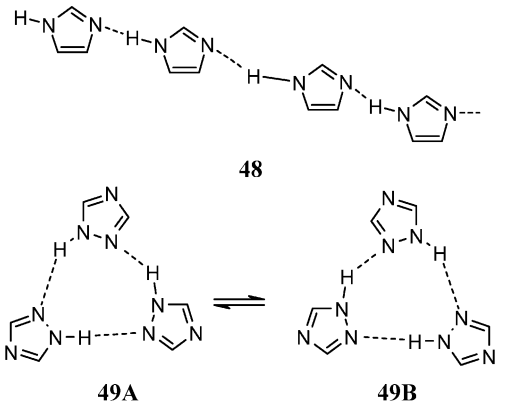
(a) The increased thermodynamic stability of aromatic compounds is the basis of the energy scale.

(b) The geometry of the ring was proposed as a criterion for the degree of aromaticity. Today, inter- and intramolecular bond length data are easily collected by routine X-ray measurements. On the basis of these measurements, the harmonic oscillator model of aromaticity (HOMA) concept has been successfully used as evidence of the aromatic character in many π-electron systems. This model relates the decrease of aromaticity to two geometric/energetic factors: one describing the bond length alternation (GEO) and the other describing the extension of the mean bond length (EN).

(c) Magnetic property measurements led to a quantitative approach to aromaticity. Diamagnetic susceptibility was the first magnetic property studied in connection with the concept of resonance energy. More recently, ^{1}H NMR spectroscopy has become a tool in the study of ring currents in cyclic π-conjugated systems.

Aromaticity varies with change of state because of the influence of the molecular environment on the interactions that determine aromaticity quantitatively, particularly in nonsymmetrical heterocycles. Comparative calculations of aromaticity indices for molecules in the gas phase and in condensed media with dielectric constants >1, with or without hydrogen-bonding, showed coherent results for a set of nitrogen heterocycles, including imidazole, pyrrole, pyrazole, 1*H*-1,2,4-triazole, and benzimidazole. The

Scheme 20. Hydrogen-Bonding in Imidazole and Triazole



48 **49A** **49B**

aromaticity indices based on AM1 and ab initio calculations increase from the gas phase to condensed phases (dioxane and aqueous solutions, or solid phase).[1,52b] For heterocycles with a high degree of hydrogen-bonding, such as imidazole in the solid phase, **48**, the aromaticity increase is not significant, presumably because of the increase in length of the 1,2-bond induced by hydrogen-bonding through N(1)—H(1)···N(2) (Scheme 20). Therefore, comparisons between levels of aromaticity of heterocycles need to be performed with data collected for the same molecular environment.

Solid-state proton transfer of triazole derivatives has been recently evidenced by NMR.[54] It has been shown that the type of aggregation in the solid state depends on the substitution in the triazole ring, similarly to imidazoles. Substituted triazoles can form cyclic trimers **49A**,**B** in the solid state by degenerate or quasi-degenerate triple proton transfer. Ab initio calculations, dipolar NMR, and crystallographic data provided results in agreement with the NH···N hydrogen bond geometries obtained from the proton-transfer barriers as calculated by dynamic solid-state ^{15}N NMR.[54]

3. The Extent and Classification of Heteroaromatic Compounds

The chemistry of aromatic heterocycles has been exhaustively reviewed in a book,[55] and discussions of aromatic heterocycles are compiled in a few monographs on heterocyclic systems.[1,3] Starting from 1979 to date, the literature related to heterocyclic chemistry, including heteroaromatics, is periodically reviewed by Belen'kii and co-workers in *Advances in Heterocyclic Chemistry*,[56−59] while earlier surveys were published by Katritzky and co-workers.[60,61] Two multivolume treatises of *Comprehensive Heterocyclic Chemistry*, published in 1984 and 1996, have thoroughly reviewed all heterocyclic systems, including heteroaromatics, and relevant chapters are cited throughout this review.

In the following sections, heterocycles are discussed in the same order as in an earlier monograph,[55] namely in the order of increasing number of ring atoms. Within a certain ring, heterocycles with one heteroatom are discussed first, in the increasing order according to the atomic number on the periodic table. Heterocycles with several heteroatoms are classified according to the atom with the lowest atomic number.

Table 1. Numbers $R(x,y,z)$ of Basic Monocyclic Aromatic Rings $X_xY_yZ_z$ Having a π-Electron Sextet,[62] with $4 \le (x + y + z) = m \le 8$

				number of basic monocyclic aromatic rings		
m	x	y	z	unrestricted	without adjacent Z-type atoms	without adjacent X- or Z-type atoms
4	2	2	0	2	2	1
	3	0	1	1	1	0
5	1	4	0	1	1	1
	2	2	1	4	4	2
	3	0	2	2	1	0
6	0	6	0	1	1	1
	1	4	1	3	3	3
	2	2	2	11	7	5
	3	0	3	3	1	1
7	0	6	1	1	1	1
	1	4	2	9	6	6
	2	2	3	18	4	3
	3	0	4	4	0	0
8	0	6	2	4	3	3
	1	4	3	19	6	6
	2	2	4	33	2	2
	3	0	5	5	0	0

3.1. The Available Building Blocks

3.1.1. Neutral and Charged Heteroatoms

Carbocyclic and heterocyclic aromatic systems contain sp^2-hybridized atoms that form a delocalized "π-electron aromatic closed shell" with electrons from their nonhybridized p-orbital. According to Pauli's principle, each such orbital can contain zero, one, or two electrons, and therefore one has three and only three possible types of atoms that can form aromatic rings: X-type (with two electrons), Y-type (with one electron), and Z-type (with an unoccupied p-orbital). A monocyclic planar aromatic system $X_xY_yZ_z$ will therefore have only a few allowed structures that can be predicted by using a graph theoretical approach. If the ring size is m-membered, and if there are $4n+2$ π-electrons in the delocalized molecular orbitals, the allowed integer solutions of the following two Diophantine equations (in terms of the three unknowns x, y, and z) can be used to predict all structures for any given $m \ge 3$ and $n \ge 0$ values:

$$x + y + z = m$$
$$2x + y = 4n + 2$$

Solutions for a π-electron sextet ($n = 1$) are presented in Table 1.[62] Analogous tables were obtained for a doublet of π-electrons ($n = 0$) and for a decet ($n = 2$) but are not displayed here.

Tables 1 and 2 in combination delineate the extremely large variety of monocyclic heterocycles obeying Hückel's rule. If one adds to Table 1 heavier atoms (even including metals, as will be exemplified for osmabenzene), the diversity is even richer. Most of this diversity remains to be explained: for example, very few of the possible combinations involv-

Table 2. Atom Types and Corresponding "Aromaticity" Constants k_H for R = H

		3	4		5		6
n	Type	a	b	a	b	a	b
2	Ẍ						
				-100	-77	-26	-3
1	Ẏ						
		-72	-50	0	+23	+74	+97
0	Ż						
		+28	+50	+100	+123		

ing boron atoms in the monocyclic heteroaromatics have been prepared and investigated so far.

The tripartite grouping of the first-row elements (Table 2) was arrived at almost simultaneously but independently in 1958 by both Balaban and Katritzky; the former author published his result in Romania,[62] but the latter author's results were never published. The only difference between the two authors' works had been the reversed assignment of X and Z labels! Numbers in Table 2 will be discussed under (a) below; they were not yet involved at that stage.

The above treatment of heteroatoms in terms of X-, Y-, and Z-type atoms was included in four books.[4b,55,63,64]

Restrictions that apply are as follows:

(a) Excessively high or low electronegativity of atom types (or "aromaticity constants") causes destabilization; one can arbitrarily assign a scale of relative electronegativity values, k[A], for atoms A in Table 2 by taking carbon atoms as standard with k_H[Y4b] = 0 (as in benzene), k_H[X4b] = −100 (as in the cyclopentadienide anion), and k_H[Z4b] = +100 (as in tropylium cation), assuming additivity of k[A] over the whole ring.[65] A consequence is a more precise evaluation of π-deficient (with positive sum of k[A] values) or π-excessive aromatics (with negative sum of k[A] values). The sum over all the atoms in an aromatic ring is usually within the range from −200 to +200; for various R groups in Table 2, the Hammett parameter σ_{p-R} can be used:

$$k_R[A] = k_H[A] + 20\sigma_{p-R}$$

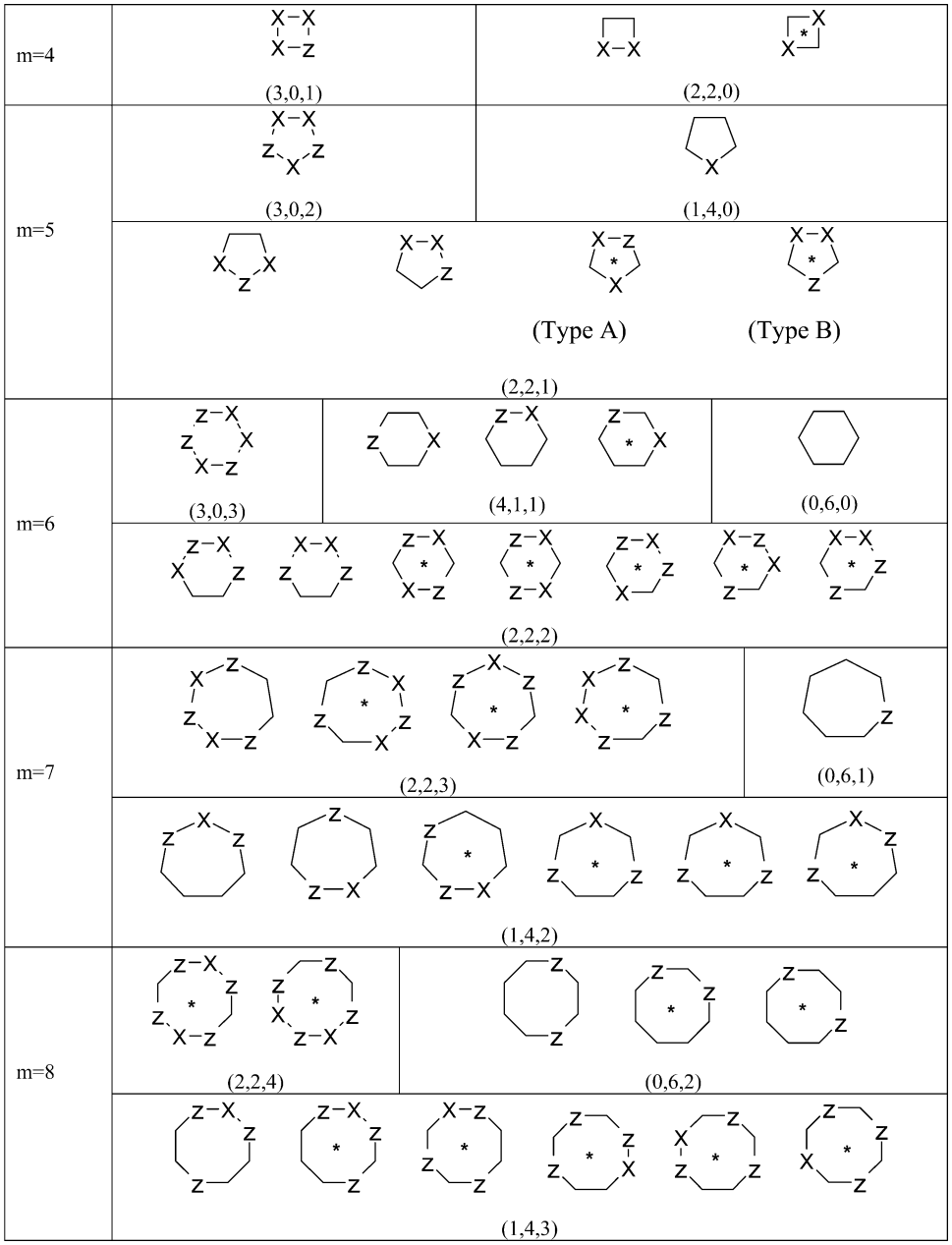
(b) With atoms heavier than those from the first row, Hückel's rule has exceptions, as exemplified by phosphonitrile chlorides, which are as stable for $(N{=}PCl_2)_3$ as for $(N{=}PCl_2)_4$. However, sulfur heteroatoms can replace oxygen heteroatoms, respecting in this case the Hückel rule. Owing to its lower electronegativity, sulfur does not decrease the electronic delocalization as much as oxygen. Indeed, thiophene and thiazole are more aromatic than furan and oxazole, respectively, as will be presented later. On the other hand, selenium and tellurium heteroatoms have a destabilizing effect, owing to the larger covalent radius (hence diminished p orbital overlap) and higher propensity toward oxidation.

(c) With adjacent atoms of the same type (either X- or Z-type), the free electron model predicts destabilizing effects. This allows a reduction of the number of possible structures, which otherwise would increase steeply by adding only Z-type atoms. The numbers of possible ring structures with or without this restriction are indicated in Table 1. As an example, all possible monocyclic systems with no adjacent Z-type atoms are shown in Table 3.[62]

(d) For three- or four-membered heterocycles, in addition to ring strain, a restriction results by considering the occupancy of the bonding levels by a π-electron sextet. According to the Frost−Musulin rule,[66] in [m]annulenes the energies of molecular orbitals in the Hückel molecular orbital theory correspond (in β-units) to distances above or below the center of the corresponding regular polygon with m vertices inscribed in a circle with a unit-size radius, such that one vertex is at the lowest energy level. Thus, a three-membered ring has one bonding and two antibonding orbitals; therefore, no aromaticity can be associated with a "cyclic ozone" because it would possess occupied antibonding orbitals. In the case of four-membered rings with two X-type heteroatoms, the two nonbonding levels of cyclobutadiene that would be fully occupied in an X_2Y_2 molecule would add a low contribution to the resonance energy because they would lie closely below the nonbonding level. Such an electronic-occupancy restriction does not apply, however, to three- or four-membered rings with a π-electron doublet.

