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Quantitative Measures of Aromaticity for Mono-, Bi-, and Tricyclic Penta- and Hexaatomic Heteroaromatic Ring Systems and Their Interrelationships

Alan R. Katritzky*

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200

Karl Jug

Theoretische Chemie, Universität Hannover Am Kleinen Felde 30, 30167 Hannover, Germany

Daniela C. Oniciu

Esperion Therapeutics, Inc., 3621 S. State St., Ann Arbor, Michigan 48108

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Contents

I. The Significance of Quantitative Measures of Aromaticity

It would be inconceivable to attempt to teach or practice organic chemistry in any serious manner without utilizing the concept of aromaticity.[1−6] Turning to heterocyclic chemistry, here the concept of aromaticity is truly a cornerstone,[7,8] and all treatments of the subject from the simple (e.g., ref 9) to the advanced (e.g., refs 10−12) rely heavily on the classification of compounds according to their possession of and indeed their degree of aromaticity. This despite the fact that, as recently documented by Anderson and Bauer,[13] some popular American general organic texts do not provide a clear treatment of aromaticity.

The characteristics that distinguish an aromatic from a nonaromatic compound have been realized for a very long time:

(1) cyclic compound with a large resonance energy (RE);

(2) tendency to react by substitution rather than addition;

(3) aromatic sextet and reversion to type (R. Robinson);

(4) $4n + 2$ π electrons (Hückel rule);

(5) ability to sustain a diamagnetic ring current.

Cyclic compounds are routinely divided into aromatic, nonaromatic, and antiaromatic (Scheme 1), and this qualitative distinction is usually quite clear. However, it is also well recognized that aromaticity is a quantitative as well as a qualitative concept. Thus, as shown in Scheme 2, some compounds are clearly more aromatic than others, and accordingly much effort has gone into attempts to provide quan-

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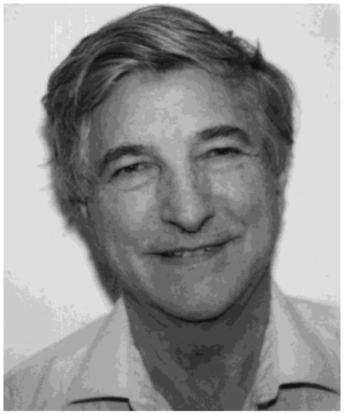
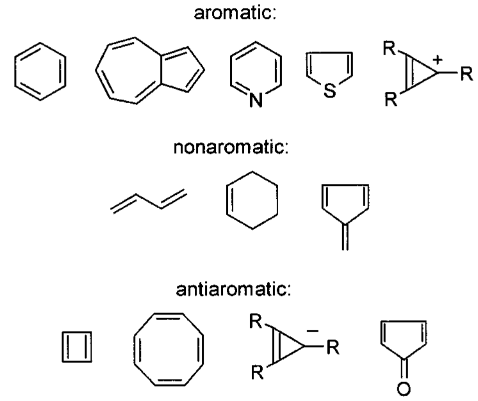


Alan Katritzky grew up in England, but in mid-career he migrated to the United States where he is Kenan Professor of Chemistry and Director of the Florida Institute of Heterocyclic Compounds at the University of Florida. His group is active in various aspects of heterocyclic and computational chemistry, with particularly good connections internationally and industrially. The series of Florida Conferences on Heterocyclic Chemistry that he has initiated, brings together those interested from many parts of the world each March to the Florida campus. For full details, see the Web site at www.arkat.org.

Karl Jug was born in Essen, Germany, in 1939. He studied physics in Frankfurt/Main, where he received his Diploma in physics in 1964 and his Dr. phil. nat. in physical chemistry in 1965. His research work, under the direction of Hermann Hartmann, was on quantum chemical modeling of the spectra of inorganic and organic compounds. From 1965 to 1967, he was head of staff of Theoretica Chimica Acta in Frankfurt/Main before he moved to the IIT in Chicago to work with Peter Lykos. He was Assistant Professor in 1969 and Associate Professor in 1971 at St. Louis University. He returned to Germany in 1975 to take up a position as Professor of Theoretical Chemistry at the University of Hannover. His research interests have focused on the development of semiempirical methods and the theoretical basis of chemical concepts (charge, bonding, diradicals, aromaticity). In applied work, he has been concerned with thermal and photochemical reactions of organic compounds, the structures and reactivities of organic and inorganic compounds and clusters, the cluster simulation of solid-state surfaces, and heterogeneous catalysis.

Daniela Carmen Oniciu received her M.S. in organic chemistry and chemical engineering from the University "Polytechnica" of Bucharest (Romania) in 1980. After completing an industrial training, compulsory in the communist times, she worked as a Senior Scientist in radioimmunochemistry at the Institute of Endocrinology in Bucharest. 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 in Alachua, Florida, as Director of Chemistry, working in pharmaceutical research and development. Since February 2001, she has been the Director of Chemistry at Esper*ion* 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.

Scheme 1. Examples of Aromatic, Nonaromatic, and Antiaromatic Compounds



titative measures of aromaticity. The quantitative assessment of the aromaticity of heterocycles has been reviewed previously.[6,14,15] The present review attempts to bring this subject up-to-date.

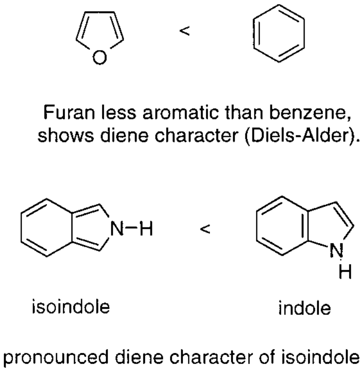
Heterocycles with conjugated π systems have a propensity to react as saturated rather than as unsaturated systems. The most familiar qualitative expression of the aromaticity of heteroaromatic systems is their reaction by electrophilic substitutions. However, the presence of two or more heteroatoms tends to decrease the electron availability at the ring carbons of a heteroaromatic compound and thus render it less sensitive to electrophilic substitution. The quantitative expression of aromaticity in terms of chemical reactivity is complicated especially by the interplay of thermodynamic and kinetic factors. Thus, although a number of chemical techniques have been applied, physical methods are generally used to provide a quantitative measure of aromaticity.

The principal methods applied to try to obtain quantitative measures of aromaticity may be divided into four main groups:[15−17]

(1) experimental measurements of the energy (heat of formation) of aromatic compounds and comparison of this with the estimated heat of formation of a hypothetical model analogue lacking cyclic conjugation;

(2) experimental measurement of the geometries of aromatic compounds and their comparison with geometries of nonaromatic analogues either measured or estimated;

Scheme 2. Obvious Differences in Quantitative Aromaticity in Heterocycles



(3) experimental measurement of magnetic properties of aromatic compounds and comparison with those expected for nonaromatic analogues;

(4) quantum chemical calculations corresponding to all of these experimental approaches.

The quantification of the aromaticity encounters inherent inconsistencies and discrepancies caused by the nature of the measured parameters and/or by the aggregation state where the measurement was taken. Theoretical approximations also bring inconsistencies explicitly, as related to the definition of the nonaromatic model to be compared with the aromatic compound, and implicitly because of differences in the electronic structures of heteroatoms and carbon. These problems render the measurement, and indeed the definition, of quantitative measures of aromaticity subjective and contentious. We try in the present treatment to present an unbiased overview.

II. Energy-Based Measures of Aromaticity

Empirical resonance energy (ERE) values for heteroaromatic systems have, in the main, been obtained from heat of combustion and heat of hydrogenation data. The difficulty in quantitatively hydrogenating many heterocycles has rendered the latter approach rather less generally applicable than the former. Errors in the experimental determination of heats of combustion are normally of the order of 0.5 kcal/mol, and are somewhat larger than those of heat of hydrogenation data. More serious uncertainty in earlier determinations may have arisen during the estimation of the thermochemical data for the localized model, particularly when calculating the heat of formation from values of bond energies for bonds between carbon and heteroatoms. Calculations normally rely further on the assumption that thermochemical bond energy terms are additive and tend to neglect other contributions to energies such as ring strains.

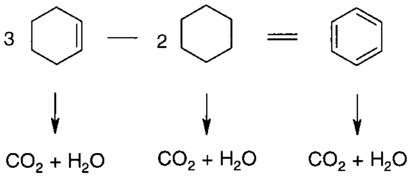
Most modern treatments of thermodynamical data rely on the use of isodesmic, homodesmic, and hyperhomodesmic reactions: an excellent background to such treatment has been given earlier.[15]

A. From Heats of Reactions

i. Combustion

Combustion and hydrogenation were among the first methods used to measure aromatic stabilization energies, by direct measurement of ΔH values.[18] Combustion analysis utilizes the approach shown in Scheme 3 for benzene,[19] which was further applied to pyridine.[14] These methods need to be applied with caution to heterocycles. In combustions, the presence of nitrogen atoms can lead to significant errors due to the formation of nitrogen oxides and oxyacids, which can in turn give secondary reactions with the equipment, as illustrated by Scheme 4. Table 1 displays the results of such early determinations of aromaticity by combustion,[19] showing the large experimental errors found for combustion. Discrepancies in the early resonance energy values also arose from inconsistencies in the selection of the localized models and from experimental limitations. Nevertheless, the order of aromaticity observed was always benzene > thiophene > pyrrole > furan (Table 1).[21−23]

Scheme 3. Aromaticity of Benzene by Combustion[19]



Scheme 4. Complications in the Measurement of the Aromaticity of Pyridine by Combustion[14]

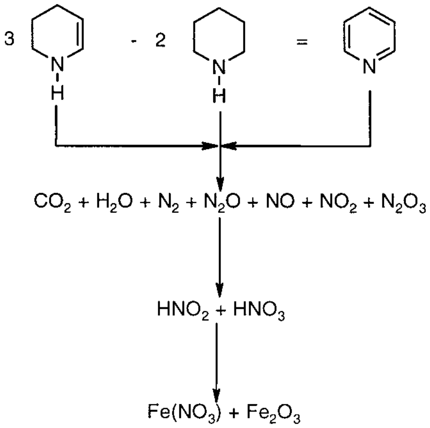


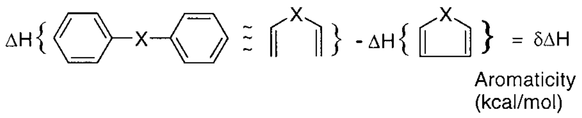
Table 1. Quantitative Measurement of Aromaticity from Heats of Combustion and Hydrogenation (Cited)[12,20−24]

	combustion (kcal/mol)	hydrogenation (kcal/mol)
benzene	36−37	36
pyridine	23−43	
thiophene	24−31	29
furan	16−23	22
pyrrole	14−31	
pyrazine		8−24
pyridazine		12
pyrimidine		8