(e) Initially it was believed that Hückel's rule could be extended to *cata*-condensed polycyclic systems, and indeed, naphthalene, phenanthrene, the acenes,

Table 3. Arrangements of Atom Types for Aromatic Monocycles with Six π-Electrons and No Adjacent Z-Type Atoms[a]



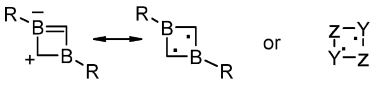
[a] Y-type atoms are not shown explicitly. Asterisks indicate mesoaromatic systems. Numbers in brackets are the (*x*,*y*,*z*) triplet values corresponding to solutions of diophantine equations (Table 1).

triphenylene, etc. are all such polycylic hydrocarbons obeying Hückel's rule. *Peri*-condensed polycyclics do not conform to Hückel's rule; however, when applied to *cata*-condensed systems, Hückel's rule works as a rough approximation, thereby extending considerably the combination richness of heterocycles. An important restriction is exemplified by benzo derivatives of the well-known five-membered heteroarenes: whereas indole is a highly aromatic system (though the electrophilic substitution favors β- instead of α-positions), isoindole is unstable due to its quinonoid structure, although N-substitution leads to isolable compounds. Some such *ortho*-quinonoid benzo derivatives are stable and easily formed, as in the case of anthranil, but they often behave as dienes in Diels−Alder reactions. A special mention must be made of polycyclic systems with heteroatoms in bridgehead positions, such as indolizine or the cyclazines, where special rules apply.

3.1.2. Exocyclic Double Bonds: C═W Groups, Betaine, and Zwitterionic Structures

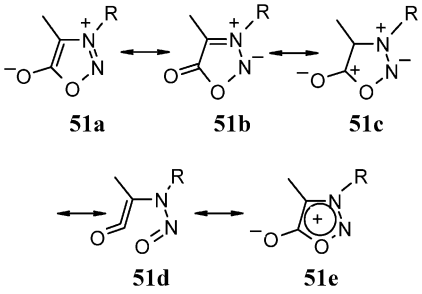
A further consequence of the foregoing discussion is a new definition generalizing the so-called *mesoionic (mesomeric betaine) systems* with two chains of odd-membered Y-type atoms separated by X- or Z-type atoms. Such systems are indicated by an asterisk in Table 1. Thus, 1,3-diborete **50** (Scheme 21) has a four-membered ring; sydnones **51** (Scheme 22), münchnones **52** (Scheme 23), and diazolones **53** (Scheme 24) are the best-known five-membered mesoionic compounds.

Scheme 21. 1,3-Diborete



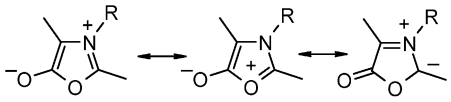
50a **50b** **50**

Scheme 22. Sydnones



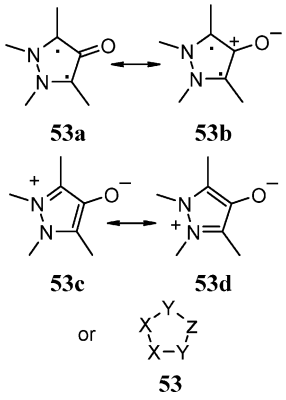
51a **51b** **51c** **51d** **51e**

Scheme 23. Münchnones



52a **52b** **52c**

Scheme 24. 1,2-Diazol-4-ones



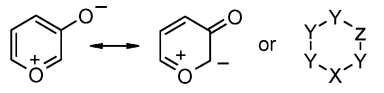
53a **53b** **53c** **53d** **53**

Baker,[67] Ollis,[68] Ramsden,[69] and other authors[70] defined mesoionic systems as five-membered rings that cannot be represented by normal covalent structures. Following Katritzky,[71] they are now universally named systematically as mesomeric betaines.

The designation mesoionic, first given by Baker et al. in 1949,[67] was refined by Ollis and Ramsden[68] as follows: "A compound may appropriately be called mesoionic if it is a five-membered heterocycle which cannot be satisfactorily represented by any one covalent or ionic structure and possesses a sextet of electrons in association with the five atoms comprising the ring." In 1955, Katritzky suggested that the representation with an encircled ± in the center of the ring should be discontinued and these compounds should be called mesomeric betaines. In 1978, Potts[72] suggested, "the term mesoionic should be restricted to five-membered heterocycles that cannot be satisfactorily represented by normal covalent structures but are better represented as a hybrid of all possible charged forms."

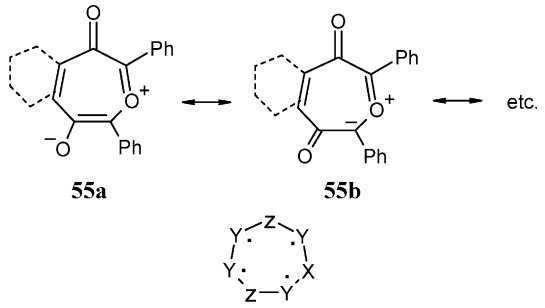
Pyrylium 3-oxides **54** (Scheme 25) should be considered as heteroaromatic six-membered mesomeric betaines. A diketo-oxepine **44** (Scheme 26) has two equivalent identically polarized limiting structures

Scheme 25. Pyrylium 3-Oxide



54a **54b** **54**

Scheme 26. 2,7-Diphenyl-benzo[*d*]oxepin-3,6-diones

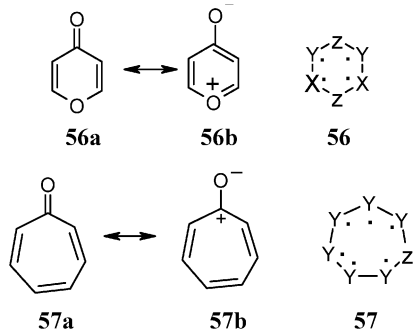


55a **55b** **55**

(e.g., benzoxepine **55a**−**c**); therefore, all such systems might better be called "mesoaromatic" instead of "mesoionic". Although Ollis and Ramsden[68a] had earlier restricted the term "mesoionic" to five-membered systems, we believe that the new definition in terms of chains with odd-numbered Y-type atoms is more general and accounts for a larger amount of data and structures.

As seen in the above structures, carbon atoms with exocyclic C═W bonds (where W symbolizes an electron-withdrawing group such as O, NR, or S) count as Z-type atoms. Indeed, 4*H*-pyrone **56** and tropone **57** (Scheme 27) may be considered to be normal

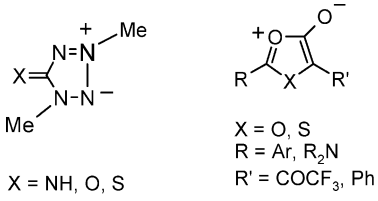
Scheme 27. 4*H*-Pyrone and Tropone



56a **56b** **56** **57a** **57b** **57**

aromatics X_2Y_2Z and Y_6Z, respectively. Although tropone has ^{1}H NMR coupling constants that indicate bond alternation characteristic for polyenes,[68b,c] the chemical behavior of such systems (protonation and alkylation at the exocyclic oxygen) indicates that the reactivity of such systems involves contributions from the zwitterionic limiting structure. Sydnones have a planar ring, as indicated by X-ray crystallography:[73] the *exo* C═O and the large *endo* C—O bond correspond to double and single bonds, respectively, and the *exo* C—C—O bond angle of 136° indicates a significant contribution of the ketene canonical form **51d** (Scheme 22). The mesoionic münchnones **52** (Scheme 23) are often considered aromatic because of their stability, although Boyd claimed in his review[74] that both X-ray data and calculations did not show any evidence of their aromaticity. Mesoionic tetrazole systems **58** (Scheme 28) could present an

Scheme 28. Tetrazoles, Dioxolium, and Oxathiolium Salts



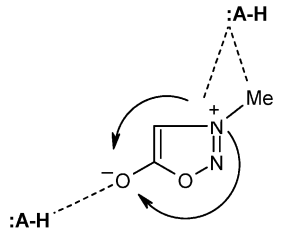
58 59

exocyclic conjugation to a nitrogen atom[75] or to oxygen and sulfur.[76,77]

Hückel's $4n+2$ π-electron rule is a necessary but not a sufficient condition for aromaticity. Coplanarity and electronegativity restrictions of constituent atoms represent the most important restrictions. Phosphole is a marginally aromatic five-membered heterocycle[76] (see further examples and discussion). Mesoionic compounds, mesomeric betaines, and 2*H*- and 4*H*-pyrone have all been considered to be weakly aromatic or non-aromatic, though their conjugated acids are aromatic. Spectroscopic data evidenced the aromaticity of dioxolium and oxathiolium cations **59** (Scheme 28) and mesoionic oxathioles not in the classical sense but by their ring currents and chemical stability.[77]

Solvent effects on the nitrogen NMR shieldings of 3-methylsydnone (**60**) are different from those observed for oxazoles and oxadiazoles, which suggests that conformity to Hückel's rule is insufficient to determine aromaticity in such systems.[78a] The exocyclic oxygen atom in sydnone **60** is the primary acceptor of hydrogen bonds from solvent molecules, and the electron flow is directed toward this oxygen. The interactions involved are due to the solvent polarity: hydrogen-bonding from solvent to solute through the lone pairs of the exocyclic oxygen atom and on the other side hydrogen atoms of the solvent and the positively charged heteroaromatic ring in the vicinity of the positive N-3 produces the electron charge flow as described in Scheme 29. Experimental data and ab initio DFT−GIAO calculations of nitrogen shielding correlate well.

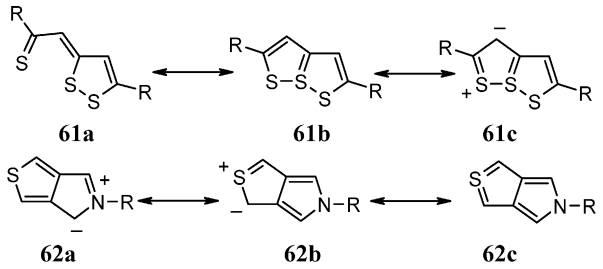
Scheme 29. Schematic Representation of Electron Charge Flow in 3-Methylsydnone (60) As Suggested in Ref 78



60

Bicyclic systems such as trithiapentalene **61** or thia-aza-pentalenes **62** (Scheme 30) show significant charge separation. Alternative representations for the above systems include nonclassical structures **61b**,**c** and **62c** with S(IV). Density functional calculations showed that the stability and aromaticity of bis-

Scheme 30. Other Five-Membered Systems

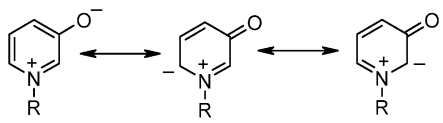


61a 61b 61c

62a 62b 62c

heteropentalenes depend on the position of the heteroatoms, with the [3,2-*b*] isomer being the most stable and the [3,4-*c*] with the heteroatoms as in **62** being the least stable.[78b−d] Six-membered systems, such as 1-substituted pyridinium-3-olates **63** (Scheme 31), are analogous to pyrylium 3-oxides **54** (Scheme 25).

Scheme 31. Six-Membered Betaines



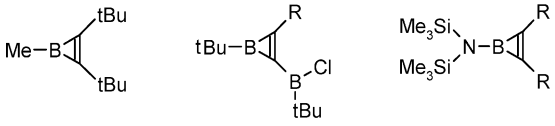
63a 63b 63c

A recent theoretical investigation of oxocarbon dianions suggested that the dianion of the cyclic carbon monoxide trimer, $(CO)_3^{2-}$, is aromatic.[79]

3.2. Known and Potential Monocyclic Three-Membered Heterocyclic Rings

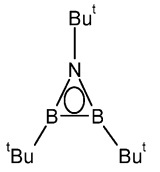
Boron. Neutral boron-containing systems with a π-electron doublet (heterocyclic counterparts of the cyclopropenyl cation[55] are called borirenes (**64**−**66**, Scheme 32) and azadiboriridines (**67**, Scheme 33)[80,81]

Scheme 32. Borirenes



64 65 66

Scheme 33. Tri-*tert*-butylazadiboriridine



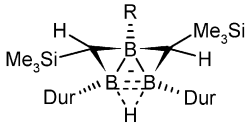
R = H, *t*Bu, Ar, N*i*Pr$_2$

67

and were synthesized by Berndt and co-workers (**64**),[82,83] Habben and Meller (**65**),[84] and Paetzold, Schleyer, and their co-workers (**66**) (Scheme 33).[81,85−88] In azadiboriridines **67**, the B−B bond distances range from 156 to 162 pm, indicating considerable double bond character. Amino groups attached to boron somewhat decrease the delocalization energy.[89]

Two-π-electron ($n = 0$) bis-homoaromatic compounds, such as bis(homotriborirane) anions **68**, were

Scheme 34. Bishomotriborirane Anions with a B−H−B Bridge As Formulated in Ref 90



68

Dur = 2,3,5,6-tetramethylphenyl
R = H, Ph, Me, Cl, D

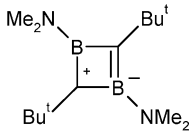
recently synthesized (Scheme 34).[90] Characterization of these compounds by NMR spectroscopy and X-ray diffraction clearly demonstrated their homoaromaticity.

3.3. Known and Potential Monocyclic Four-Membered Heterocyclic Rings

Both cases with $n = 0$ and $n = 1$ in the Hückel rule of $4n+2$ π-electrons can be achieved for four-membered heterocyclic rings. However, the stability of the resulting system is low in either case, owing to ring strain, the adjacency of two X- or Z-type atoms, or the mesoaromatic character when such heteroatoms are not adjacent, as in 1,3-diborete.

Siebert and co-workers reported the synthesis of 1,3-diboretes **50** (Scheme 21) and **69** (Scheme 35).[91] Although the ring of **69** is puckered, with a dihedral angle of about 130°, the authors concluded from bond distances that the four B−C bonds have delocalized π-character, in agreement with calculations.[92,93]

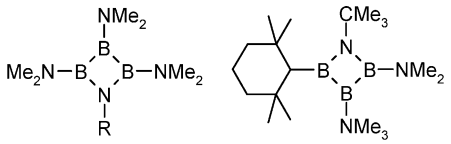
Scheme 35. 1,3-Diborete



69

Azatriboretidines **70** and **71** (Scheme 36) are stable because the electron deficit is compensated by exocyclic dialkylamino groups, but their aromaticity has not been proven.[94]

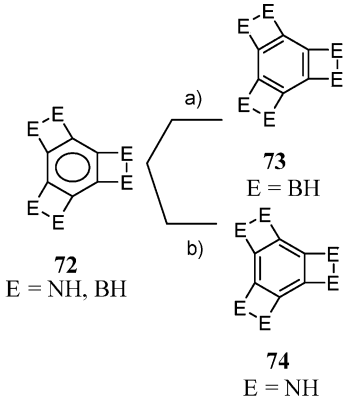
Scheme 36. Azatriboretidines



70 **71**

Ab initio calculations for systems **72** (Scheme 37) indicated that strain-induced bond localization (SIBL) rather than aromaticity of the small annulated rings is responsible for the alternating bond lengths in Vollhardt's analogous hydrocarbons.[95a] According to Hückel's concept, the number of π-electrons determines whether a structure is aromatic or antiaromatic, regardless of the type of atoms in the conjugated π-system. Aromaticity in σ-strained three- and four-membered rings is reduced in some cases by bond localization. A positive ΔR means that the bonds exocyclic to the annulated small rings are

Scheme 37. Geometrical Effects of SIBL and Aromaticity[a]



72
E = NH, BH

73
E = BH

74
E = NH

[a] (a) Aromaticity in the small rings and (b) aromaticity in the circumference.

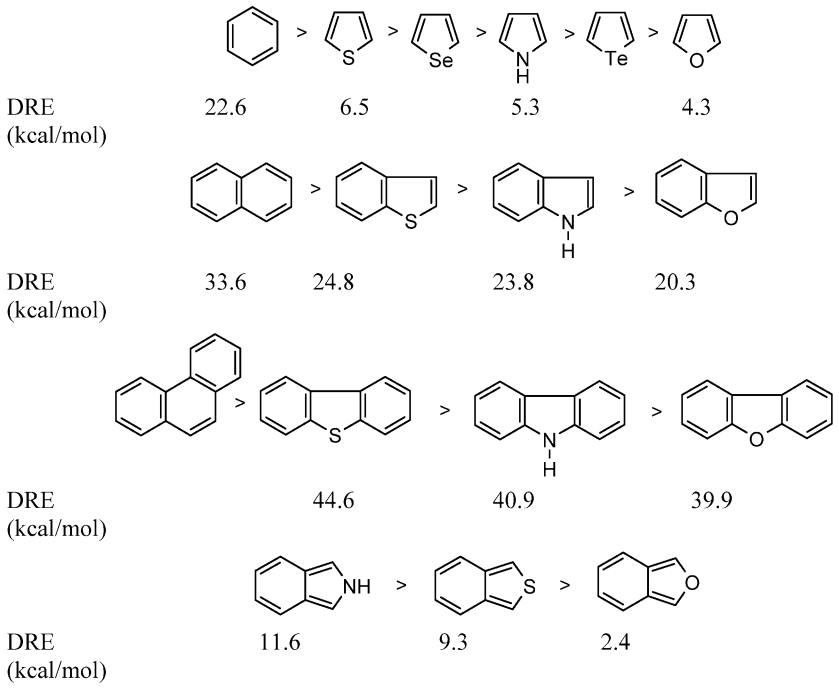
shorter than the endocyclic bonds (Mills−Nixon distortion).[95b] By the classic π-approach, if the benzene ring electrons in **72** (Scheme 37) were delocalized, the four-membered ring would have four π-electrons and the ring would be anti-aromatic, while the localization of the π-electrons would avoid the antiaromatic destabilization. This approach predicts a negative ΔR for rings with $4n+2$ π-electrons.[95b] A second approach explains the bond localization by SIBL, which is based on strain effects that cause rehybridization in the strained atoms (see, however, other reports[96]).

Counting the electrons in the circumference predicts that compounds **72** (E = NH or B) should show positive ΔR. However, calculations show that SIBL and not aromatic factors is responsible for the distortion of the six-membered ring. In **74** (E = NH), aromaticity factors suggest negative ΔR because of the six electrons ($4n+2$ π-electrons) in each ring, whereas SIBL predicts positive ΔR, as nitrogen is electronegative, which makes the bonds much less curved. When the electrons in each four-membered ring are counted separately, aromaticity factors and SIBL predict a negative ΔR aromaticity for **73** (E = BH) because of the two π-electrons in each four-membered ring; SIBL accounts for the large bond curvature (the boron atom is electropositive), and therefore the effective bond angle is much larger than the observed bond angle.

3.4. Known and Potential Heteroaromatic Five-Membered Rings

Structures and nomenclature for the most important five-membered monocycles with one or more heteroatoms are depicted in Scheme 1. The aromaticity scale in five-membered heterocycles has been long debated.[97−101] The decreasing order of aromaticity based on various criteria is (DRE values in kcal/mol): benzene (22.6) > thiophene (6.5) > selenophene > pyrrole (5.3) > tellurophene > furan (4.3). Pyrrole and furan have comparable ring strains (Scheme 38). The aromaticity of furan is still controversial;[100] the NMR shielding by ring current estimated it at about 60% of the aromaticity of benzene, and other methods reviewed earlier[102] estimated it at less than 20%.

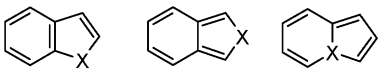
Scheme 38. Aromaticity Scales in Five-Membered Heterocycles



A larger covalent radius such as of sulfur, selenium, or tellurium reduces the ring strain; d-orbital participation in thiophene is not significant in the ground state, and thiophene exhibits a pronounced aromatic character that is substantiated by its physical and chemical properties.[103]

In the benzo[*b*]-annulated series **75** the order of aromaticity is similar, as described by the DRE values (kcal/mol): naphthalene (33.6) > thionaphthalene (24.8) > indole (23.8) > benzofuran (20.3); for the dibenzo series, phenanthrene > dibenzothiophene (44.6) > carbazole (40.9) > dibenzofuran (39.9) (Schemes 38, 39). Benzo[*c*]-annulation (**76**)

Scheme 39. Benzo-annulated Aromatic Five-Membered Rings



75 **76** **77**

causes an inversion between NH and S heterocycles: isoindole (11.6) > benzo[*c*]thiophene (9.3) > benzo[*c*]furan (2.4).[99] Quantum-chemical calculations of indolizine (**77**, X = N) and its aza derivatives showed that the resonance stabilization is mostly due to the presence of the pyrrole ring, and the π-stabilization brought by the introduction of a nitrogen atom increases in the order indole (**45** and **75**, X = N) > isoindole (**44** and **76**, X = N) > indolizine (**77**, X = N), as shown by the comparison of their resonance per electron (REPE) energy values.[104]

Five-membered heterocycles with two heteroatoms have the π-electron deficiency of Y-type heteroatoms compensated by the π-electron excessive character of the X-type atoms; therefore, this category includes some of the most stable heterocycles. For example, NMR spectral data and chemical behavior (e.g., resistance to oxidation by potassium permanganate) suggest that pyrazole and imidazole have delocalizations comparable with that of benzene.[105,106] Theoretical calculations produced similar aromaticity indices that were reviewed earlier for pyrazole[105] and imidazole.[106] Thiazole and oxazole as well as their iso-counterparts are less aromatic. Anions and cations of diazoles are symmetrical, allowing for multiple tautomers and showing considerable stability.[107,108] Tetrazoles, oxadiazoles, thiazoles, and pentazole are less aromatic than diazoles, which is reflected in their physical and chemical properties (e.g., crystalline pentazoles explode at their melting points).[109,110]

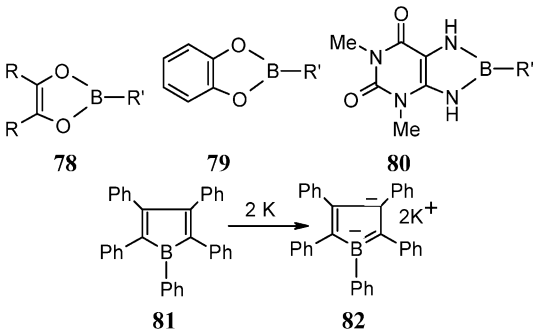
The aromaticity of five-membered rings with two or more heteroatoms was discussed in detail in earlier reviews.[52,100,111] In a comprehensive survey on the quantitative measurements of aromaticity,[112] it has been shown that basicity-based quantification of aromaticity gave more reproducible resonance energies than other methods, such as heats of formation, ring currents, magnetic susceptibilities, and theoretical indices.

Several recent papers analyzed the properties of five-membered heterocycles (azoles, oxoles, thio derivatives) in terms of their higher or lower aromaticity.[113−120]

Aromaticity indices in connection with five-membered heterocycles have been reviewed earlier[5,98,121] and are extensively discussed in a recent paper.[6b] The widely used Bird index is based on a statistical evaluation of the deviations in peripheral bond orders, which are readily obtainable from bond lengths.[122,123] Bird's indices were applied to both five- and six-membered rings; however, in some cases unrealistic values have been quoted. Further work by Katritzky and coworkers[124] established a good correlation between the aromaticity indices and resonance energies, and this relationship was used by Bird to define a unified aromaticity index for heterocycles, I_A, that is based on the extent of variation of ring bond orders and is directly proportional to the resonance energy.[125]

Boron. Five-membered aromatic rings containing a boron atom and two X-type heteroatoms display six π-electrons and are consequently aromatic. Such systems are 1,3,2-dioxaborole (**78**) and its benzo derivative (**79**, Scheme 40).[126−129] 5,6-Diamino-1,3-

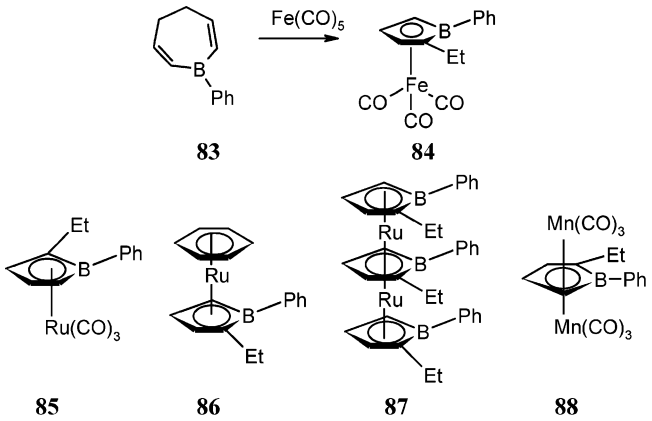
Scheme 40. 1,3,2-Dioxa- (78) and 1,3,2-Benzodioxaboroles (79), Analogues of Purines (80), and Pentaphenylborole (82)



dimethyluracil reacts with boronic acids to yield boron analogues of purines **80**.[130] In contrast with the above aromatic systems, boroles are anti-aromatic; however, pentaphenylborole **81**, reduced with potassium metal in THF, afforded a crystalline blue dipotassium salt **82**, isoelectronic with the aromatic sodium cyclopentadienide with six π-electrons.[131] Borole salts and their chemistry have been reviewed.[130]

1-Phenyl-4,5-dihydroborepin (**83**) (Scheme 41) is the building block (after rearrangement to ethylborole) for a series of aromatic ion tricarbonyl complexes with iron, rhodium, ruthenium, and manganese, such as **84**−**88**, in which the boron heterocycle is isoelectronic with the cyclopentadienyl anion. Their aromaticity has been discussed in an earlier review.[130]

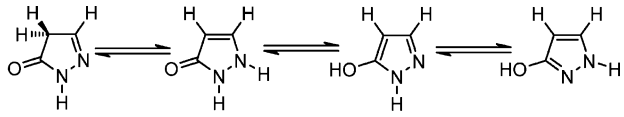
Scheme 41. Transition Metal Complexes of 1-Phenyl-4,5-dihydroborepin



Nitrogen. Krygowsky et al. applied their HOMA aromaticity criterion as well as the NICS index to pyrazoles[132] and found that the aromaticity of pyrazole decreases when the double-bond character of the exocyclic bonds to substituents in the 3- and 4-positions increases.

3-Hydroxypyrazoles and the corresponding pyrazolinone tautomers were investigated by Perez, Elguero, and co-workers by flash vacuum pyrolysis and

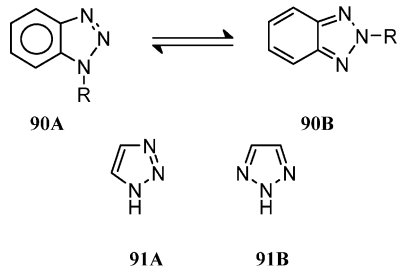
Scheme 42. Keto−Enol Tautomerism of Pyrazolinones



ab initio calculations; it was found that hydroxypyrazoles **89C** and **98D** are as aromatic as pyrazole or pyrrole, the NH-pyrazolinone **89B** is less aromatic, and of course the methylene tautomer **89A** is nonaromatic (Scheme 42).[133]

Among the five-membered heterocycles with three nitrogen atoms, triazoles and benzotriazoles are of significant practical importance. In the case of benzotriazole, the aromaticity of the benzenoid 1*H*-benzotriazole (**90A**, R = H) has been considered to be greater than that of the quinonoid 2*H*-benzotriazole (**90B**, R = H) (Scheme 43).[134] However, the difference in aromaticity between tautomers is greatly dependent on the dielectric constant of the medium.

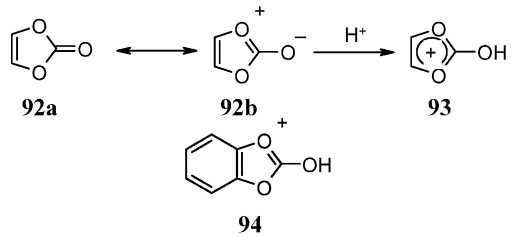
Scheme 43. Benzotriazole and 1,2,3-Triazole Tautomers



The aromaticity of triazole tautomers was assessed by the Bird indices:[122] 2*H*-1,2,3-triazole (**91B**, $I = 88$) was found to be slightly more aromatic than its 1*H*-isomer (**91A**, $I = 73$). The small difference in Bird indices supports only a weak influence of the aromaticity, and the lower stability of the 1*H*-isomer was explained by the nitrogen lone-pair repulsion that destabilizes cyclic azo derivatives.

Oxygen. The very weak aromaticity in vinylene carbonate (**92**) and *o*-phenylene carbonate is enhanced by protonation to **93** and **97**, respectively, as evidenced by electronic spectra of **94**[135] and ^{1}H NMR spectra of **93**[136] (Scheme 44).