More recently, many of these difficulties have been overcome. The enthalpies of formation for heterocycles can now be measured very accurately using the static bomb combustion calorimetry method,[24] the vacuum sublimation drop calorimetry method,[25] and the Knudsen-effusion method.[26,27] In this way, accurate enthalpies of formation for four azoles—1-methylimidazole, 1-methylpyrazole, 1-benzimidazole, and 1-benzylpyrazole—were measured,[27] and their total, relative, and zero-point vibrational energies were calculated. Enthalpies of formation of N-substituted imidazoles and pyrazoles were initially calculated from the corresponding atomization reactions at 298 K in gas phase. If isodesmic reactions are used (i.e., the number of bonds between each pair of atom types is preserved), the deviations from experimental values are reduced compared to calculations based on atomization energies. The calculated enthalpies were in good agreement with the experimental data for the N-substituted imidazole series and in less good agreement for the N-substituted pyrazole series.

Hosmane, Liebman, and co-workers have elaborated[28-30] an experimental model for the quantitative estimation of aromaticity based on the Dewar–Breslow definition[31,32] and the thermochemical relationship of substituted benzenes and ethylenes (Scheme 5). The model is based on the assumption that $\delta\Delta H$ as expressed in Scheme 5 is a measure of the relative aromaticity of heterocycles. Experimental heats of formation for compounds of type Ph-X-Ph are available, as these derivatives are easier to synthesize than their acyclic counterparts, and calculations were therefore possible for a set of five- and six-membered heterocycles with N- and O-heteroatoms. The calculated values of relative aromaticity for these ring systems are presented in Table 2. The model predicts that benzene is more aromatic than azines or azoles, and it is in agreement with the observation that both types of compounds deviate considerably from benzene in electrophilic and nucleophilic aromatic substitutions. The results obtained by this method correlate with those computed on the basis of other criteria of aromaticity. The method was generalized for one ring species by the quantitative equation displayed in Scheme 6.[30]

Scheme 5. Hosmane–Liebman Treatment of the Heteroaromaticity[29]



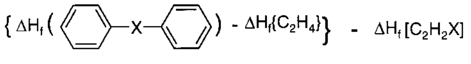
ii. Hydrogenation

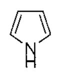
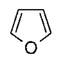
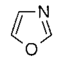
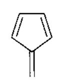
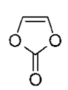
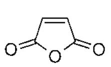
The application of hydrogenation to aromaticity determination is exemplified in Scheme 7 for benzene.[19] However, in hydrogenations, compounds containing nitrogen and sulfur atoms can poison the catalyst;[19] therefore, errors are significant and the method has limited applications (see Table 1 for early results).

iii. Dehydration

An alternative method for the estimation of aromaticity is from heats of dehydration.[33] Calorimetric determinations of heats of dehydration showed that isoxazole derivatives dehydrate less readily than the corresponding pyrazoles and pyrroles, which dehydrate on recrystallization. This phenomenon suggests that isoxazole is less aromatic. Heat changes recorded on dissolving hydroxy-dihydro derivatives [Arom-HOH] (ΔH_A) and the corresponding aromatic compounds [AromH] (ΔH_A) in sulfuric acid and in chloroform (as an inert solvent) were used to relate the

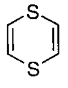
Table 2. Prediction of Relative Aromaticities Based on the Dewar–Breslow Model[29]



		[A]	[C]	
Heterocycle	X	Acyclic [A] - Cyclic [C] = ΔHf (g)	ΔHf (g)	Rel. Aromaticity δΔHf (kcal/mol)
	-CH=CH-NH-	(68.0-12.5)	25.8	29.7
	-CH=CH-O-	(28.2-12.5)	-8.3	24.0
	-N=CH-O-	(27.9-12.5)	-37.0	19.0
	-CH=CH-C=CH$_2$	(70.7-12.5)	44.4	13.8
	-O-C(O)-O-	(-74.4-12.5)	-100	13.1
	-CH=CH-CH$_2$-	54.6-12.5	32.1	10.0
	-C(O)-O-C(O)-	(76.2-12.5)	-95.1	6.4

Scheme 6. Hosmane–Liebman Model of Heteroaromaticity Exemplified for 1,4- and 1,2-Dithiin[30]

$$\text{cyclo-}\sum_{i=1}^{N}(\text{CH=CH})_{n_i}X^i + \sum_{i=1}^{N}(n_i-1)H_2 \rightarrow \sum_{i=1}^{N}[(\text{CH}_2\text{=CH})_2X^i + (n_i-2)C_2H_4]$$

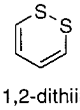


$N = 2$, $n_1 = n_2 = 1$, $X^1 = X^2 = S$

1,4-dithiin

$$\text{cyclo-1,4-(CH=CH)}_2S_2 \rightarrow 2(\text{CH}_2\text{=CH})_2S\text{-}2C_2H_4$$

$$\text{cyclo-1,4-(CH=CH)}_2S_2 + 2C_2H_4 \rightarrow 2(\text{CH}_2\text{=CH})_2S$$

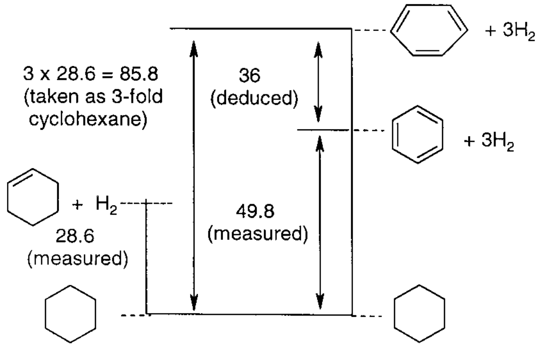


$N = 1$, $n_1 = n = 2$, $X^1 = X =$ -SS-

1,2-dithiin

$$\text{cyclo-1,2-(CH=CH)}_2S_2 \rightarrow (\text{CH}_2\text{=CH})_2SS$$

Scheme 7. Heats of Hydrogenation To Assess the Aromaticity of Benzene[19]

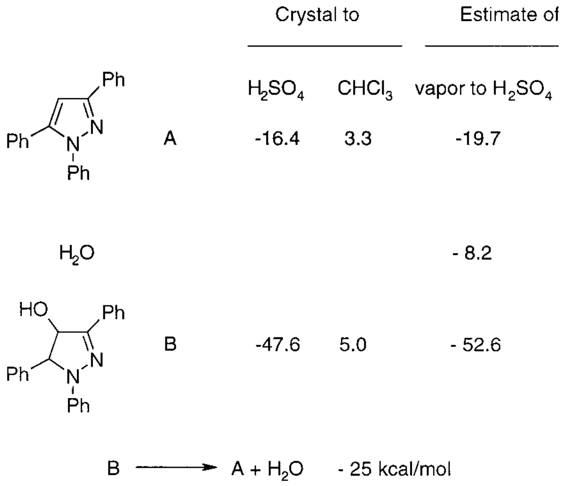


E_R = 3 x 28.6 - 49.8 = 36 kcal/mol

heat of dissolution to the heat of vaporization/sublimation.

The heats of dehydration (determined with a precision of ±3 kcal/mol) were used for empirical resonance energy (ERE) evaluations, taking into account the approximations described in Schemes 8 and 9.

Scheme 8. Resonance Energy of Pyrazole from Heats of Dehydration[33]



Resonance energy of pyrazole: 25 + 4* - 3# = 26 kcal/mol

* N - N = C resonance in B (approximated to enamine resonance energy)

5-Ph/ring resonance in A (approximated from the difference in ERE of styrene and benzene)

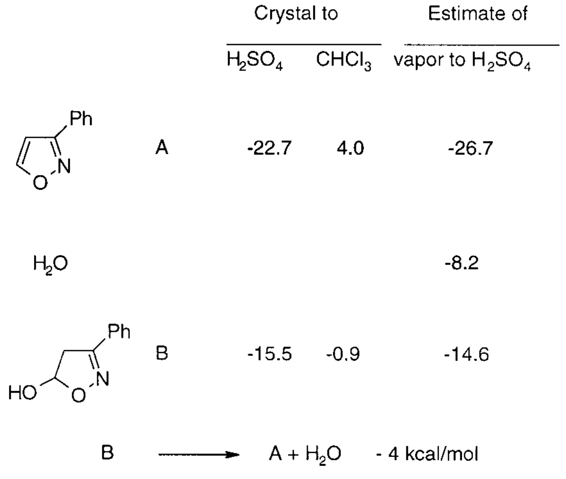
The conjugation energies for pyrazole and isoxazole bonded to a 5-phenyl substituent were approximated to 14 and 1 kcal/mol, respectively, lower than the ones reported for pyrrole (15 kcal/mol) and benzene (22 kcal/mol). Both ERE and conjugation energies obtained for pyrazole and isoxazole show that while pyrazole and pyrrole have comparable resonance stabilization, isoxazole is less aromatic.