Scheme 44. Carbonates



The weak aromaticity of oxazole is reflected by its chemical behavior, demonstrating a high degree of bond localization (illustrated by the propensity for cycloaddition reactions),[137] and is supported by theoretical calculations (ring current indices, i.e., the bond

with the lowest bond order would determine the magnitude of the ring current) or by statistical evaluation of the deviations in peripheral bond orders. For instance, Bird's analysis, based on the statistical evaluation of the deviations in peripheral bond orders,[122] showed that oxazole was the lowest on the aromaticity scale of 29 heterocycles. The lowest bond order occurs for the C(5)−O bond. Katritzky and co-workers[124] analyzed by the principal component analysis (PCA) technique a set of 16 heterocycles, among them oxazole and isoxazole. In essence, the method involved the treatment of a total of 12 variables by the SIMCA method. The variables covered a broad range of properties: four geometric (the Bird indices derived from experimental data, the Bird indices derived from AM1 calculated ring geometries, the Jug measure of ring current, and the Pozharskii indices), five energetic (Dewar resonance energies derived from experimental quantities and from AM1 calculated geometries, Hess−Schaad resonance energies, and heats of formation both experimental and calculated by AM1), and three magnetic (molar magnetic susceptibility, diamagnetic susceptibility exaltation, and the average ^{15}N chemical shift). The data set for the 12 characteristics and 16 compounds gave the lowest score to isoxazole, followed by oxazole.

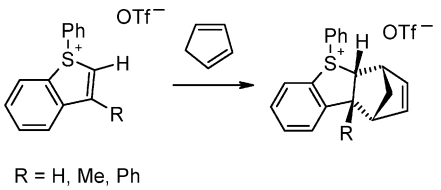
The aromaticity of isoxazole has been reviewed in terms of theoretical and structural studies,[138,139] and the conclusion is that it is slightly less aromatic than oxazole and furan.

The aromaticity of oxadiazoles was evaluated by means of the Bird unified aromaticity index I_A as being much lower than those of the corresponding thiadiazoles.[125] The resonance energies of a series of heterodiazoles (oxygen, selenium, sulfur, etc.) were calculated from experimental heats of formation and correlated with the indices previously introduced for differing ring systems. The unified Bird indices I_A were calculated as follows: 48 for 1,2,4-oxadiazole, 52 for isoxazole, 53 for 1,2,5-oxadiazole, 53 for furan, and 62 for 1,3,4-oxadiazole, which is the increasing order of aromaticity (for structures, see Scheme 1). Sulfur and seleno derivatives show higher I_A indices, i.e., 58 for 1,2,5-selenadiazole and 104 for 1,2,5-thiadiazole. The aromaticities of thiadiazole computed by the PCA technique[140] are in agreement with their chemical properties. On the other hand, 1,2,5-thiadiazole-1-oxide and -1,1-dioxide are not aromatic.

Sulfur. Thiophene and benzo[*b*]thiophene are both aromatic heterocycles, as discussed earlier in this review. Isothiazole is a planar molecule with an aromaticity comparable with those of thiazole and pyrazole, and higher than those of isoxazole and oxazole,[122,140] as evaluated on the basis of Bird's aromaticity index I_A, based upon the statistical degree of uniformity of the bond orders of the ring periphery. Theoretical calculations and experimental data in connection with the aromaticity of isothiazole have been reviewed.[141] Thiazole is also viewed as an aromatic molecule, similar to thiophene. It lacks an "experimental aromaticity" value, but the heat of formation together with bond lengths and angles have been calculated by various computational methods, including the semiempirical techniques AM1, PM3, and MNDO, in combination with the thermochemical basis sets of Benson and Steire.[142] Thus, by applying Benson's method, the heat of formation of thiazole was calculated to be 36.78 kcal/mol.

On converting 1-benzothiophene into 1-phenyl-1-benzothiophenium triflate (**95**), this salt becomes a dienophile and reacts readily with cyclopentadiene or 1,3-diphenylisobenzofuran to give the adduct **96** (Scheme 45).[143] This example of the dienophilic nature of the double bond in the benzothiophene ring arises from reduced aromaticity.

Scheme 45. The Olefinic Nature of the Thiophenium Ring

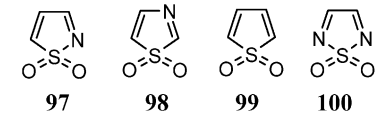


R = H, Me, Ph

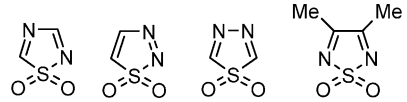
95 **96**

Thiophene-1-oxide and 1-substituted thiophenium salts present reduced aromaticity.[144] A variety of aromaticity criteria were used in order to assess which of the 1,1-dioxide isomers of thiophene, thiazole, isothiazole, and thiadiazole was the most delocalized (Scheme 46).[145] The relative aromaticity of those molecules is determined by the proximity of the nitrogen atoms to the sulfur, which actually accounts for its ability to participate in a push−pull system with the oxygen atoms of the sulfone moiety. The relative aromaticity decreases in the series isothiazole-1,1-dioxide (**97**) > thiazole-1,1-dioxide (**98**) > thiophene-1-dioxide (**99**); then, one has the series 1,2,5-thiadiazole-1,1-dioxide (**100**) > 1,2,4-thiadiazole-1,1-dioxide (**101**) > 1,2,3-thiadiazole-1,1-dioxide (**102**) > 1,3,4-thiadiazole-1,1-dioxide (**103**) in the order of decreasing aromaticity. As 1,2,5-thiadiazole-1,1-dioxide (**100**) was not synthesized, the approximations used extrapolations of data obtained for its 3,4-dimethyl-substituted analogue **104** (Scheme 46).

Scheme 46. Thiazole-, Isothiazole-, and Thiadiazole-1,1-dioxides



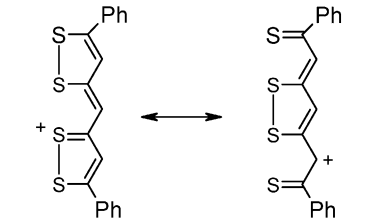
97 **98** **99** **100**



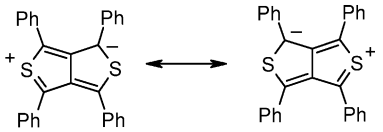
101 **102** **103** **104**

Tri-thiapentalenes **61** and the tetrathia cationic analogue **105** are aromatic compounds[146,147] (Schemes 30 and 47). In the bicyclic canonical structures **61b**, the central tetravalent sulfur makes an important contribution to the aromatic character. The "nonclassical bicyclic thiophene" **61c**, with 10 π-electrons, is fully stabilized by aromatic delocalization[148] (Scheme 47). Tetrathio derivative **106** presents evidence for S−S bonding along the whole range of sulfur at-

Scheme 47. Di-, Tri-, and Tetrathiapentalenes



105a **105b**

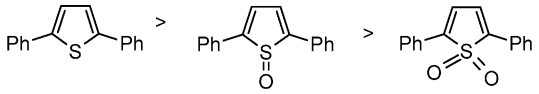


106a **107b**

oms.[147] Due to their almost orthogonal position relative to the plane of **106**, the four phenyl rings provide little electronic stabilization.

Several aromaticity indices (bond lengths, bond orders, Jug and François's aromaticity index) indicate that, despite the nonplanarity of the five-membered ring in 2,5-diphenylthiophene-1-oxide (**108**), this compound is intermediate in aromaticity between the corresponding thiophene **107** and the nonplanar 1,1-dioxide **109** (Scheme 48).[149] The theoretical calculations were supported by experimental electrochemical data.[150]

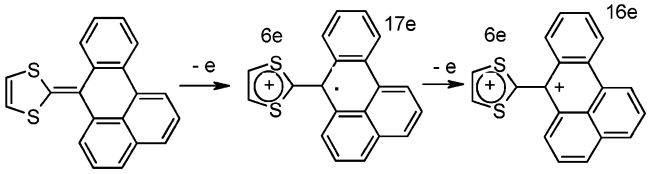
Scheme 48. Thiophene Derivatives



107 **108** **109**

Novel substituted π-electron-donor tetrathiafulvalenes are described in connection with the synthesis of dendrimeric molecules with electrically conducting or semiconducting properties.[151] Compounds such as **110** (Scheme 49) show two one-electron

Scheme 49. Oxidation of a 1,3-Dithiole Unit Conjugated with an Acene

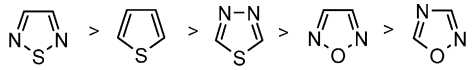


110 **111** **112**

oxidation waves by cyclic voltammetry measurements, corresponding to the formation of the radical cation and dication species. The dication was demonstrated to be fully aromatic with a closed electronic shell, a singly charged, planar polycyclic benzenoid unit, and a singly charged dithiole ring. The high aromaticity of the dication, coupled with the donor properties of the benzanthronic unit, seems to be the cause of its electrochemical behavior.

In the oxa- and thia-diazole series **113**−**117**, an earlier review concluded that the aromaticity is dependent upon the relative positions of the heteroatoms in the ring.[111] Based on a compilation of X-ray and microwave spectroscopy data, which gave relevant information on the planarity of these systems, the study produced the order of decreasing aromaticity based on bond lengths, as displayed in Scheme 50: 1,2,5-thiadiazole > thiophene > 1,3,4-thiadiazole > 1,2,5-oxadiazole > 1,2,4-oxadiazole.

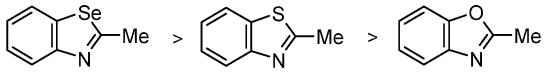
Scheme 50. Aromatic Diazoles



113 **114** **115** **116** **117**

In 2-heterosubstituted benzo derivatives (Scheme 51), the effect of the heteroatom X on the ring is similar to the azole series above, and the decreasing scale of aromaticity is 2,1,3-benzoselenadiazole (**118**)- > 2,1,3-benzothiadiazole (**119**) > 2,1,3-benzoxadiazole (**120**).[111]

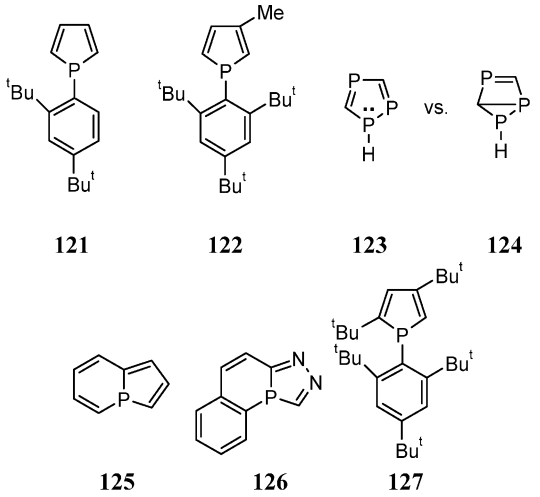
Scheme 51. Aromatic 2-Benzo Five-Membered Hetarenes



118 **119** **120**

Phosphorus. Early reports on the aromaticity of phospholes (Scheme 52) were controversial.[152] X-ray crystallographic data show that 1,2,5-triphenylphosphole has a nonplanar phosphole ring, while NMR, chemical, and thermodynamical data account for delocalization. Low inversion barriers of the phosphorus atom compared to the saturated congeners suggest n/π conjugation.[153,154]

Scheme 52. Phospholes and Other Phosphorus Heterocycles



121 **122** **123** **124**

125 **126** **127**

Nyulaszi succeeded in synthesizing phospholes with planar tricoordinate phosphorus.[155] Replacing CH groups by phosphorus has a great impact on the aromaticity of rings due to changes in bond lengths and planarity.[156] Bulky substituents on the phosphorus atom flatten the phosphorus pyramidal shape by a buttressing effect. Due to the reduction in pyramidality of the tricoordinate phosphorus in phosphole, the aromatic character is increased. The aromaticity of 1-(2,4-di-*tert*-butylphenyl)phosphole (**121**, Scheme 52), as determined by molecular calculations−

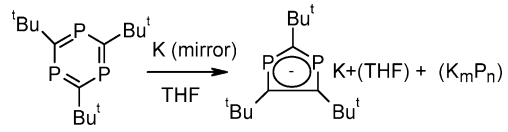
MNDO, HF/6-31G*, and B3LYP/6-31G*—and from its ionization energy, is similar to the aromaticity of furan.[155] The gradual flattening of the tricoordinate phosphorus in phosphole with the increasing steric bulk of the substituent group is revealed by the HF/6-31G* optimized geometries of alkylarylphospholes. With decreasing pyramidality, aromaticity indices increase by increased conjugation. In photoelectron spectra, the increase in aromaticity is evidenced by the decrease in ionization energy of the phosphorus lone pair. Indeed, 1-(2,4,6-tri-*tert*-butyl)-3-methylphosphole (**122**) is the first phosphole demonstrated to undergo electrophilic substitution.[157] 1-(2,4,6-Tri-*tert*-butyl)-3-methylphosphole (**122**) has the lowest ionization energy value ever reported for a phosphole, indicating increased aromaticity, and several aromaticity indices are in agreement with experimental data.[156]

Molecular calculations at the B3LYP/6-311+G** level for diphospholes, triphospholes **123**, and phosphaindolizines (**125** predicted and **126** synthesized and under investigation[156]) point to aromatic structure. The aromaticity of π-systems with planar tricoordinate phosphorus is largest among those rings containing nitrogen or chalcogen heteroatoms.

1-(2,4-Tri-*tert*-butylphenyl)-3,5-di-*tert*-butyl-1,2,4-triphosphole (**127**, Scheme 52) displays a highly aromatic planar system, according to several aromaticity indices.[158]

2,4,6-Tri-*tert*-butyl-1,3,5-triphosphabenzene (**128**, Scheme 53) undergoes a ring contraction over a potassium mirror,[159] with the elimination of potassium phosphine and formation of the aromatic 2,4,6-tri-*tert*-butyl-1,3-diphosphacyclopentadienide anion **129** with three bulky substituents (Scheme 53). The driving force of this reaction could be the higher aromaticity of the five-membered ring.