B. From Equilibria

i. Protonation Equilibria

The hydrogenation or combustion procedures considered above measure ΔH directly. By contrast, methods depending on the study of equilibria measure ΔG. It is therefore necessary to convert ΔG values to ΔH values. As discussed in detail earlier,[6,14] alternative methods for this conversion include the following:

Scheme 9. Resonance Energy of Isoxazole from Heats of Dehydration[33]



Resonance energy of isoxazole: 4 + 4* = ca 8 kcal/mol

* O - N = C resonance in B

(1) utilization of measured temperature variations of K_T values;

(2) using temperature variations of basicities;

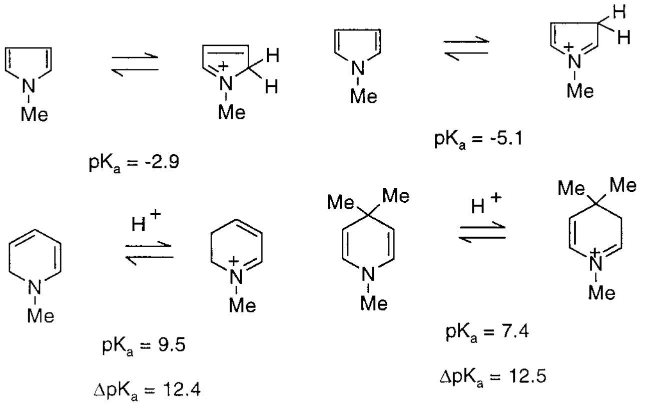
(3) taking ΔG as an approximation for ΔH_{int} which excludes solvent interactions as suggested by Larson and Hepler;[34]

(4) from a general consideration of the variation of acidity functions with temperature[35] which suggests that $\Delta H = 1.1\ \Delta pK_a$.

Unfortunately, very few experimental measurements of temperature variations of basicities, and still fewer of K_T, are available, which precludes the general use of methods 1 and 2. Therefore method 4 has generally been used to estimate ΔH values for measured ΔG.

Pyrrole is a very weak base, whose low basicity compared to enamines is a consequence of the loss on protonation of aromaticity in all possible tautomeric forms of its cation (Scheme 10). Measured pK_a

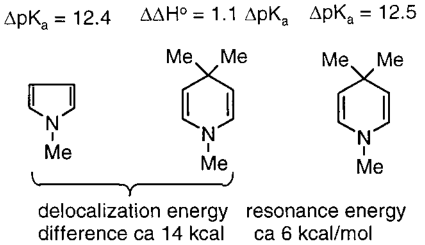
Scheme 10. Basicity of Pyrrole[36]



values show that both N and C-methylation enhance the ring basicity. The aromatic resonance energy for pyrrole was estimated by conversion of the linear free energy relationship $\Delta\Delta G°$ (i.e., ΔpK_a) into $\Delta\Delta H°$ values. On the basis of literature values and pK_a determinations, it was found that the resonance energy of *N*-methylpyrrole is ca. 20 kcal/mol.

The somewhat similar, but nonaromatic, compounds, 1,2- and 1,4-dihydropyridine, are both much stronger bases, which undergo protonation as also shown in Scheme 10.[36] The differences between the basicities of pyrrole and the model compounds can be used to calculate the aromatic stabilization energy of pyrrole, according to the method of Scheme 11.[36–38]

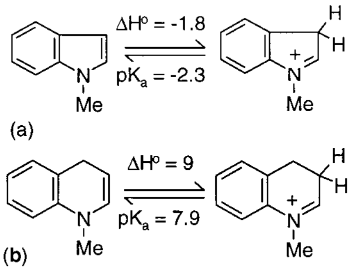
Scheme 11. Aromaticity of Pyrrole[36]



Resonance energy for pyrrole: ca 20 kcal/mol

Using analogous comparisons, similar differences of basicities have been used to determine the aromaticity of other heteroaromatics, including indole (Scheme 12), carbazole, and indolizidine.[36] For instance, the pK_a value for indole is −2.32. This value is compared with the one for the nonconjugated model (pK_a = 7.9) and, assuming that the resonance energy of the latter is 42 kcal/mol, the computed resonance energy is 53 kcal/mol, in agreement with earlier published similarly calculated values (43.5 kcal/mol) and thermodynamical data (41.8 to 57.6 kcal/mol).[38]

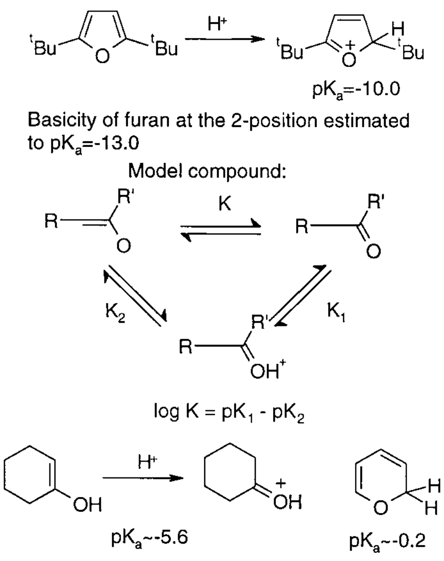
Scheme 12. Aromaticity of Indole[36]



ΔpKa = 10.2 compared to ΔH° of 11
Resonance energy for (**b**):
36 (benzene) + 6 kcal/mol = 42 kcal/mol
Resonance energy for indole: *ca* 53 kcal/mol

The basicity method has also been applied to furans, although this is more difficult because of the very low basicity of furan and the need to grapple with the additional complication of the definition of acidity functions in these strongly acidic regions—see Scheme 13.[36] The resonance energy for 2,5-di-*tert*-butylfuran was estimated from the pK_a value for half-protonation and from the basicities of furan and the model nonconjugated dienol-ether. The basicity of 2,5-di-*tert*-butylfuran was measured by UV and was found to be of ca. −10; the pK_a value for furan itself at the 2-position was estimated to be −13. The enthalpy of formation was evaluated from the pK_a value and then was compared with the model nonconjugated dienol-ether, as described in Scheme 13.[36] The keto−enol tautomerism equilibrium constant for cyclohexanone can be estimated from kinetic data as 2.0×10^5, which provides a value of −0.2 for the pK_a of the model enol ether. Assuming that the resonance stabilization is comparable with the one for the model X = N-Me described in Scheme 13, the total resonance stabilization energy for furan is 18 kcal/mol.

Scheme 13. Aromaticity of Furans[36]



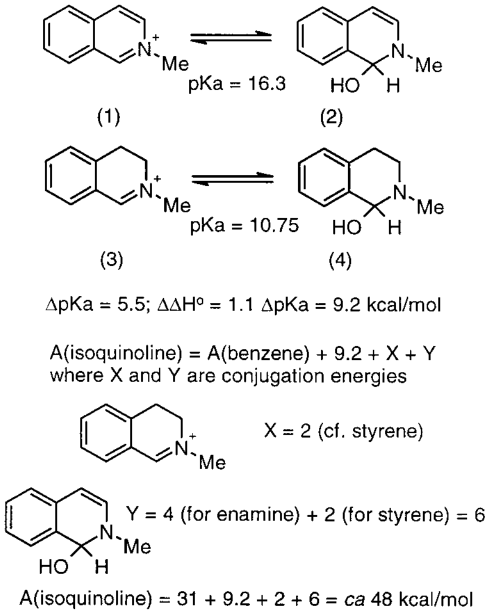
Aromaticity of furan: 14 kcal/mol
Stabilization of dienol: ca 4 kcal/mol
Resonance energy for furan: ca 18 kcal/mol

ii. Pseudo-Base Equilibria

Application of the above-mentioned basicity method is limited, and it can be applied only to systems whose aromaticities are destroyed on protonation. Heteroaromatics such as pyridine and quinoline conserve their aromaticity during protonation; therefore a different method is applied, that of considering the basicities of pseudo-bases derived from *N*-methylheteroaromatic cations and the corresponding nonaromatic analogues.[37] The principle is shown for isoquinoline in Scheme 14. The model compound used for comparison is 2-methyl-3,4-dihydroisoquinolinium cation. The pK_a values for the equilibrium **1** ⇆ **2** and **3** ⇆ **4** were measured; they correspond to an enthalpy difference $\Delta H°$ of 9.2 kcal/mol (*X* and *Y* are the differences in the resonance energies between **1** and benzene and **3** and benzene, respectively).

Correction was made for the additional resonance energy for styrene over that of benzene as ca. 2 kcal. The final resonance energy value for the isoquinolinium cation is 48 kcal/mol, when corrections are made for this and for the conjugation energies of the fragments (shown in Scheme 14, second part).[37]

Scheme 14. Aromaticity and Pseudo-Base Equilibria[37]



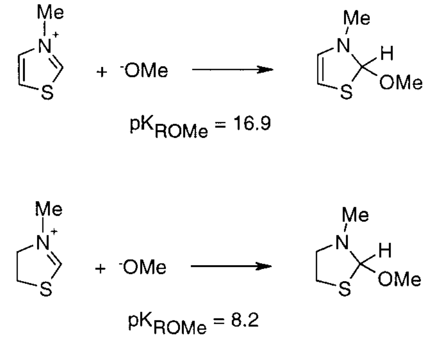
ΔpKa = 5.5; ΔΔH° = 1.1 ΔpKa = 9.2 kcal/mol

A(isoquinoline) = A(benzene) + 9.2 + X + Y
where X and Y are conjugation energies

A(isoquinoline) = 31 + 9.2 + 2 + 6 = *ca* 48 kcal/mol

This method has been extended to pseudo-bases derived from the azoles as illustrated for thiazole (Scheme 15).[39] The equilibrium constants for pseudo-base formation of the five-membered ring cations were determined from their absorptions in the UV region. The resonance energy (ERE) for the thiazolium cation was calculated in connection with the study of the aromaticity. The conjugation energy for the model dihydrothiazolium cation was approximated as described in Scheme 15.