Scheme 53. 2,4,6-Tri-*tert*-butyl-1,3-diphosphacyclopentadienide

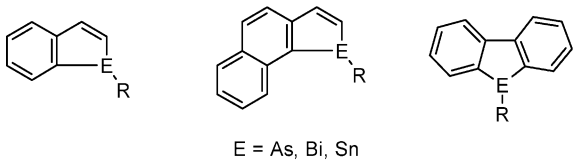


128 **129**

Azaphospholes were reviewed by Schmidpeter and Karaghiosoff,[160] who discuss the 14 possible mono-, di-, tri-, and tetra-azaphospholes and the 11 known isomers with dicoordinated phosphorus. Other papers bring spectroscopic evidence or rely on 4-31G(*) geometry optimization calculations to demonstrate that the aromaticity of azaphospholes[161] or polyazaphospholes[162] decreases with the pyramidality of the tricoordinate phosphorus and is larger among those rings containing nitrogen or chalcogen heteroatoms.

Heterocycles with Arsenic, Antimony, and Bismuth. Arsoles, stilboles, and bismoles (Scheme 54) are five-membered heterocycles for which experimental data do not indicate aromatic properties, while semiempirical calculations (CNINDO or CNDO/S) showed that the anions are aromatic. The chemistry and theoretical aspects in connection with their

Scheme 54

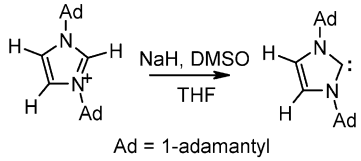


130 **131** **132**

aromaticity and electron-pair delocalization have been recently reviewed.[163]

Carbenes. Arduengo's efforts in synthesizing stable nucleophilic carbenes (e.g., **134**, Scheme 55) lasted more than 20 years and were successful in 1991, when the aromatic imidazole system was used (e.g., **133**, Scheme 55).[164,165] Soon afterward, analogous

Scheme 55. First Isolated Heterocarbene

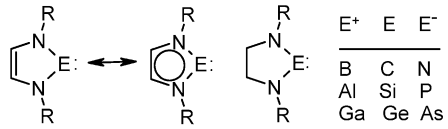


133 **134**

germylenes[166] and silylenes[167−170] were obtained having the heteroatom with a vacant orbital electron between the two nitrogen atoms, yielding systems with a π-electron sextet. The chemistry of *N*-heterocyclic carbenes has been reviewed periodically.[171−173]

In addition to the above imidazole-analogue carbenoid systems, compounds with the electron sextet at N, P, or As between the two nitrogens have also been obtained (Scheme 56);[174,175] 2-chloro-1,3,2-dia-

Scheme 56. Aromatic 1,3-Diazoles and Non-aromatic Diazolidines



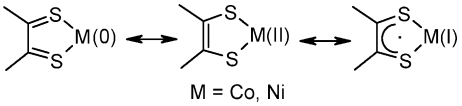
135a **135b** **135c**

zophospholenes dissociate in solution to a small extent. The atom E is functioning as a Z-type atom (Table 2). Aromatically stabilized systems **135a**,**b** showed an enhanced propensity to stabilize the heterocarbene, and this is valid for heteroelements E = Si, Ge, N^+, P^+, and As^+, similarly to their non-aromatic counterparts **135c**. This is proved by experimental data (synthesis, multinuclear NMR, single-crystal X-ray crystallography) and supported by quantum-chemical calculations.[174,175] In a series of isostructural diamino-silylenes, -germylenes, and -phosphenium cations, ab initio calculations show that the latter were the most aromatic, the evaluation being made on the basis of aromatic delocalization energies and deshielding of ring protons. For the model phosphenium cations $[RN{-}CH_2{-}CH_2{-}NR]P^+$ and $[(RN{-}CH{=}CH{-}NR)P]^+$, thermochemical stabilization energies of 25.8 (R = H) and 28.1 kcal/mol (R = Me) were obtained from isodesmic hydrogenation reactions at the RHF/MP2/6-31G*//RHF/6-31G* level. It now appears that cyclic electronic delocalization and aromaticity in **135**, with E = C, Si, Ge,

is not the only stabilizing factor.[168,176] The N → C π-electron donation into the vacant orbital of E is also stabilizing, as proved by the synthesis of nonaromatic **135c** (Scheme 56).

Metallocenes. The aromatic character of carbon rings in ferrocene or dibenzenechromium is firmly established.[177a] We will comment on the aromaticity of rings containing metal atoms. Theoretical studies have been focused on determining the electronic requirements for achieving aromaticity in a metallacycle, and have been reviewed.[177b] After the nonaromaticity of metal chelates with 1,3-diketones was established, it was surprising to find that five-membered metallacycles such as metalladithiolenes **136**, with M = Co, undergo substitutions (Scheme 57).[178] On the basis of their chemical properties, it has been suggested that metalladithiolenes have aromatic character.

Scheme 57. Metalladithiolenes

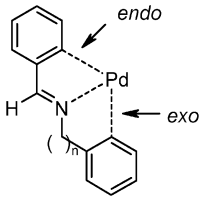


136a **136b** **136c**

136a: dithioketone
136b: dithiolate
136c: semiquinone radical anion

Five-membered cyclopalladated rings of type **137** (Scheme 58) were synthesized and studied by spectroscopic methods. Their X-ray structures were analyzed in terms of deviations from planarity, and data were used for the calculation of two aromaticity indices, *V* and HOMA,[179] which are in agreement with an aromatic structure.

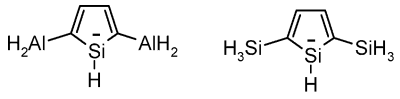
Scheme 58. Five-Membered Cyclopalladates



137

Siloles, germoles, stannoles, and plumboles have been extensively reviewed.[180] The aromaticity of these systems is still under scrutiny. In the study, the cyclopentadienyl anion had the highest aromatic character, with a NICS value of −14 and a Bird index of 100. Structures **138** and **139** also showed high and similar aromaticity indices (Scheme 59). For the planar silacyclopentadienyl anion **138**, the NICS value is −10.2 and the Bird index 80, while the values for anion **139** are −10.9 and 77, respectively.

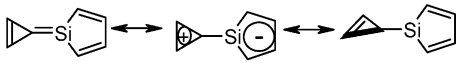
Scheme 59



138 **139**

Ab initio molecular calculations, using for geometry optimizations the MP2/6-31G* level and the MP2/6-311++G** level, have been performed to assess the aromaticity of 4-silatriafulvenes (Scheme 60).[181] NICS and Bird indices were calculated and compared. Calculations for the chalicene analogue **140b** show very low aromaticity of the silole ring, which does not increase significantly in the planar geometry **140a**. The aromaticity indices are high when the two rings are perpendicular to one another (**140c**), preventing the conjugation of the π-systems.

Scheme 60. Aromaticity of 4-Silatriafulvenes

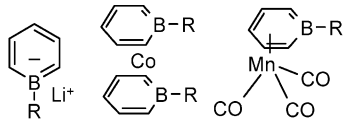


140a **140b** **140c**

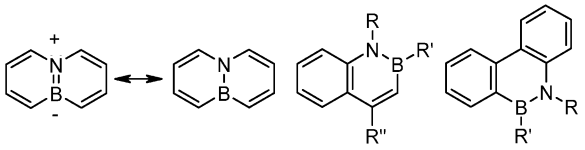
3.5. Known and Potential Monocyclic Six-Membered Rings

Boron. Earlier papers reviewed the properties of the borabenzene anion and discussed its potential aromaticity.[130,182] A few examples have been shown in Schemes 31 and 53. The borabenzene anion (borinate) **141**, with R = phenyl or methyl, gives complexes with transition metals such as Co (**142**) and Mn (**143**) (Scheme 61).[183] Aza- and polyaza-

Scheme 61. The Borabenzene Anion



141 **142** **143**



144a **144b** **145** **146**

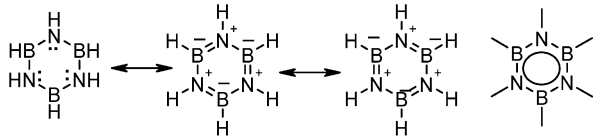
borabenzenes (**144** and **145**, Scheme 61) have already been prepared and have properties analogous to those of azines.[130] 9,10-Borazaro-naphthalene (**144a**,**b**) smells like naphthalene and (unlike the latter) does not react with maleic anhydride[184] (for a review, see ref 185).

Dewar[185−187] reported the first six-membered aromatic rings containing boron, oxygen, and nitrogen heteroatoms, and later Gronowitz[188] prepared similar systems annelated with thiophene. The chemical reactivity and NMR data indicate electronic delocalization.

The gas-phase chemistry of borazine $B_3N_3H_6$ (**147**) and the conjugate N-protonated acid $B_3N_3H_7^+$ indicates analogies with benzene,[189] although the aromatic stabilization energy of neutral borazine is only 30% that of benzene, and the reactivities of benzene and borazine are not similar (Scheme 62). Comparable conclusions were reached when HOMA and I_6 aromaticity indices were used.[190a]

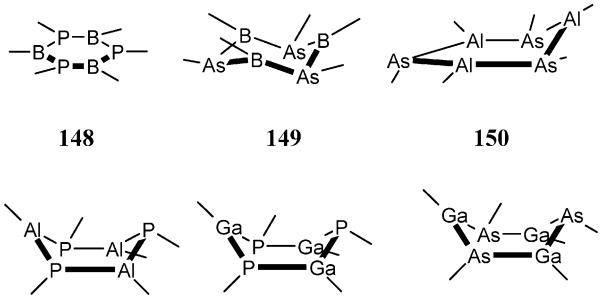
Analogues of borazine are shown in Scheme 63; the planarity of **148** indicates some aromatic character. Some compounds with P and As were found to prefer

Scheme 62. Borazine, an Inorganic Analogue of Benzene



147a **147b** **147c** **147d**

Scheme 63. Analogues of Borazine with Elements from the Same Groups of the Periodic System: Representation Suggested in Ref 190b



148 **149** **150**

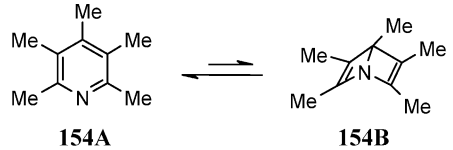
151 **152** **153**

nonplanar geometry.[190b] A few inconsistencies were found between NICS data and aromatic stabilization energies for systems **151**, which appear to be nonaromatic according to NICS indices.

Nitrogen. Pyridine is one of the most important heterocycles. The aromaticity of pyridine was intensively connected to structural considerations and chemical behavior. The relative difference between the aromaticity of benzene and pyridine is controversial; generally calculations give similar orders of magnitude and differences depend on the criterion of aromaticity considered and the mode of calculation used. A comprehensive review on the theoretical aspects in connection with the aromaticity of pyridine was published.[191] Pyridine is about as aromatic as benzene according to theoretical calculations and to experimental data, while quinoline is about as aromatic as naphthalene and more aromatic than isoquinoline.[192,193] The degrees of aromaticity of pyridine derivatives strongly depend on their substituents.

Kinetic studies on the quaternization reaction of pentamethylpyridine (**154A**, Scheme 64) and its deuterated congener suggest that there may be an equilibium between this aromatic pyridine and its valence isomer, pentamethyl-Dewar-pyridine (**154B**). It is known that such valence isomers are stabilized by steric factors such as encountered in pentamethylpyridine.[194,195] On determining conductometrically the initial rate of quaternization with methyl iodide for polymethylpyridines in acetone, it was found that all but one followed clean bimolecular kinetics. Pentamethylpyridine, however, unlike 2,3,5,6-tetramethylpyridine or other polymethylpyridines, showed a steeper initial variation that became linear after 0.2−0.3% of the pentamethylpyridine had reacted. After UV irradiation at −80 °C, the nonlinear portion increased. A plausible interpretation is the existence of a small amount of a more nucleophilic valence isomer of pentamethylpyridine with an sp^3-hybridized nitrogen atom.

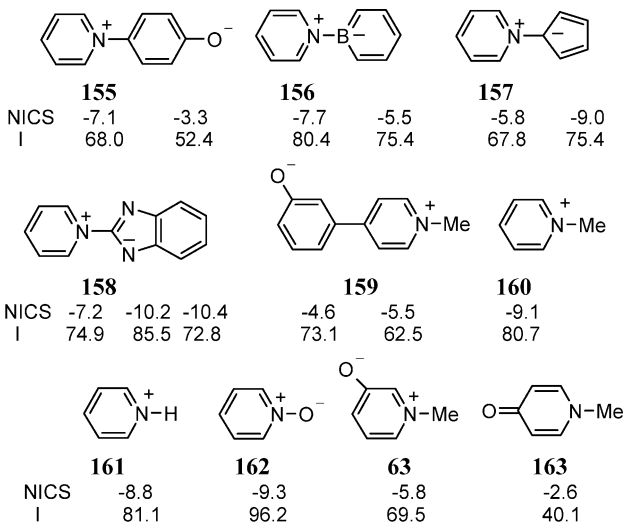
Scheme 64. Pentamethylpyridine and Its Dewar-Type Valence Isomer



154A **154B**

A series of aromaticity indices (*I* and NICS) were calculated for pyridinium betaines[196] in order to prove the aromatic character of the ring fragments. Ab initio single configuration interaction calculations showed that torsion around the interfragmental bond increases the charge separation between the molecular fragments with an increase in their aromaticity.[197] A few examples are presented in Scheme 65.

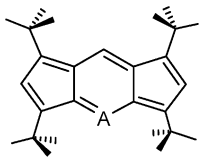
Scheme 65. NICS and Bird's I for Pyridinium Betaines



Fragments in compounds **155**−**157** exhibit aromatic bond delocalization. The lowest aromaticity is calculated for *N*-pyridinium cyclopentadienide **157**, with the interfragmental C−N bond shorter than the corresponding one in **155** and **158**. The phenolate moiety in **159** has a high NICS value (−4.6 ppm), in agreement with the one for deprotonated phenol (−6.2 ppm compared to −9.7 ppm for benzene, as cited),[196] while the acceptor pyridinium counterpart has a NICS value of −5.5 ppm, showing aromatic delocalization.

Heteroindacenes have been prepared and studied by Hafner and co-workers.[198,199] The syntheses of 1,3,5,7-tetra-*tert*-butyl-4-azaindacene, its *N*-oxide, and 1,3,5,7-tetra-*tert*-butyl-4-phospha-*s*-indacenes have been recently reported (Scheme 66).[200] The 12-π-electron delocalized systems have been studied by dynamic NMR and X-ray and were subjected to molecular orbital calculations, and there is strong evidence of electron delocalization. However, X-ray crystallographic data for 4-phospha-*s*-indacene **164** and the 4-*N*-oxide **164** show that there is a dual orientation in the crystal; this disorder with two different orientations of the molecule does not allow for conclusions regarding bond lengths or delocalization, and the mediated structures show a D_{2h} symmetry rather than C_{2h} with localized double bonds.

Scheme 66. Heteroindacenes



a: A = N
b: A = P
c: A = $^{+}$N–O^{-}

164

It seems that the substituents play an essential role in the kinetic stabilization of the molecule:[201] ab initio calculations for the formally anti-aromatic unsubstituted indacene shows that the minimum energy corresponds to a D_{2h} symmetry and a completely delocalized 12-π-electron system.[202]

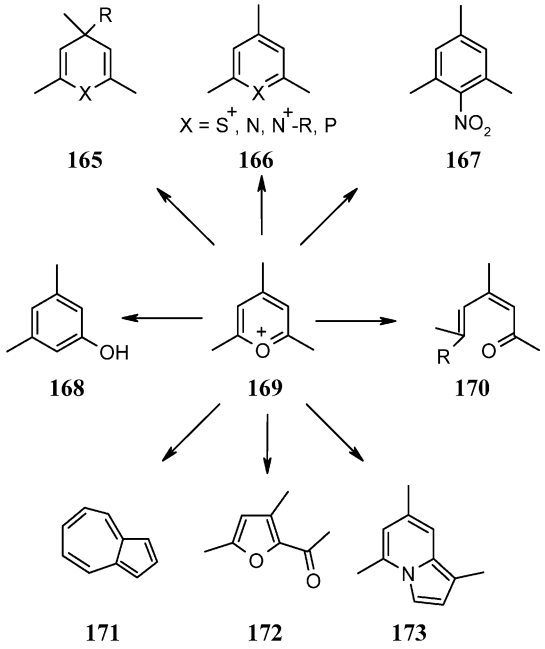
Generalized valence bond interaction energies were computed for mono/poly-nitrogenous five- and six-membered heterocycles.[203] Results that diverged from those obtained by other methods were obtained only for poly-nitrogenous systems such as pyridazine, benzotriazole, and tetrazole, which may confirm Bird's earlier finding[123,204] that electron delocalization is not a stand-alone and direct measure of aromaticity for nitrogenous heterocyclic compounds.

Azines are the most important systems with several heteroatoms (see Scheme 1 for structures). Pyridazine has a lower heat of formation than the isomeric pyrimidine and pyrazine,[205] due to the vicinity of the two electronegative heteroatoms. A thermal and hydrolytic instability has been observed in the azine series, which has been explained by the accumulation of nitrogen heteroatoms:[192,193] the instability increases in the order diazines < triazines < tetrazines. Wiberg[206] investigated the hydrogen transfer between 1,3-cyclohexadiene and the isomeric diazines resulting in benzene and a dihydroazine; only pyridazine, with a N═N bond, has reduced stabilization. Among diazines, the pyrimidine ring is the most important for life processes, as described in a preceding section.

The calculation of the vertical resonance energy[207] and of the ring currents[208] for six-membered nitrogen-containing heterocycles allowed the quantitative evaluation of their aromaticity. Bonchev and Seitz[209] applied Gimarc's principle of topological charge stabilization[210] to various nitrogen heterocycles. The idea is that electronegative atoms exert a stabilizing effect when placed in positions where the molecular topology accumulates electronic charge. This explains why, for instance, quinoline is more stable than isoquinoline.

Oxygen. Oxygen has the next highest electronegativity after fluorine; therefore, among the six-membered heterocycles with one heteroatom, the pyrylium cation is the most strongly perturbed benzenoid system, with a low aromaticity.[211−213] Therefore, nucleophilic attack in the 2(6)-position, followed by ring-opening and reclosure, i.e., ANRORC processes (or with strong nucleophiles in the 4-position), are characteristic reactions in the pyrylium class. As indicated in Scheme 67, replacement of the oxygen heteroatom by a less electronegative atom, such as

Scheme 67. Transformations of Pyrylium Salts



165 **166** **167**

168 **169** **170**

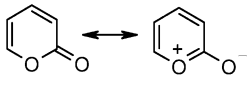
171 **172** **173**

N, P, S, or C, is thermodynamically and kinetically favored, yielding pyridine, pyridinium, phosphabenzene, thiopyrylium, or benzenoid rings. Ring-opening occurs with alkali cyanides; ring contraction to 2-acylfurans (**172)** takes place with hydrogen peroxide, and high-yield syntheses of azulene (**171)** and indolizine (**173**) are based on pyrylium salts, which are five-carbon nucleophilic (N^5) synthons. Balaban et al. have extensively reviewed the chemistry of pyrylium salts.[211−213] Substituted pyrylium salts are easily accessible via alkene diacylation (the Balaban−Nenitzescu−Praill reaction).[214]

Indolizines, aromatic heterocycles with 12-π-electron system salts, isomeric with indole and isoindole, are prepared in good yields from pyrylium salts with active α-methylene groups.[215,216] Aromatics derived from pyrylium salts by substitution of one or two β-CH group(s) with a heteroatom are also possible. 3-Azapyrylium (1,3-oxazinium) salts are known,[217,218] and their stability suggests the existence of aromatic delocalization.

The pyran-2-one ring system **174** (Scheme 68) is a potentially aromatic species, due to the contribution of the pyrylium-2-olate structure **174b**, but facile cleavage of the ring by nucleophiles makes it most likely a lactone rather than an aromatic system.

Scheme 68. 2*H*-Pyrone



174a **174b**

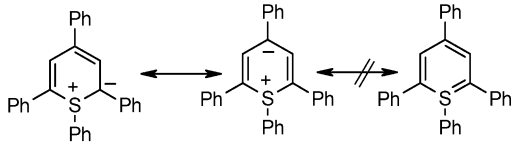
Pyran-4-one (**56a**) and its benzo derivative (chromone) show chemical properties in agreement with substantial π-electron delocalization and consistent with a betaine structure **56b** (Scheme 27). Experimental data have therefore generated numerous theoretical studies on the aromaticity of pyranones, which have been extensively reviewed.[219] Earlier studies suggested that chemical shifts and coupling constants

in pyran-2-ones indicate the presence of a diamagnetic ring current, comparable to the one in benzene.[220] Replacement of the oxygen heteroatom with sulfur induces downfield shifts of the ring protons, suggesting increased ring currents and therefore increased aromaticity in thiopyrones.[221] The aromaticity of the heterocyclic ring in pyrones and in chromone is still under scrutiny.[222] Calculated absolute magnetic shielding at the ring centers for chromone are 18.8 ppm for the benzenoid ring and 6.7 ppm for the pyrone ring, both being aromatic according to Schleyer's assumptions.

Sulfur. A comparison between pyrylium, pyridinium, and thiopyrylium salts based on ^{1}H NMR, MO calculations, and stability data has been published.[223] The significant deshielding of the β-hydrogen atoms in thiopyrylium compared to the pyrylium cation indicates an electron density transfer from the β-carbon atoms and an increase of bond order between the sulfur and the α-carbon atoms, which implies the participation of the 3d orbitals of sulfur.[224] However, the geometry of the system, which depends on the substituents, has a great role in the effectiveness of the participation if the sulfur involves 3d orbitals. Thiopyrylium cations show the same chemical reactivity as their pyrylium counterparts.[223] Selenopyrylium and telluropyrylium are known, but their aromaticity decreases because of the longer bond distances, causing lower orbital overlap, counterbalancing the decreasing electronegativity.

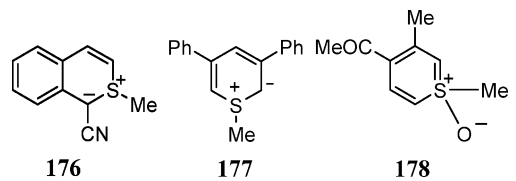
The chemical behavior of thiabenzene derivatives is in agreement with an aromatic character. 1,2,4,6-Triphenylthiabenzene has a betainic structure **175a**,**b** (Scheme 69).[223] Benzofusion or substitution with

Scheme 69. 1,2,4,6-Tetraphenylthiabenzene



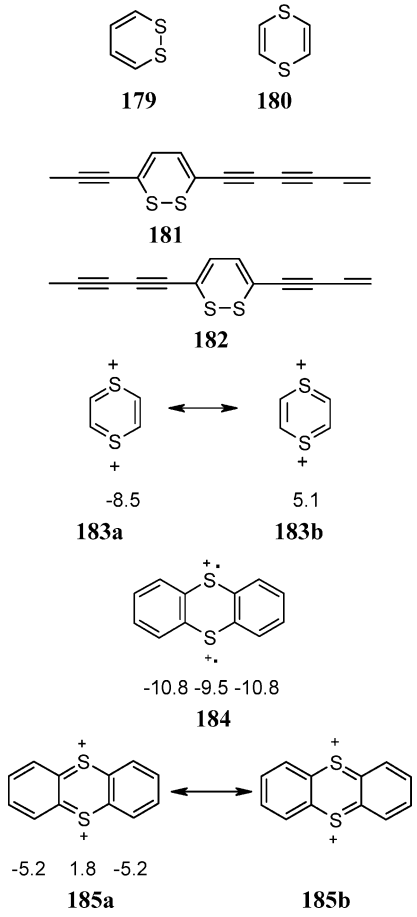
electron-attracting groups increases the stability of thiabenzene derivatives (Scheme 70): for instance, compound **176** is stable, whereas compound **177** has a half-life of 0.35 h.[225,226] Remarkably, the corresponding *S*-oxides **178** with S(IV) (Scheme 70)[227] are stable and undergo electrophilic substitutions, such as nitration with acetyl nitrate at positions 2 and 4.[225,226]

Scheme 70. Thiabenzene Derivatives



Anti-aromatic 1,2-dithiins **179** display properties opposite to those of 1,4-dithiins **180**, whose dications show aromatic stabilization. Unlike other anti-aromatic compounds, the 1,2-dithiin derivatives, with eight π-electrons (such as **181** and **182**), appear in

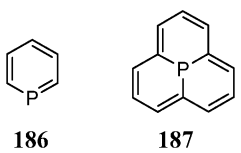
Scheme 71. 1,2- and 1,4-Dithiin Derivatives



natural products synthesized by composite plants (Scheme 71).[228,229] The Dewar resonance energies of nonplanar 1,2-dithiins are close to zero. The aromatic 1,4-dithiin dication **183** is generated by two-electron electrooxidation of the neutral 1,4-dithiin **180**. The aromaticity was established by NMR measurements and theoretical calculations.[228,229] Some NICS values are indicated in Scheme 71 and demonstrate that the singlet state for dication **184** is more stable than the triplet state **185**.

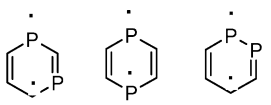
Phosphorus. Substituted phosphorus analogues of pyridine (phosphinines, λ^3-phosphabenzenes, also called phosphonins or phosphorins) were first prepared by Märkl starting from pyrylium cations; their chemical properties suggest that their aromaticity is lower than that of pyridine (e.g. phosphinine **186**, Scheme 72).[230−232] Molecular calculations for other six-membered π-systems with planar tricoordinate phosphorus, such as phospininines **186** and **187**, have evidenced their aromaticity (Scheme 72).[156]

Scheme 72. Phosphinines



Hiberty and co-workers calculated energies of the three isomeric diphosphinines by ab initio methods (Scheme 73):[233] the 1,3-isomer **188** is a stable compound, the 1,4-isomer **189** is rather unstable, and the

Scheme 73. Diphosphinines: Lowest Energy Diradical Structure for Isomer According to Ref 233

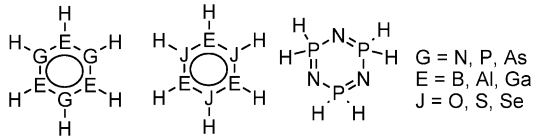


188 **189** **190**

1,2-isomer **190** (calculated to be the most stable) is not yet known.

A theoretical study on the structures, magnetical properties, and energetics of phosphorus analogues of borazine, $E_2G_3H_6$ **191** (E = B, Al, Ga; G = N, P, As), compared to those of other borazine analogues, $E_3J_3H_3$ **192** (J = O, S, Se) and to phosphazene (**194**),[234] shows that results could vary with function of the reference system. Some compounds with P and As heteroatoms were found to prefer nonplanar geometries (Scheme 74). Contradictory results were found. For instance, aromatic stabilization energy (ASE) calculations predict that **191** (E = B; G = N) and **191** (E = B; G = P) are equally aromatic, while the contrary is predicted by magnetic susceptibility exaltation (MSE) and by NICS data at the B3LYP/6-31*G level. MSE data predict that all compounds **191** with G = P are strongly aromatic, and the ones with G = As are borderline aromatic, while the ones with G = N are not aromatic. Despite the predicted aromatic properties, calculations for compounds **191** indicated nonplanar geometries. Also, the same calculations showed differences in compounds of type **192**; for instance, none of the compounds are aromatic according to NICS values, while MSE values indicate aromatic character for **192** (E = B; J = S, Se), **192** (E = Al; J = O, Se), and **192** (E = Ga; J = S). For all these compounds, MSE values are more than half of the MSE value for benzene.

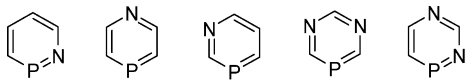
Scheme 74. Analogues of Borazine, $E_2G_3H_6$ (E = B, Al, Ga; G = N, P, As) and $E_3J_3H_3$ (J = O, S, Se), and Phosphazenes



191 **192** **193**

Derivatives of monoaza- and diaza-phosphinines **194**−**198** have been synthesized by Frison and Le Floch (Scheme 75).[235] Calculations performed on such systems using geometric and NICS criteria are indicative of the CH-by-N replacement effects on the aromaticity and reactivity of phosphinines. The study shows that the introduction of nitrogen atoms at the position adjacent to phosphorus (**194** and **198**) significantly reduces the aromatic delocalization and induces a [1,4]dipolar character through an increase of the positive charge on the phosphorus atom compared to compounds **196** and **197**, which display a poor dipolar character. Aromaticities were also estimated by calculations of the single and double bond lengths at the B3LYP/6-31*G level, using the DFT/B3LYP method (Gaussian 94).[235] Pyridine and phosphinine were used as reference compounds. As in the previous example, although calculations show aromaticity of the phosphorus derivatives, their rings are not planar (ring contractions and lower internal angles are always observed). NICS values suggest that aromaticity in the compounds of Scheme 75 is lower than in pyridine and phosphinine, in agreement with bond length calculations.