Scheme 15. Thiazolium Pseudo-Bases[39]



Assuming ΔH° = 1.1 ΔpK_a
$A_{thiazolium}$ = 1.1 (16.9 - 8.2) + 10* ~ 20 kcal/mol

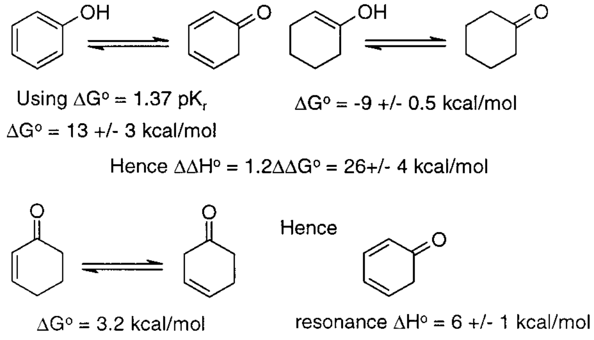
* rough estimate of resonance interaction in thiazolium pseudo-base

iii. Tautomeric Equilibria and Related Approaches

Many heterocycles containing two or more heteroatoms can exist in more than one tautomeric form. Both external (polarity of the solvent, intramolecular hydrogen bonding) and internal (relative resonance stabilization of the conjugated system, stabilities of the functionalities) factors influence such tautomeric equilibria. For five- and six-membered rings, frequently more than one tautomer preserves the aromatic character.[40] Comparisons of tautomeric equilibria in the alicyclic series with those of aromatic compounds allow calculations of the stabilization energies. When these models are applied in the heteroaromatic series, restrictions are induced by the medium. The aromaticities of 2-pyridone and 2-quinolone were thus estimated on the basis of tautomeric equilibrium constants in aqueous solutions,[40] as is explained below.

a. Benzene. Because of its aromaticity, phenol exists as such in the hydroxy form and not as cyclohexadienone whereas cyclohexanone exists as such in the carbonyl form and not as cyclohexenol. By comparing the tautomeric equilibrium constants, it is possible to derive a measure of this stabilization energy. Scheme 16 describes the calculation of the $\Delta G°$ values for the aromatic ring of phenol on the basis of tautomeric equilibrium constants.[37] When $\Delta G°$ values can be converted into $\Delta H°$ values, the resonance energy differences between two structures can be determined. The value found for the benzene aromatic resonance energy (32 kcal/mol) is in agreement with other experimental and calculated data.

Scheme 16. Aromaticity Resonance: Energy of Benzene as Calculated from Tautomeric Equilibria[37]



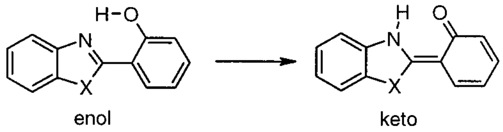
So, aromaticity of benzene = 32 +/- 5 kcal/mol

Recently, an ab initio 6-31*G basis set calculation reaffirmed that phenol is significantly more stable than both 2,4- and 2,5-cyclohexadienone.[41] Total electronic energies at 0 K and thermodynamic parameters were calculated for phenol, 2,4-cyclohexadienone, and 2,5-cyclohexadienone. Energy calculations were performed using the restricted Hartree–Fock (RHF) and second-order Møller–Plesset formalisms on the RHF optimized geometries. The study has shown the following: (i) phenol is more stable than the two ketones by around 18 kcal/mol; (ii) the ketone with the C-sp^3 para to the carbonyl is slightly less stable than the one with the C-sp^3 ortho to the carbonyl; (iii) thermodynamic data calculated for the ketones versus the enol forms for the three species confirm the already known fact that phenol is more stable in the enolic form (Scheme 16).

The equilibrium constant calculated from the ΔH values for the equilibrium phenol $\rightleftharpoons$ 2,4-cyclohexadienone was 2×10^{-13}, i.e., $pK_T = 12.7$, in agreement with other experimental data.[37] The calculation was for the gas phase; however, the equilibrium constant for the tautomerization agreed with experimental results for aqueous solution. This example confirms that the aromaticity is actually the driving force in setting the course of the tautomeric equilibrium.

The aromatic character of the phenol ring explains the higher stability of the enol form with respect to the keto form in the ground state.[42] Variations in the aromatic character (induced by substitution or heteroatoms) influence the forward and reverse energy barriers for the proton transfer between the keto and enol forms. Thus, it has been found for 2-(2′-hydroxyphenyl)imidazole (Scheme 17) that the energy differences between the keto and enol form in the ground and excited states are quite large, which are consequences of the stabilization brought by aromaticity in the six-membered ring of the enol form in the ground state.

Scheme 17. Keto-Enol Tautomerism of 2(2′-Hydroxyphenyl)benzimidazole[42]

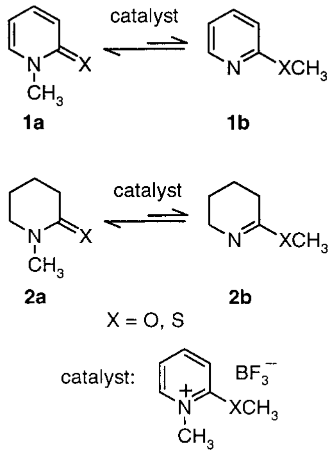


b. Pyridones. The quantitative difference in empirical resonance energy between two tautomeric forms has been estimated by comparing with appropriate models for the hypothetical localized systems: (1) heteroaromatic tautomeric equilibria and (2) equilibria in which a methyl group shifts.

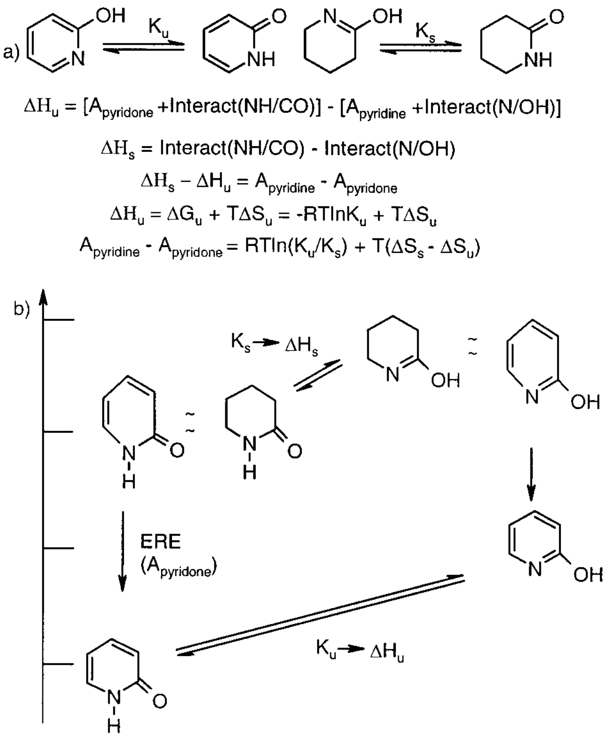
Beak et al.[43] determined calorimetrically ΔH° for the equilibrium between *N*-methyl-2-pyridone (**1a**, X = O) and 2-methoxypyridine (**1b**, X = O) ($\Delta H_{\mathrm{deloc}}^\circ$) and also for that between the saturated analogues (**2a**,**b**, X = O) ($\Delta H_{\mathrm{loc}}^\circ$). Equilibrations were performed using catalytic amounts of the appropriate common alkylated derivatives. The ERE of 2-methoxypyridine was found to be 6 ± 7 kcal/mol greater than that of *N*-methyl-2-pyridone. Difficulties in equilibrating the aliphatic models required for other determinations limit the general applicability of this method.[44] *N*-Methyl-2-thiopyridone (**1a**, X = S) and 2-methylthiopyridine (**1b**, X = S) have been equilibrated, however, and the latter predominates. Tautomeric equilibrium constants determined from ionization constants for the corresponding protomeric isomer pair, by contrast, indicate predominance of the NH-tautomer.

External factors as well as internal factors influence the tautomeric equilibria of compounds such as 2-pyridone:[46] the high dependence on the medium implies that aromatic stability also depends on the medium. Comparison of the tautomeric equilibium constant for 2-pyridone with that for tetrahydro-2-pyridone taken as a model allows estimation of the difference between the aromatic stabilization energies of 2-hydroxypyridine and 2-pyridone in aqueous solution. The calculation procedure is shown in Scheme 18 and the corresponding energy diagram in Scheme 19.[45] The aromaticity of 2-pyridone was calculated on the basis of the tautomeric equilibrium, considering as a nonconjugated model the equilibrium between tetrahydropyridone and the corresponding enol. Evidence was presented that the NH/CO interactions are comparable in the saturated and unsaturated systems as are those of N/COH interactions.

Scheme 18. Tautomeric Equilibria[43,44]



Scheme 19. Estimation of the Aromaticity of 2-Pyridone on the Basis of Tautomeric Equilibrium Constants;[45] Aromatic Resonance Energy for 2-Pyridone[45]



$$\Delta H_u = [A_{\mathrm{pyridone}} + \mathrm{Interact(NH/CO)}] - [A_{\mathrm{pyridine}} + \mathrm{Interact(N/OH)}]$$

$$\Delta H_s = \mathrm{Interact(NH/CO)} - \mathrm{Interact(N/OH)}$$

$$\Delta H_s - \Delta H_u = A_{\mathrm{pyridine}} - A_{\mathrm{pyridone}}$$

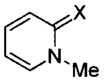
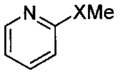
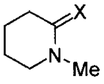
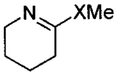
$$\Delta H_u = \Delta G_u + T\Delta S_u = -RT\ln K_u + T\Delta S_u$$

$$A_{\mathrm{pyridine}} - A_{\mathrm{pyridone}} = RT\ln(K_u/K_s) + T(\Delta S_s - \Delta S_u)$$

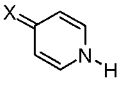
The ΔH° values obtained as described in Scheme 20 demonstrate that 2-pyridone and 2-pyridinethione retain most of the aromatic resonance energy of pyridine, and that 2-pyridone imine is also strongly aromatic, while 2-pyridone methide is much less so.

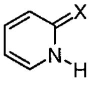
Combining these results with the aromatic stabilization energies deduced as described above for the parent pyridine, quinoline, and isoquinoline molecules, gives the differences in the aromatic resonance stabilizations for these pyridone-like compounds as compared to the parent heterocycle (Scheme 21).[45,47,48] The results show that aromatic resonance energies for pyridines are similar in the 2- and 4-series. For bicylic compounds such as quinolines

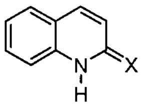
Scheme 20. Results for the Aromaticity of 2-Pyridone and Related Compounds[45]

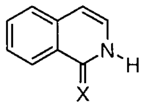
X	 pK$_a$	 pK$_a$	ΔG$_u$ kcal/mol	 pK$_a$	 pK$_a$	ΔG$_s$ kcal/mol	ΔG$_u$-ΔG$_s$ kcal/mol
S	-1.22	3.62	-6.7	-1.76	6.9	-12.0	5.3
O	0.32	3.28	-4.1	0.19	7.5	-10.0	6.5
NH	13.02	6.86	8.5	Assumed equal by symmetry		0.0	8.5
CH$_2$	19.8	5.97	19.0	11.4	9.43	2.7	16.3

Scheme 21. Comparison of Aromatic Resonance Energy Differences for Heterocycles (kcal/mol)[45,47,48]









X	A$_{pyridine}$ - A$_{pyridone}$		A$_{quinoline}$ - A$_{quinolone}$	A$_{isoquinoline}$ - A$_{isoquinolone}$
	2-series	4-series		
S	6	-	3	4
O	7.5	8	2	4
NH	10	10	5	6
CH$_2$	18	20	7.5	7

and isoquinolines, differences in aromaticity between the (iso)quinolinoid and (iso)quinolonoid structures are significantly reduced.