Scheme 75. Aza- and Diazaphosphinines



194 **195** **196** **197** **198**

Other congeners of phosphinins—arsenin, antimonin, and bismin—have been shown to be definitely less aromatic than benzene by diverse theoretical treatments that have been reviewed.[236] For instance, the Bird aromaticity index for arsenin was found to be 67, compared to 100 for benzene.[123] Table 4 summarizes a few parameters used to estimate the aromaticity of heterobenzenes: resonance energies

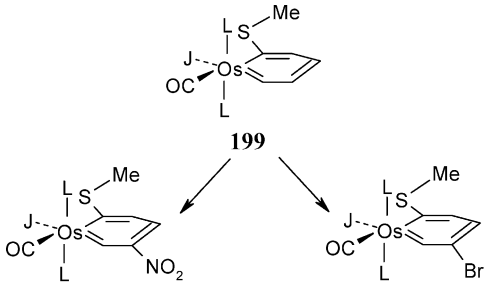
Table 4. Aromaticity of Heterobenzenes

Property	Unit	Benzene	Pyridine	Phosphorin	Arsenin	Antimonin
						
Resonance energies [237]	eV	0.821	0.618	0.661	0.545	0.607
Dipole moments, calc. [238]	D	0	2.13	0.94	0.74	
Dipole moments, exp. [238]	D	0	2.20	1.54	1.10	
Delocalization enthalpies [239]	kcal/mol	61.3	64.0	56.6	53.9	50.5

from π-electron potentials calculated from UV photoelectron spectra (Herndon[237]), dipole moments (Schweig[238]), and delocalization enthalpies (Baldridge and Gordon[239]).

Metallabenzenes (M = Os, Ir) (Scheme 76) have been synthesized and their structures determined by X-ray. The compounds are planar and have NMR spectra and geometries indicative of aromatic character.[240−242] Recently, osmabenzene derivatives **199** were shown to undergo electrophilic substitutions, affording nitro (**200**) and bromo (**201**) derivatives (Scheme 76).[243] However, some reactions are at

Scheme 76. Electrophilic Aromatic Substitutions of Osmabenzene

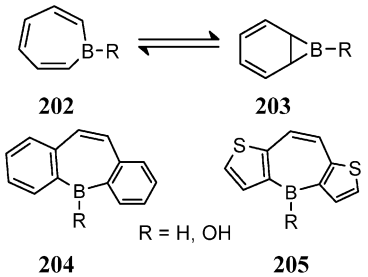


variance with the aromaticity, namely cycloadditions and rearrangement to cyclopentadienyl complexes.[243] Other metallabenzenes are unstable with respect to rearrangement to cyclopentadienyl-metal complexes. Thus, comparing a ruthenabenzene, a ruthenanaphthalene oxide, and a ruthenaphenanthrene oxide, it was found that ruthenabenzene decomposed by carbene migratory insertion, but the process is significantly slower than in the other two ruthenium derivatives, a fact which could be explained by the aromatic stabilization of ruthenabenzene.[244]

3.6. Known and Potential Monocyclic Seven-Membered-Ring Heteroaromatics

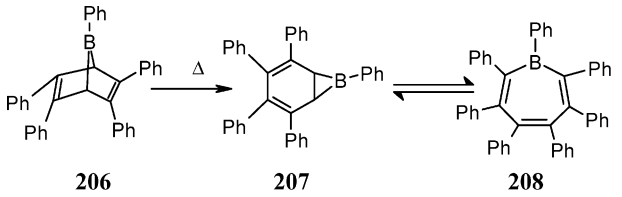
Borepin is the heterocyclic analogue of the tropylium cation with a π-electron sextet. Few borepin derivatives have been reported: a monocyclic 1-methylborepin **202**,[245] benzo derivatives **204**,[246] and a dithienoborepin **205**[247] (Scheme 77). Heptaphenyl-

Scheme 77. Borepin Derivatives



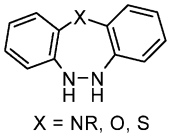
borepin (**208**) is also aromatic,[248] and is in equilibrium with the bora-norcaradienic derivative **207** (Scheme 78). Its stability is proved by the thermal isomerization of **206**.

Scheme 78. Heptaphenylborepin



It is also possible to construct seven-membered aromatic heterocycles with a π-electron decet if the heteroatoms have sufficient electronegativity to produce seven bonding orbitals with 10 π-electrons, as in compounds of type **209** (Scheme 79). For thio derivative **209** (X = S, Scheme 79), ^{1}H NMR data show deshielded NH protons compared to the system with X = CH_2, a fact which was explained by aromatic delocalization.[249]

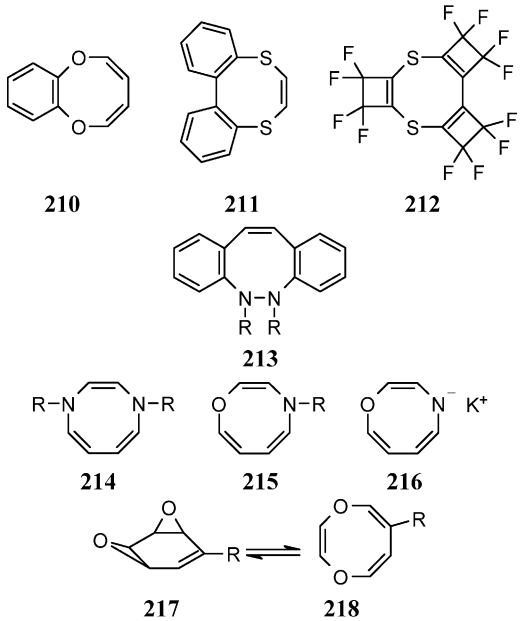
Scheme 79. Seven-Membered Rings with Heteroatoms



3.7. Known and Potential Monocyclic Eight-Membered-Ring Heteroaromatics

On the basis of topological criteria, Balaban predicted in 1965 the aromaticity of compounds with 10-π-electron systems in eight-membered rings with two heteroatoms (analogous to the cyclooctatetraene dianion).[250] Schroth and co-workers were among the first to investigate the systems experimentally, and they synthesized compounds **210**−**213** (Scheme 80).[251−255]

Scheme 80. Eight-Membered Rings with Heteroatoms



1,4-Diazocines of type **214** (Scheme 80) were synthesized by Vogel and co-workers:[256] when R is a

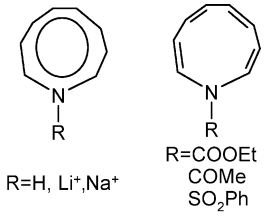
donor group, the molecule is aromatic and a ring current is evidenced by NMR. When R is an acceptor group such as arylsulfonyl, the compound is nonplanar and shows no ring current.

Prinzbach and co-workers prepared 1,4-oxazocines **215**. Comparisons of NMR data allowed assumptions on the aromaticity of these compounds compared to 1,4-dihydrodiazocines. Compounds with NH and N-alkyl are planar and diatropic, while the N-tosyl derivative is nonplanar.[257] NMR data for anion **216** are in agreement with an aromatic stabilization.[257,258] 1,4-Dioxocines **218** are in turn paratropic and exist in equilibrium with their $2\sigma \rightarrow 2\pi$ valence isomers: *syn*-benzene dioxides **217** (Scheme 80).[259] Their chemistry and behavior in magnetic fields have been evaluated.[260,261]

3.8. Known and Potential Monocyclic Nine-Membered and Larger Rings

Reviews on medium-ring nitrogen heterocycles including azonines have been published.[262−264] Azonines **219** (Scheme 81) are aromatic if the electron lone pair is available to form a conjugated 10-π-electron system. Azonines such as **220** with acceptor R groups, where this lone pair is involved in exocyclic conjugation, do not exhibit diamagnetic ring currents and are anti-aromatic.

Scheme 81. Azonines



219 **220**

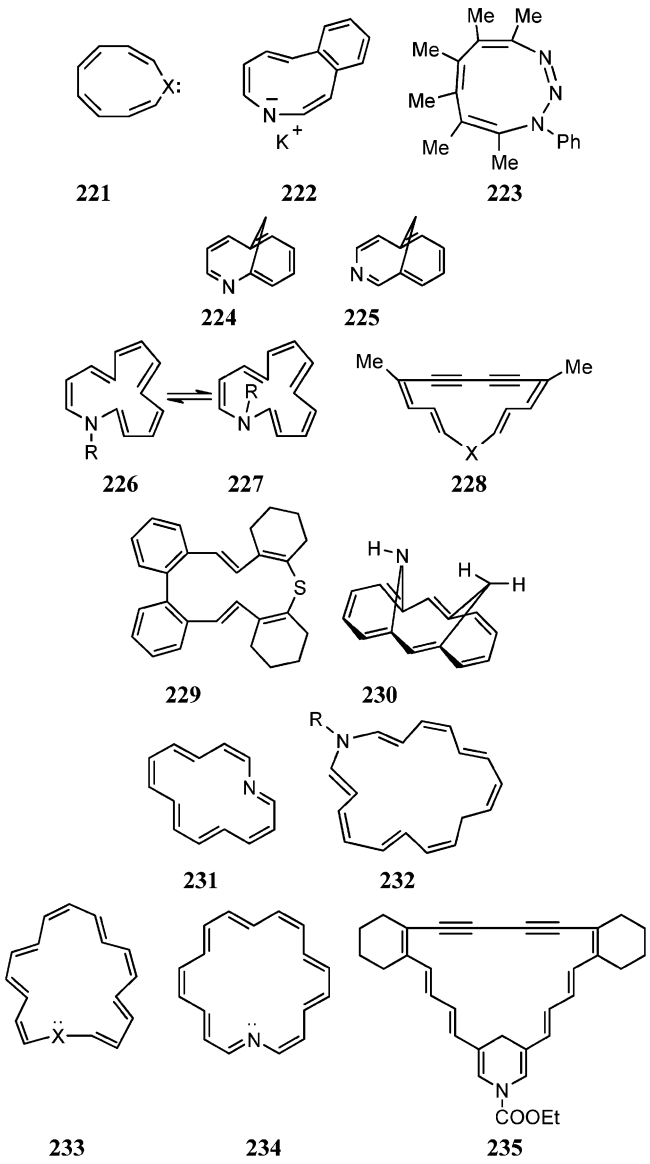
The chemistry and properties of heteronins **221** (Scheme 82) have been reviewed.[264−266] These compounds are thermally stable and possess delocalized planar molecules with strong diamagnetic ring currents.[267a] Schleyer and co-workers calculated by ab initio and density functional methods aromatic stabilization energies as well as other properties of heteronins, and found that only **221** anions with X = N and P are aromatic and planar.[267b]

The benzo-annulated heteronin anion **222** (Scheme 82) exhibits an aromatic character, as shown by ^{1}H NMR spectral data.[266] Heptamethyl-1-phenyl-1,2,3-triazonine (**223**) has a 10-π-electron system and is a stable compound.[268]

Diatropic systems result when nitrogen heteroatoms are introduced in bridged [10]- (**224**, **225**), [13]- (**226**−**230**), [14]- (**230**, **231**), and [17]annulenes **232** and **233**, which have been extensively reviewed.[269]

NMR data for aza[18]annulene **234** show a wide separation between the centers of the inner and outer proton ^{1}H NMR multiplets ($\Delta\delta = 11$ ppm), indicative of a strong diamagnetic ring current.[270,271] The bisdehydro system **235** with 22 π-electrons in the aromatic ring is diatropic.[272]

Scheme 82. Nine-Membered and Larger Rings with Heteroatoms



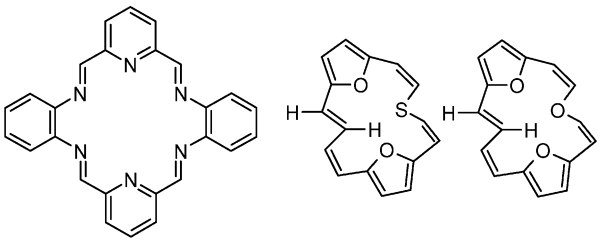
221 **222** **223** **224** **225** **226** **227** **228** **229** **230** **231** **232** **233** **234** **235**

3.9. Bicyclic and Polycyclic Hetarenes

Boron-containing macrocycles have become of large interest. Gimarc's topological charge stabilization was shown by Schleyer to operate for anionic and neutral *closo*-mono/di-carbaboranes, $CB_{n-1}H_n^-$ and $C_2B_{n-2}H_n$.[273,274] Comprehensive ab initio calculations at the RMP2(fc)/6-31*G level showed that the relative energies on positional isomers generally increase when the cluster size is increased from $n = 5$ to $n = 12$ vertices and exhibit a higher stability and three-dimensional aromaticity on the basis of NICS values and magnetic susceptibility. An open question is whether similar systems with $n > 12$ will be accessible.

A bispyridine derivative of dibenzo-hexaaza[18]-annulene **236** was prepared by Bell and Guzzo.[275] Furan building blocks were used in the syntheses of the diatropic compounds **237** and **238**.[276−278] The chemical shifts of the indicated hydrogens show that the diamagnetic ring current decreases in the order **237** > **238** (Scheme 83).