C. From Theoretical Concepts

Ever since the work of Hückel[49−51] on the stability of π electron systems and the famous $4n + 2$ rule for ring systems, energetic criteria have remained a basic measure for the characterization of aromaticity. In molecular orbital (MO) theory, a delocalization energy (DE) can be defined as the difference between the energy E_{loc} of a model system with localized π electron pair bonds and the energy E_{del} of the real system with a delocalized π electron distribution.

$$DE = E_{loc} - E_{del} \tag{1}$$

The various approaches for DE differ in the way in which E_{loc} and E_{del} are calculated.

Alternatively, the valence bond (VB) theory provides an original basis for the definition of the resonance energy (RE) which is considered as the difference between the energy E_{SVB} of a state described by a single valence bond structure and the energy E_{MVB} of the true state described by a linear combination of many valence bond structures.[52]

$$RE = E_{SVB} - E_{MVB} \tag{2}$$

Eventually, the ideas of delocalization energy DE and resonance energy RE were mixed and interchangeably used.

The simplest approximation to the delocalization energy is on the level of the Hückel method. For benzene the energy of the delocalized π electron system can be described as the sum of the orbital energies of the three doubly occupied orbitals. For the localized system, the π electron energy of three ethylene molecules is chosen.

$$DE = 3(2\alpha + 2\beta) - 2(\alpha + 2\beta) - 4(\alpha + \beta) = -2\beta \tag{3}$$

The delocalization energy is always positive. On this level, it was considered as a measure of the stabilization of the ring system by the delocalization of the π electrons. We shall address this point later. Since the reference to three ethylenes and the restriction to π electrons are rather artificial, the idea of resonance energy rather then delocalization energy was mostly pursued. In this context, the idea of an empirical resonance energy was introduced.[52,53] Here the assumption is made that the energy of a single valence bond structure can be described as the sum of contributions of bond energies of single and multiple bonds. Tables of bond energies permit the calculation of the heats of formation of molecules to which a single VB structure can be assigned.[52]

The difference between the observed heat of formation and that calculated for a single VB structure of a molecule based on bond energies is called an empirical resonance energy ERE. For benzene, the reference is a hypothetical molecule with a Kekulé structure involving noninteracting double bonds. The empirical resonance energy of benzene is, in this case, 37 kcal/mol.[52] If different bond energies are used for C−H, C−C, and C═C bonds, an empirical resonance energy of 64.4 kcal/mol may appear.[53]

Because of the implicit and incorrect assumption that average bond energies are independent of environment, resonance energies based on such a simplifying assumption may not be reliable. It was shown, however, that a linear relationship can be found between the empirical RE and the DE/β from the Hückel method.[53] Then, the next step would be to distinguish between empirical resonance energy and the vertical resonance energy. The former refers to a reference with alternating single and double bonds, the hypothetical hexatriene, whereas the latter makes reference to the unchanged benzene structure, but with single and double carbon−carbon bonds for the bond length of benzene. This latter procedure is based on the statement that a valence bond resonance structure of benzene must possess the same geometry as the total system. With an estimated distortion energy of 27 kcal/mol for the conversion of the cyclohexatriene structure to the benzene structure with single and double bonds,[54] a vertical resonance energy of 64 kcal/mol is obtained from an empirical resonance energy of 37 kcal/mol. Streitwieser points out that the vertical resonance energy corresponds more exactly to the delocalization energy.

Resonance energies on the molecular orbital level were introduced by Brickstock and Pople[55] on the semiempirical self-consistent field (SCF) level.[56] Dewar improved such resonance energies on the molecular orbital level by the consideration of σ electrons. π Binding energies were calculated by the semiempirical π electron method derived from Pople's SCF approach,[56] and bond energies for σ bonds were added to arrive at heats of formation. Initially a common value for the σ bond energy for C−C bonds[57,58] and C−N bonds[59] was used and a resonance energy derived.

To improve the situation with the average reference bond energies, Dewar and co-workers developed a new scheme for the calculation of bond energies. The Dewar resonance energy (DRE) was defined for hydrocarbons as follows:

$$\begin{aligned}\mathrm{DRE} = \Delta H^{\mathrm{C}} - \Delta H = {} & N'E' + N''E'' - N_{\mathrm{CC}}E_{\mathrm{CC}} - E_{\pi\mathrm{b}} = \\ & N_{\mathrm{CC}}\Big[-E_{\mathrm{CC}} + \frac{1}{2}(E'' + E') - \\ & \frac{1}{2}(E'' - E')(N' - N'')/N_{\mathrm{CC}}\Big] - E_{\pi\mathrm{b}} \end{aligned} \quad (4)$$

Here ΔH is the heat of formation of a hydrocarbon

$$\Delta H = NE_{\mathrm{CH}} + N_{\mathrm{CC}}\,E_{\mathrm{CC}} + E_{\pi\mathrm{b}} \quad (5)$$

and ΔH^{C} the heat of formation of a classical structure

$$\Delta H^{\mathrm{C}} = NE_{\mathrm{CH}} + N'E' + N''E'' \quad (6)$$

N' is the number of single C−C bonds of bond energy E', and N'' the number of double bonds of energy E''. N_{CC} is the number of C−C bonds in a conjugated system with a common bond energy E_{CC}. $E_{\pi\mathrm{b}}$ is the total π electron energy. The contributions of C−H bonds cancel out in eq 4.

The bond distance dependence of the reference energies was explicitly accounted for.[60,61] Here the standard bond energies E_{CC} were corrected by compression energies c' and c'' using the Morse functions

$$\begin{aligned} c' &= E_{\mathrm{C-C}}(1 - \mathrm{e}^{-a'(r'-r)})^2 \\ c'' &= E_{\mathrm{C=C}}(1 - \mathrm{e}^{-a''(r''-r)})^2 \end{aligned} \quad (7)$$

The constants a' and a'' are determined by force constants of the bonds and the bond energies. This was necessary in the case of polyenes, where the bond lengths vary greatly. Whereas the σ bond energies were initially adjustable parameters to fit heats of formation for a selected number of compounds, they were now calculated directly as a function of the bond length. In this way, a smaller value of 20 kcal/mol was obtained for the resonance energy of benzene. It was found that even the Hückel method would give quite reasonable results for resonance energies of aromatic compounds, once the β parameter was fitted to a so-called experimental resonance energy. However, the Hückel method failed to differentiate between aromatic and nonaromatic compounds,[61] whereas the Dewar resonance energies (DRE) arrived at small positive values for nonaromatic and negative values for antiaromatic compounds.

The question of an energetic criterion for aromaticity was revived on the Hückel level by Hess and Schaad.[62−67] They estimated it by a chemical procedure similar to Dewar who had found that the bond energies of acyclic polyenes are additive.[58] Therefore the total energy of an acyclic polyene can be calculated as the sum of all bond energies. Using these bond energies one can calculate the energies of artificially localized structures of cyclic polyenes and obtain resonance energies. Hess and Schaad used the same approach at the Hückel level. First, they showed that the total π energy of linear polyenes is indeed additive[62] by plotting the HMO π energies versus the number of carbon−carbon single bonds. They used the slopes and intercepts of the resulting straight lines to calculate $E^{\pi}{}_{\mathrm{C-C}}$ and $E^{\pi}{}_{\mathrm{C=C}}$ values. Since these values were different for different kinds of polyenes, they introduced five types of carbon−carbon double bonds and three types of carbon−carbon single bonds. The values for these eight types of bonds were obtained by a least-squares fitting procedure for the eight π bond energies involving more than eight acyclic compounds. With this reference scheme, the Hess−Schaad resonance energy (HSRE) for a compound energy was obtained as

$$\mathrm{HSRE} = E_{\mathrm{HMO}} - E_{\mathrm{loc}} \quad (8)$$

Because of the wide variation in the size of molecules, Hess and Schaad suggested that a better way to compare the resonance energy per electron (REPE), which is normalized to the number n of electrons:[62]

$$\mathrm{REPE} = \mathrm{RE}/n \tag{9}$$

Only on the latter scale is benzene more aromatic than naphthalene or other large benzenoid hydrocarbons.

It is most significant that in this procedure negative resonance energies appear for antiaromatic compounds. This was not possible with the simple Hückel expression of eq 1, where any localized structure including cyclobutadiene would have a vanishing delocalization energy.