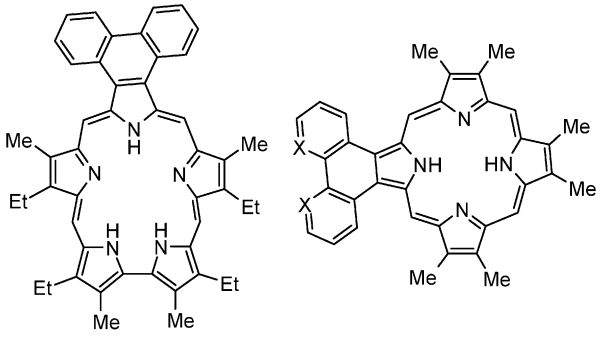
Scheme 83. Annulenes with Pyridines and Furan Building Blocks



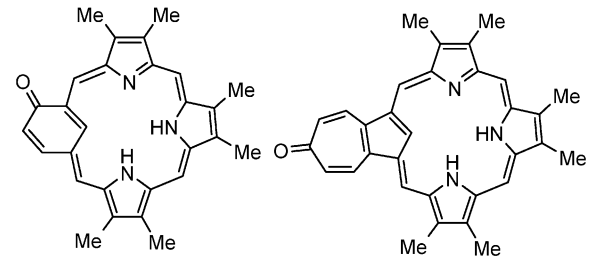
236 **237** **238**

The porphyrin ring system remains a fascinating one because of its high biological significance as a carrier for oxygen and carbon dioxide when chelating iron. Photosynthesis is all-important for present-day life on earth and depends on chlorophyll, which has magnesium in the center of a porphyrin ring. When one fully understands its role in light-harvesting systems,[279,280] many practical applications will follow.[281] Recently, other heteroatoms, such as O, S, and Se, have been introduced in the porphyrin ring,[282−284] producing compounds with potential biological applications (Scheme 84). Expanded porphyrins and their heteroanalogues have also been reviewed in connection with their potential biomedical applications. The aromaticity of porphyrins is well established.[269]

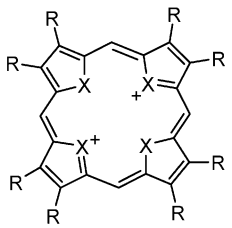
Scheme 84. Porphyrins



239 **240**



241 **242**



243

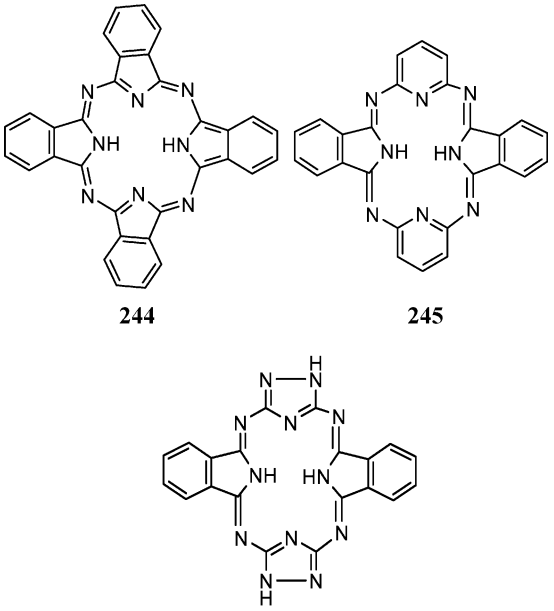
Self-aggregation of porphyrins with or without coordinated central metallic ions such as zinc has been an intensely investigated area for synthesizing new supramolecular assemblies and nanostructures. A successful approach has used natural and synthetic porphyrins with hydroxyl and ketonic groups, where the aggregation was triggered by hydrogen-bonding.[285]

The aromatic nature of porphyrins is proven by the presence of strong diamagnetic ring currents in the proton NMR spectra. For instance, the ^{1}H NMR spectrum of compound **240** showed a strong diatropic ring current with a broad signal at −8 ppm for the internal NH, which confirms the 22-π-electron delocalization.[286a] The replacement of one of the pyrrole rings with a carbocycle (i.e., **241** and **242**, Scheme 84) preserves the aromaticity, as shown by diatropic ring currents.[286b] In the presence of acid the effect is enhanced, due to the capability of the aromatic system to allow charge delocalization. Oxonia analogues of type **243** (X = O, Scheme 84) are 18-π-electron aromatic systems with electronic spectra similar to those of porphyrins. The presence of the strong diamagnetic ring current is confirmed in the ^{1}H NMR spectra by the upfield shift of the inner CH to −7 ppm, and the downfield shift of the *meso*-protons between 8.80 and 10.30 ppm.[284] Recently, T. S. Balaban et al. have tailored porphyrins for self-assembly by mimicking natural bacteriochlorophylls that form the chlorosomal light-harvesting system.[287a,b] Also, they have shown that the central metal is an additional stereocenter, and that diastereotopic ligation of chlorophylls within a protein environment must have a structural role, which has been conserved during evolution.[287c]

Phthalocyanines **244** and hemiporphyrins **245** and **246** are aromatic systems. Extended conjugation confers special properties to these molecules that make them building blocks for new molecular organic materials with useful electric and nonlinear optical applications (Scheme 85).[288]

Heterofullerenes and congeneric cage molecules with spherical aromaticity have recently attracted considerable attention. The dimer $(C_{59}N)_2$ can be oxidized by breaking the C(sp^3)−C(sp^3) bond, affording a salt of $C_{59}N^+$ silver(I) biscarborane anion: $C_{59}N^+[Ag(CB_{11}H_6Cl_6)_2]$.[289] Azafullerenes were synthesized by Wudl's and Hirsch's research groups and reviewed by them.[290,291] Prediction of extended aromaticity in $C_{48}N_{12}$ azafullerene structure was performed by quantum-mechanical calculations at the density functional B3LYP/6-31G* level.[292] Both the monoaza-[60]- and -[70]fullerenes are now known; as dimers, diazafullerenes $C_{58}N_2$ are stable diamagnetic monomeric compounds.[290−293] Bond resonance energies were used for predicting kinetic (in)stability of heterofullerenes; borafullerenes are predicted to be kinetically unstable.[294] Schleyer and co-workers computed aromatic stabilization energies using GIAO−B3LYP for various heterofullerenes $C_{48}X_{12}$ (X = N, P, B, Si) and found that both the global aromaticity and the presence of Clar-type triphenylene units contribute to stabilize positional isomers differing in the distribution of heteroatoms.[295]

Scheme 85



Hirsch and co-workers calculated NICS values for tetrahedral clusters of N, P, As, Sb, and Bi, as well as for the corresponding tetra-anions composed of Si, Ge, Sn, or Pb atoms, finding diatropic values for $2n(n+1)$ π-systems.[296a,b] It was postulated by Hirsch, Schleyer, and their co-workers that for icosahedral fullerenes and their hetero-analogues the Hückel rule, involving $4n+2$ π-electrons, should be replaced by the $2(n+1)^2$ electron rule.[296]

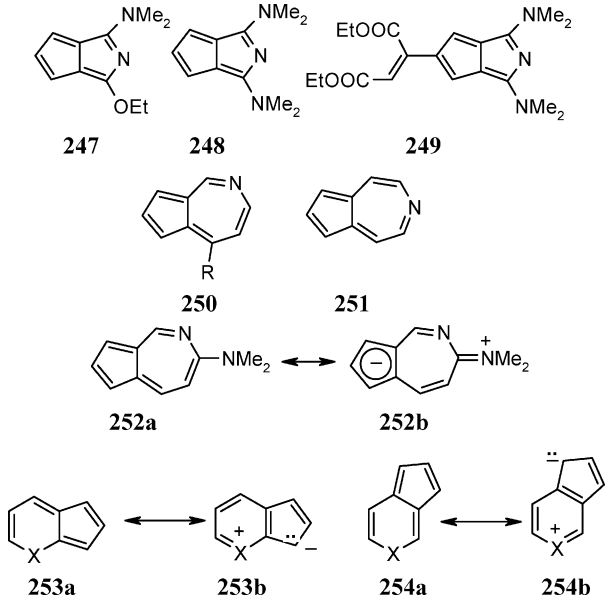
In the same way as for C_{60} and C_{70} fullerenes, boron clusters with magic numbers B_5^+ and B_{13}^+ appear as prominent peaks in mass spectra. These boron clusters were calculated for various geometries by several authors and were considered to present 3D aromatic stabilization.[297−299]

3.10. Heterobicyclic Systems with Zero-Atom Bridges

Heteroatom-containing derivatives of pentalene and azulene are 8- and 10-π-electron systems, respectively, and have been extensively studied by Hafner and co-workers.[301−304] A few examples are presented in Schemes 30, 47, and 86. Electron-rich azapentalenes **247**−**249**[305,306] and various aza-azulenes **250**−**252**[300−302] have intense colors and are stable but oxygen-sensitive compounds. Azulenes with nitrogen heteroatoms placed in positions with high electron density, such as position 5, or positions 5 and 7, present a hypsochromic effect, while a heteroatom in position 6, with low electron density, exerts a bathochromic effect. When both types of positions are substituted by heteroatoms, their effect is canceled out.[307] The bond lengths in **252** (Scheme 86), as determined by X-ray, indicate delocalization as in **252a** and **252b**.[308,309]

By adding one X-type heteroatom in pentalenes, one can obtain-10 π-electron systems such as **253** and **254** similar to azulenes, called pseudoazulenes.[310]

Scheme 86. Pentalenes and Azulenes



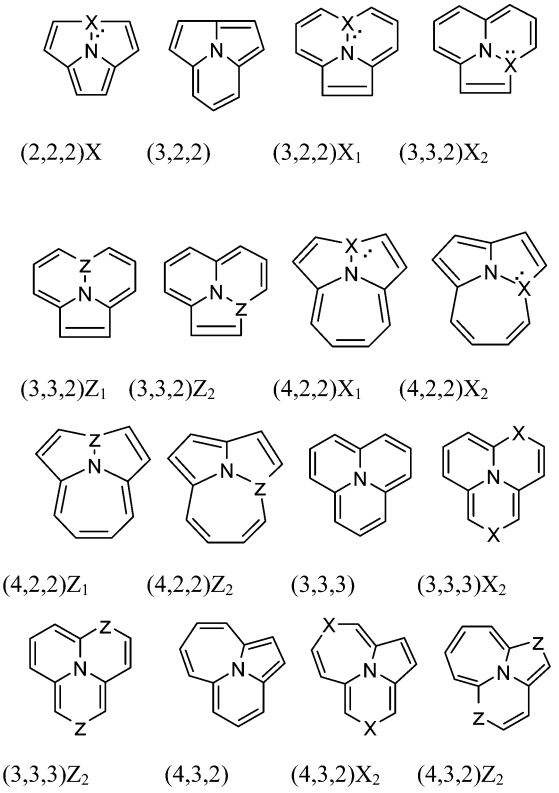
There are early reviews discussing the chemistry and properties of pseudoazulenes.[311,312] Unsubstituted pseudoazulenes are rather unstable, but benzocondensation and substituents stabilize the molecule, for the latter in agreement with the electronegativities of the heteroatoms. No Diels−Alder reactions occur between pseudoazulenes and dienes, a fact which is consistent with a certain degree of aromaticity. A pseudoazulene with a pyranic ring was formed from benzyl and cyclopentadiene with sodium methoxide.[313]

3.11. Cyclazines and Related Annulenes

According to Boekelheide, cyclazines are molecules having a conjugated sp^2-hybridized periphery connected by three covalent bonds to an internal nitrogen atom.[314] Cyclazines are related to both annulenes and *peri*-condensed systems such as phenalenyl (*peri*-naphthalenyl) or aceindenyl.[315,316] The theoretical possibilities are listed in Table 5.[316]

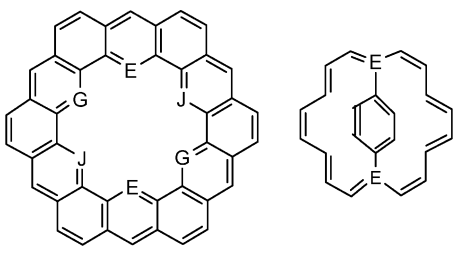
Theoretical calculations show that an annulene perimeter could act as a potential host for stabilizing novel structures such as a planar carbon atom.[317,318] Also, a π-system may be enclosed inside the annulene perimeter.[319] It was shown, however, by Staab and Diederich that kekulene (**255**, E = G = J = CH) does not consist of two concentric annulene perimeters.[319] Katritzky and Marson[320] synthesized an oxonia congener and obtained dodecahydro-18,21-dioxoniakekulene **255** ($E = O^+$; G = J = CH). Balaban[321] discussed the properties of aza analogues with E, G, or J being CH and/or N groups. The possibility of "choker-annulenes" **256** (E = C) has been discussed in the literature as a potential aromatic system,[322] but the attempted synthesis of a bis-azonia derivative of **256** (E = N) with four annelated six-membered rings (by condensing *para*-phenylenebis(2,6-dimethyl-4-phenylpyridium) cations with *o*-phthaldialdehyde) failed to produce conclusive results (Scheme 87).

Table 5. Theoretical Possibilities for Cycl[*a*,*b*,*c*]azines with $9 \le m \le 12$



formula	peripheral atoms *a*	*b*	*c*	*m*	*X*	*Z*	no. of peripheral π-electrons	predicted character
(2,2,2)X	2	2	2	9	1	0	10	aromatic
(3,2,2)	3	2	2	10	0	0	10	aromatic
$(3,2,2)X_1$	3	3	2	11	1	0	12	anti-aromatic
$(3,3,2)X_2$	3	3	2	11	1	0	12	anti-aromatic
$(3,3,2)Z_1$	3	3	2	11	0	1	10	aromatic
$(3,3,2)Z_2$	3	3	2	11	0	1	10	aromatic
$(4,2,2)X_1$	4	2	2	11	1	0	12	anti-aromatic
$(4,2,2)X_2$	4	2	2	11	1	0	12	anti-aromatic
$(4,2,2)Z_1$	4	2	2	11	0	1	10	aromatic
$(4,2,2)Z_2$	4	2	2	11	0	1	10	aromatic
(3,3,3)	3	3	3	12	0	0	12	anti-aromatic
$(3,3,3)X_2$	3	3	3	12	2	0	14	aromatic
$(3,3,3)Z_2$	3	3	3	12	0	2	10	aromatic
(4,3,2)	3	3	3	12	0	2	10	aromatic
$(4,3,2)X_2$	4	3	2	12	2	0	14	aromatic
$(4,3,2)Z_2$	4	3	2	12	0	2	10	aromatic

Scheme 87. Heteroanulenes



255 **256**

4. General Conclusion

A large proportion of the known organic compounds are heteroaromatic, and their number will certainly increase. Nucleic acid bases and the majority of natural alkaloids and of medicinal drugs contain heteroaromatic groups. Combinatorial chemistry and high-throughput screening are focused on druglike molecules that are predominantly heteroaromatic.

Heterocyclic chemistry offers a much wider prospect for exploring the possibilities and limitations of the aromaticity concept than hydrocarbon chemistry. As a result, quantitative measures for aromaticity have been devised, and improved molecular calculation methods allow for a better evaluation of the experimental data already obtained and predictions of novel aromatic heterocycles.

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