In a subsequent paper,[63] Hess and Schaad compared their REPE values with those generated from Dewar's resonance energies. The major difference is that Dewar values are given in eV, whereas their own values are given in units of β. Hess and Schaad finally furnished a comparison of HSRE per electron (HSREPE), DRE per electron (DREPE), and DE with p band frequencies of benzenoid hydrocarbons and found that HSREPE has a better linear relationship than DREPE and that DE totally fails to establish a linear relationship. Numerous applications followed.[64−68]

Encouraged by the success of the Hess−Schaad approach on the Hückel level, a topological approach was advanced by the Zagreb group[69−73] and by Aihara.[74,75] It is based on the computation of an acyclic polynomial in the framework of graph theory.[73] This is used to describe the acyclic polyene-like reference structure. The topological resonance energy (TRE) is defined as

$$\mathrm{TRE} = \sum_{j=1}^{N} g_j\,(x_j - x_j^{\mathrm{ac}}) \tag{10}$$

Here N is the number of vertices in a graph (which corresponds to the number of atoms in a conjugated molecule), x_j are the roots of the characteristic polynomial of the aromatic system, and x_j^{ac} are the roots of the acyclic polynomial of the polyene-like reference system. In essence this corresponds to the procedure of the Hückel method to solve for the eigenvalues x_j of the Hückel matrix in units of β. Finally, g_j is the orbital occupancy number. The method was applied to a large number of conjugated hydrocarbons[71,72] with results for TREPE that usually show a similar trend as the HSREPE values. Aihara[76,77] extended the concept to three-dimensional systems, in particular polyhedral boranes. However, soon afterward, controversial difficulties arose with this approach.[78−81]

In particular, Heilbronner questioned the compatibility of the topological resonance energy with the HMO model and with chemical experience. Quite disturbing was also the failure to account for the properties of oxocarbon systems. It was claimed not only that $C_3O_3^{2-}$ is aromatic, but also that C_3O_3 is aromatic or nonaromatic depending on the parameters used.[82] This was criticized by one of us,[83] because C_3O_3 should be antiaromatic by the Hückel rule and is not even stable in a structural optimization, which resulted in fragmentation into three CO molecules.

After the advent of Dewar and Hess−Schaad resonance energies on the basis of the MO theory, a new VB approach to the resonance energy was advanced.[84−86] The method is rather formalistic in using VB structures in a way similar to how the old Hückel method used connectivity. For benzenoid hydrocarbons, a linear relationship between these VB resonance energies and the DRE values could be established.

Eventually the idea of resonance energy was carried over to ab initio methods.[87] Besides the discussion of basis set and correlation dependence, a most interesting development was the quantitative distinction of a vertical and an adiabatic excitation energy. Resonance energies of conjugated hydrocarbons were calculated as the energy difference between ab initio SCF energy and the energy expectation value with respect to a model wave function in which the SCF π orbitals were replaced by noninteracting localized π MOs as reference state. The delocalized orbitals were localized with the Boys procedure and then truncated.

$$\mathrm{KRE_v} = E_{\mathrm{loc}}{}^{\mathrm{v}} - E_{\mathrm{del}}$$
$$\mathrm{KRE_a} = E_{\mathrm{loc}}{}^{\mathrm{a}} - E_{\mathrm{del}} \tag{11}$$

The σ orbitals were allowed to relax. The SCF energy and the energy of the reference state of benzene were studied as a function of the C−C distance. This procedure allowed a natural distinction between the vertical and adiabatic resonance energy. Later this method was improved by a new localization technique[88] where not only the separation of σ and π electrons was introduced in the Fock matrix by their corresponding σ and π blocks, but also the π electrons could be localized by setting off-diagonal elements of nonresonating atoms in the reference molecules equal to zero. The π part of the Fock matrix was separated into several blocks, one for each localized part of the molecule. The localized blocks of π electrons were separated by fictitious walls, which they cannot penetrate. In this way, vertical and adiabatic delocalization energies were defined and calculated on a semiempirical level.

$$\mathrm{JDE_v} = E_{\mathrm{loc}}{}^{\mathrm{v}} - E_{\mathrm{del}}$$
$$\mathrm{JDE_a} = E_{\mathrm{loc}}{}^{\mathrm{a}} - E_{\mathrm{del}} \tag{12}$$

The KRE values and the JDE values for benzene are very similar, but larger than the HSRE values. Finally, the $\mathrm{JDE_a}$ values were normalized to the number of separating walls to achieve a better comparison for π electron systems of different size similar to that done by REPE. In this way a large variety of ring compounds including antiaromatic systems could be classified.

For five-membered heteroaromatic compounds, it was found[89] that the extent of the transfer of electron density from the p_z orbital of the heteroatom to the ring of the π system is the best measure of the aromaticity of these heterocycles.

Theoretical calculations supplement the limited number of reference thermodynamic quantities derived from experimental measurements of hydrogenation and combustion; such data are needed to deduce aromatic stabilization energies. Enthalpies of formation were computed for *N*-substituted pyrazoles and imidazoles[27] using G2(MP2) and B3LYP/6-311*G-(3df,2p)//6-31G(d) approaches, and they were compared with experimental enthalpies of formation measured by various calorimetric methods. Heats of formation for tetrazole derivatives[90] were calculated with the ab initio density functional theory (DFT)-B3LYP methods by means of designed isodemic and isogyric reactions. The 6-31G(d) basis set (B3LYP/6-31*G calculational level) was used to calculate enthalpies of formation and strain energy values for three- and five-membered nitrogen and phosphorus heterocycles,[91] diazasiloles,[92] five-membered nitrogen heterocycles[93] (using the GAUSSIAN 94 package), *N*- and *C*-substituted pyrazoles,[94] and hypervalent sulfur heterocycles[95] (using the GAUSSIAN 92 package).

III. Geometry-Based Measures of Aromaticity

The geometrical criteria of aromaticity are structurally based. They all rely on the idea that the essential factor in aromatic stabilization is the π delocalization and its manifestations: planar geometry, equalization of the bonds lengths and angles, and symmetry. The empirical nature of these geometrical criteria imply that the methods could be less useful for molecules containing novel types of chemical bonds.

A. Krygowski HOMA Indices and Their Forerunners

Attempts to relate aromaticity to structure occurred much later than the early development of energy criteria for aromaticity. It is obvious that bond alternation reduces the aromaticity. The bond lengths in benzene are all equal which is not true for most other conjugated hydrocarbon ring systems. The use of this intuitive idea to define an aromaticity index was by Julg and François,[96,97] who suggested an index *A* of the following type:

$$A = 1-225/n \sum_{r,s} (1 - d_{rs}/\bar{d})^2 \qquad (13)$$

Here d_{rs} is the bond length of the $C_r{-}C_s$ bond, and $\bar{d}$ is the average bond length in the ring system; n is the number of electrons. This formula results in a reference value of 1 for equal ring bond lengths. This definition suffers from several defects: (a) all compounds with equal bonds lengths have the same aromaticity index 1, e.g., benzene, cyclopentadienyl anion, borazine; (b) different types of bonds such as C−C, C−N, or C−O bonds cannot be properly compared, because the bond length does not reflect the corresponding bond order; (c) a clear distinction between aromatic, nonaromatic, and antiaromatic compounds is not possible. This holds even if inner ring bonds in multiple-ring systems are considered along with the peripheral bonds.

A big step forward was made when Kruszewski and Krygowski[98] proposed a more realistic model, which they called the harmonic oscillator model aromaticity (HOMA) index. HOMA starts from the assumption that energy changes in a hydrocarbon ring system are caused by a change in the C−C bond length. The energy changes are described by the harmonic oscillator model where the energy change ΔE_r of a bond r is proportional to the square of the bond length change of that bond:

$$\Delta E = \frac{1}{2}k_{\mathrm{s}}(R - R_{\mathrm{s}})^2 + \frac{1}{2}k_{\mathrm{d}}(R - R_{\mathrm{d}})^2 \qquad (14)$$

Here “s” refers to a single bond and “d” to a double bond. k_{s} and k_{d} are the respective force constants. Minimization of the total energy change over all bonds allows an optimized bond length R_{opt} to be found.

$$R_{\mathrm{opt}} = (k_{\mathrm{s}}R_{\mathrm{s}} + k_{\mathrm{d}}R_{\mathrm{d}})/(k_{\mathrm{s}} + k_{\mathrm{d}}) \qquad (15)$$

$$\mathrm{HOMA} = 1 - \alpha/n\sum(R_{ij} - R_{\mathrm{opt}})^2 \qquad (16)$$

Finally, the HOMA is defined as in eq 16, when n is the number of bonds taken into summation and α is an empirical constant fixed in a way to result in HOMA = 0 for a Kekulé structure of a typical aromatic system and equal to 1 for a system with all bond lengths equal to the optimal value R_{opt}. To apply the HOMA index to study the aromatic character of a given π electron system the following data are needed: (a) the precise geometry of the studied molecule, i.e., its bond lengths R_{ij}, (b) the optimized values R_{opt} for all relevant bonds, (c) the values for the relevant constants α.[99,100]

Initially[98] the dependence of α on the range of single bond lengths R_{s} and double bond length R_{d} was not recognized. These single and double bond lengths must be estimated for each kind of bond for which R_{opt} is estimated. This leads to a more specific form[100] for HOMA than the general form of eq 16. The ultimate goal is to use the HOMA concept of aromaticity in crystallographic studies, where inter- and intramolecular interactions can modify the molecular geometry. The advantage is that structures for such systems are available in databases, such as the Cambridge Structural Database.[101] With the HOMA index it is possible to measure the influence of distortion from planarity and substitution on aromaticity, and even local aromaticity can be described for single rings in condensed systems. Finally the influence on hydrogen bonding in a crystal lattice can be studied.

A wealth of applications have been reported by Krygowski and his colleagues: on the variation of molecular geometry and aromatic character of chrysene and perylene,[102] on global and local aromaticity in porphyrins,[103] on through space substituent effects[104] and $4n\pi$ annulenes,[105] on structural aromaticity of systems with BN bonds,[106] and finally on the separation of energetic and geometric contributions to aromaticity.[107−116]

$$\mathrm{HOMA} = 1 - \mathrm{EN} - \mathrm{GEO} \tag{17}$$

If the HOMA is rewritten in the form of eq 17 with $\mathrm{EN} = \alpha(R_{\mathrm{opt}} - R_{\mathrm{av}})^2$ and $\mathrm{GEO} = (2/N)\sum_i(R_{\mathrm{av}} - R_i)^2$, one can see that the aromaticity is decreased by an increase of the mean bond length in the system (EN) and an increase of bond alternation (GEO). The papers quoted show wide variety in geometrical arrangements and their diverse influence on aromaticity.

B. Bird Aromaticity Indices

The Bird aromaticity indices were defined as in eq 18 initially for five-membered rings[117] and later for six-membered rings,[118,119] an approach that is an expansion of earlier aromaticity coefficients based on ring geometrical parameters. Later, an unified system was adopted.[120] Data on structural and energetic indices of aromaticity are contained in Table 3.

Table 3. Bird Structural Indices of Aromaticity (Percentage to Benzene Molecule Taken as 100%)[117]

compound	*I* (%)
pyrazole	73
imidazole	64
1*H*-1,2,3-triazole	73
2*H*-1,2,3-triazole	88
1*H*-1,2,4-triazole	81
1*H*-tetrazole[a]	72
isoxazole	47
oxazole	38
isothiazole	59
thiazole	64
1,2-dithiolium	62

[a] Sodium derivative.

$$I_{5(6)} = 100[1 - (V/V_{\mathrm{k}})]$$

$$\text{where}\quad V = (100/N_{\mathrm{o}})\sqrt{[\textstyle\sum(N - N_{\mathrm{o}})^2]/n} \tag{18}$$

$$V_{\mathrm{k}} = 35 \text{ for a five-membered heterocycle}$$

$$= 33.3 \text{ for a six-membered heterocycle}$$

$$N_{\mathrm{o}} = (\textstyle\sum_n N)/n$$

$$\text{where}\quad N = \text{bond order and}\quad n = \text{number of bonds in cycle}$$

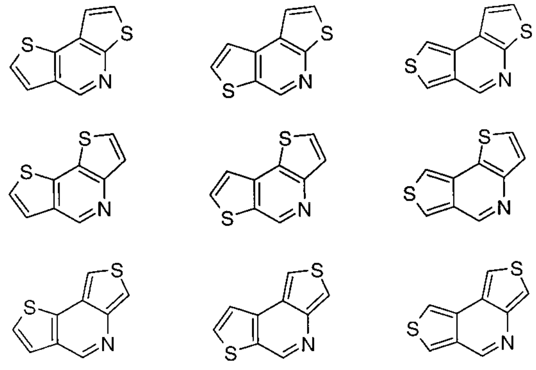
Bird indices were also developed for bicyclic heterocycles,[121] leading to the interesting conclusion that benzo[*c*]heterocycles are often of comparable aromaticity to the benzo[*b*]analogues.

Bird's structural index *I* decreases in the sequence pyridine > pyrazole > pyrrole. This is consistent with the general rule according to which a pyridine-like heteroatom provides more effective cyclic π conjugation than a pyrrole-like heteroatom. This tendency is manifested even inside a single condensed heteroaromatic system.

Bird indices of ca. 60 indicate that 2- and 4-pyridones retain much of the aromaticity of the 2- and 4-hydroxypyridine tautomers (indices of ca. 80).[118] This approach was later extended to a general study of the tautomerism of hydroxy- and mercapto-azines and shown to be in good agreement with other work.[122]

Bird aromaticity indices have been calculated by Rademacher for nine isomeric angular dithienopyridines (Scheme 22).[123] The author characterized the structural differences in the isomers by several aromaticity indices based on bond orders: V_6 for the pyridine ring, V_{5b} and V_{5d} for the thiophene rings, and V_{565} for the tricyclic system, the latter calculated by using a value of V_{k} of 35.2. In addition, an index V_{12} for the perimeter was calculated using a V_{k} value of 34.72 for structures in the first row of Scheme 22, 35.44 for structures in the second row, and 34.72 for structures in the third row. It was found that the π-electron-deficient central ring and its π-electron-rich neighbors interact more effectively when the annelation occurs at the C2−C3 bond of the thiophene ring. The aromaticity index V_6 of the central pyridine is linearly correlated with the stability of the isomers, while indices V_{565} of the tricycle and V_{12} of the perimeter correlate linearly with their energy.

Scheme 22. Dithenopyridines Used in Calculations of Bird Aromaticity Indices[124]



Heterocycles with phosphorin-type P atoms have indices similar to those of their nitrogen analogues, while As-heterocycles are much less aromatic.[124] The Bird indices have been used to examine the effect on aromaticity of molecular distortion[125] and of *N*-oxide[126] and zwitterions formation,[127] and they have been quoted as evidence for the aromaticity of phospholes.[128]

The Bird I_6 and I_5 aromatic indices have also been calculated from semiempirical and ab initio geometries and were compared with those calculated from experimental bond lengths.[129] None of these semiempirical theoretical methods were successful when the number of heteroatoms exceeded the number of carbon atoms. For other heterocycles, the AM1 and ab initio 3-21G basis set gave the best results, and for rings containing carbonyl groups MINDO/3 provides the best I_6 estimate.

Bird's aromaticity indices show satisfactory correlations with other aromaticity criteria, such as the classical,[114,130] absolute hardness,[131] and magnetical[130] criteria.

C. Other Geometric Measures

If we think of structural criteria for the aromaticity of benzene and the antiaromaticity of cyclobutadiene, we immediately end up with the observation that the bond lengths of benzene are all equal and the bond lengths of cyclobutadiene are pairwise quite different.

An explanation for this fact was usually based on the Hückel method, according to which the π electrons stabilize the benzene structure, by π electron delocalization, whereas they prefer the localized structure in cyclobutadiene. Here a delocalization is not possible due to the orbital occupancy of the π electron system. This view was recently challenged when it was found that a distortion of benzene from D_{6h} to D_{3h} is resisted by the σ electrons but favored by the π electrons.[132,133] This holds for any distortion, if the σ and π electron energy is properly defined and the nuclear repulsion correspondingly separated.[134] It holds for aromatic, nonaromatic, and antiaromatic systems.

Regardless of the origin of the molecular structure of aromatic and antiaromatic compounds, a geometric measure of aromaticity is natural. To characterize bonds as single, double, and triple bonds, the concept of bond order can be introduced. This was done on the π electron level by Coulson,[135] on the basis of the Hückel method without overlap and extended to nonorthogonal orbitals.[136] Later a generalization to σ and π electron systems was achieved.[137] This bond order is intimately related to the bond length of any type of bond, because it was found empirically that there is an approximately linear dependence between bond order and bond length for π electron systems[138] and for σ and π electrons systems[137] alike. Consequently, the use of bond orders instead of bond lengths for aromaticity can lead to geometric criteria.[139] The bond order criterion by Bird was already discussed. Another such criterion was introduced by Pozharskii.[140] This makes use of the average fluctuation $\Sigma\Delta N$ of all the ring bonds:

$$\Delta N = \sum \Delta N/n \tag{19}$$

Here n is the total number of differences between each possible pair of bond orders.

Bond order was also the basis for another aromaticity criterion RC. The argument was that the magnitude of a ring current is determined by the weakest link in the ring. This was considered as the bond with the lowest bond order $P_{ij}{}^{\min}$ between two ring atoms i and j.[83]

$$\mathrm{RC} = P_{ij}{}^{\min} \tag{20}$$

Although the bond order was an indication of a geometric criterion, the interpretation via the ring current was magnetic. In this sense, the interpretation was not geometric, but magnetic. The argument was that the weakest ring bond causes the most significant decrease of the cyclic ring current. In this sense, this criterion is a mixed geometric and magnetic criterion. It was initially applied to monocyclic and polycyclic hydrocarbons and to monocyclic systems with heteroatoms. The relationship of structure and aromaticity were investigated for [14]annulene and [18]annulene.[141] In other applications, rings with Be atoms were also studied and classified as aromatic.[142]

Already in early papers,[83,143] it was emphasized that aromaticity would not be directly related to UV spectra, which refer to excited electronic states. However, excited states of π electron sytems could and should also be classified by the RC criterion.[83,143] Nitrogen-containing five-membered heterocycles, moderately aromatic in the ground state, had excited states with greatly reduced aromaticity by this criterion.[144] Similar conclusions were reached for excited states of monosubstituted[145] and disubstituted[146] benzenes. This reduction is expected, because the change of occupation from occupied to virtual π orbitals causes an increase in antibonding between adjacent atoms. The magnitude of reduction of the degree of aromaticity was found to be dependent on state and substituent. Such studies were also performed on antiaromatic systems[147,148] because it was expected that the excited state of such systems could be aromatic when occupied antibonding orbitals are replaced by bonding virtual orbitals. This expectation was confirmed for a variety of hydrocarbons. Even for nonaromatic compounds, excited states can show an increase in aromaticity[149] due to increased delocalization of the π electrons.

IV. Magnetism-Based Measures of Aromaticity

A. Ring Currents

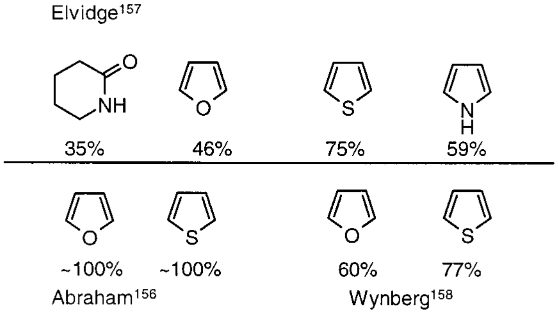
The idea of a ring current goes back to early work by Pauling[150] who suggested that the diamagnetic anisotropy of aromatic molecules is due to the $2p_z$ electrons, which are free to move under the influence of an electric field from a carbon atom to its adjacent carbon atom.

It has long been recognized that the conjugated system of π electrons in an aromatic compound supports a ring current, which exerts a deshielding effect on atoms outside the ring and a shielding effect on atoms inside the ring. Therefore, ring currents have been viewed as the cause of the unusual magnetic susceptibility effects in organic ring systems.[151,152] Numerous attempts have been made to apply this in a quantitative way. However, early workers found it extremely difficult to choose appropriate correct model compounds and make the right corrections.[153] The nuclear magnetic shielding and the magnetic susceptibility expressed as the sum of diamagnetic and paramagnetic contributions are still investigated in connection with the ring current concept. Recently, this phenomenon was reviewed using the quantum mechanical perturbation theory,[154] and this review should be consulted for a more theoretical treatment of ring currents.

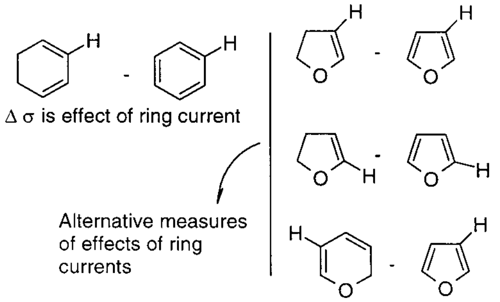
It has also been shown that, for monocyclic heteroaromatics, proton shieldings reflect the cyclic stabilization/destabilization effects as measured by homonuclear homodesmotic reaction energies, and they can thus quantify the aromaticity/antioaromaticity.[155]

In early work (Scheme 23), quite different quantitative estimates of aromaticity were reached from ring currents.[156−158] Some are illustrated in Scheme 24.[159] The difficulties in choosing a nonaromatic model in chemical shift studies were discussed early by Abraham and Thomas,[160] who also reasserted the view that the ring current criterion as a quantitative

Scheme 23. Quantitative Measurements of the Aromaticity by NMR Ring Currents



Scheme 24. NMR Ring Current Method for the Calculation of the Aromaticity[159]



assessment of aromaticity is suspect, a view which has received support elsewhere.[161-163]

However, despite these various difficulties and a criticism of the generality of the ring current criterion even for qualitative work,[164] the concept has been and remains for many authors a useful diagnostic test of aromaticity. Indeed, ^{1}H NMR data have been cited in discussion of the aromatic character of an extensive range of compound classes, and the following examples serve to illustrate this: tellurophene,[165] the indole, benzothiophene, and benzofuran series,[166,167] benzofurazan (4,5-benzo-2,1,3-oxadiazole),[168] cyclo[3,2,2]azine,[169] pyrazolo[1,2-a]pyrazole,[170] 1,10-phenanthroline,[171] borazaronaphthalene[172] and borazarothienopyridine,[173,174] 7-methylpyrano[4,3-*b*]pyran-2,5-dione,[175] 3-phenyl-3-benzoborepin,[176] and the heterocyclic analogues of pentalenyl dianion.[177-180]

The aromaticity of the heterocyclic ring in pyrones and in chromone has been recently reevaluated.[181] Calculated absolute magnetic shieldings 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 the nuclear independent chemical shifts (NICS) indices.

Calculated ring currents[182] for monocyclic six-membered nitrogen-containing heteroaromatics such as pyridine, pyrimidine and its isomers, and *s*-triazine and its isomers suggested that they all present ring currents very similar to the ring current in benzene. Moreover, polycyclic heteroaromatic systems such as quinoline and quinazoline have ring currents similar to those in their carbon counterparts. The calculations were performed using the Pariser–Parr–Pople Hamiltonian; full (for small rings) or approximate (for large systems) configuration interaction (CI) calculations were carried out.

Anisotropy data[183,184] for furan, pyrrole, and thiophene were considered to demonstrate a ring current increase in the series in the order given. Flygare, Beak, et al.[185] reported values for a parameter Δ_χ, the out-of-plane minus the average-in-plane molecular susceptibilities for the molecules benzene, furan, 2-pyrone, and 4-pyrone. The values of Δ_χ were separated into local and nonlocal contributions with the aid of values for localized groups obtained from nonaromatic compounds. The authors concluded from the apparent absence of nonlocal contributions in the pyrones that pyrones are not aromatic.

Closely related to anisotropy, the concept of diamagnetic susceptibility exaltation was discussed early on by Craig[186,187] and Dauben et al.[188,189] These groups suggested that the difference, the exaltation, between the observed molar magnetic susceptibility χ_M and that calculated from atomic and bond contribution $\chi_{M'}$ provides a useful criterion for assessing aromaticity. Dauben et al.[190] have provided a survey, authoritative at the time, of the subject and a comprehensive compilation of exaltation values for benzenoid, nonbenzenoid, and pseudo-aromatics, aromatic cations, keto aromatics, and heteroaromatics. Some uncertainties arise in the calculations of $\chi_{M'}$ for five-membered heteroaromatics.

In a critical appraisal, Jones[191] early on expressed the view that diamagnetic susceptibility exaltation provides a qualitative rather than a quantitative criterion for aromatic character. He argued that "the uncertainties in the value used for the diamagnetic constants for atoms and bonds, the need to use constitutive corrections,[188,189] and in particular the uncertainties in the origin of the susceptibility, which are clearly related to the problems of the ring current model, prevent the meaningful use of this phenomenon as a quantitative criterion."

The "intensity" of the ring current can also be measured by the A_M (magnetic parameter), which is related to the p_z orbital coefficients of the ring atoms of the $2n + 1$ "aromatic" molecular π orbital, as described in eq 21,[14] where n is the number of ring atoms. The summation is taken of the $(2n + 1)$th π orbital over all the ring atoms, and the c's are the MO coefficients at the $2n + 1$ "aromatic" π orbital.

$$A_M = \sum_i \prod_\mu (c_{i\mu})^{2/n} \tag{21}$$

B. Miscellaneous NMR Methods

i. o-Benzylic and Other Coupling Constants

Sternhell et al. were the first to propose the use of the *o*-benzylic coupling constants $^4J(^1H^1H)$ as a measure of relative "degree of aromaticity".[192] They treated 57 compounds and showed that a good correlation exists between the *o*-benzylic coupling constants $^4J_{Me-CH=CH-H}$ (denoted as $^4J_{OB}$) and bond order when the methyl group is not α to the heteroatom. This method can therefore be used as an experimental means of determining bond orders in heteroaromatic systems, and it gives a measure of the relative "degree of aromaticity" for heterocycles. Good correlations of $^4J_{OB}$ with bond orders calculated by the SCF-MO method suggests that it is possible to make comparisons of bond orders between heteroaromatics by comparing their $^4J_{\mathrm{OB}}$ values, regardless of the presence and number of heteroatoms or of the π electron density. The "degrees of aromaticity" calculated from $^4J_{\mathrm{OB}}$ are compared with those reported earlier by Katritzky (geometric criteria[16]) and Dewar (heats of formation[193]), and were found monotonic (Table 4).

Table 4. "Degree of Aromaticity" from $^4J_{\mathrm{OB}}$[190] Compared to That Obtained from Geometric Criteria ($I_{5,6}$)[16] and Heats of Formation (ΔH_f)[193]

	A^a $^4J_{\mathrm{Me,H}x+1}$	B^a $^4J_{\mathrm{Me,H}x-1}$	A/B	$I_{5,6}$	ΔH_f (kcal/mol)
3-methylpyridine	−0.76	−0.77	0.99	85.7	25.6
5-methylpyrimidine	−0.85	−0.85	1	84.3	25.0
4-methylpyridazine	0.78	0.96	0.81	78.9	22.7
3-methylpyrrole	−0.55	−1.02	0.54	69.0	22.5
3-methylfuran	−0.45	−1.23	0.37	43.0	12.1

[a] x is the position of the methyl group.

Later, Elguero and co-workers studied the chemical shifts and coupling constants of 23 1-substituted pyrazoles by ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy in solution, to determine how substituent effects are transmitted through the nitrogen atom and how the aromaticity of the ring is affected by these substituents.[194] Fourteen NMR properties were selected, among them the *o*-benzylic coupling constants. Instead of the *o*-benzylic coupling constants ^4J, the ratio $^2J_{45}/^3J_{34}$ (where J_{34} and J_{45} are the coupling constants between the appropriate adjacent hydrogen atoms in the pyrazole ring) was used for correlations. Assuming that the larger the value the less aromatic the pyrazole should be, an increasing order of aromaticity for 1-substituted pyrazoles was found as follows:

$$\mathrm{COMe} < \mathrm{SO_2CF_3} < \mathrm{NO_2} < \mathrm{CONH_2} < \mathrm{SiMe_3} = \mathrm{PPh_3} < \mathrm{NHCHO} < \mathrm{Ph} < \mathrm{Bn} < \mathrm{N{=}CHPh} < \mathrm{Et} < \mathrm{Me} < \mathrm{NH} < \mathrm{Me} < \mathrm{NH_2} < \mathrm{OBn} < \mathrm{N{=}PPh_3} < \mathrm{O^-Na^+}$$

The potential application of C−C coupling constants in assessing the aromaticity of five-membered heterocycles has been discussed.[195]

ii. Dilution Shift Parameter

The dilution shift $\Delta\delta_1$ (the difference between the chemical shift of an aromatic proton in the pure liquid and that in an infinitely dilute solution in nonpolar solvent) is inversely proportional to the molar volume (V_m) of the solute and directly proportional to the difference in the magnetic susceptibilities parallel and perpendicular to the axis of the ring.[196,197] From this, Khetrapal and co-workers argued[197,198] that the percentage aromaticity (A) of a system relative to benzene (100%) could be calculated from the expression displayed in eq 22.

$$A = \frac{(\Delta\delta_1 V_m)\text{ for ring protons of the compound }(\times 100)}{(\Delta\delta_1 V_m)\text{ for benzene protons}} \qquad (22)$$

The following percentage aromaticities were derived from data obtained in CCl$_4$: pyridine, 61 ± 7; furan, 42 ± 5; thiophene, 69 ± 11. Later, the aromaticities of various thiophenes were determined.[199] Measurements in benzene[200] have been recommended, in which the shifts of the benzene solvent peak are determined solutions. The low value for pyridine may be due to the neglect of the presence of lone pairs of electrons.

iii. Solvent Shift Parameter S

Anet and Schenck[201] have suggested that the magnitude of the strong shifts induced by aromatic solvents in the ^{1}H NMR spectra of dipolar molecules provides information about the molecular magnetic isotropies of these solvents. The proton chemical shift difference between acetonitrile and cyclohexane (internal reference) in solvent X is $\Delta\sigma_X = \Delta\sigma_{\mathrm{gas}} + \Delta\sigma_{\mathrm{medium}}$. Referring all $\Delta\sigma_X$ values to $\Delta\sigma_{\mathrm{cyclohexane}}$, defined as the observed chemical shift between acetonitrile and cyclohexane in neat cyclohexane, the relative solvent shifts S, equal to $\Delta\sigma_X - \Delta\sigma_{\mathrm{cyclohexane}}$, may be obtained.

For aromatic compounds, S values are large: here the dominant effect is the preferential location of the acetonitrile dipole above the plane of the ring where π electron density and diamagnetic shielding are greatest. In practice, the association constants of acetonitrile with the aromatic ring will affect the magnitude of S, though for hydrocarbon solvents these may be regarded as being sufficiently similar to make S as a measure of the anisotropy experienced. The S value for benzene is 1.00 ppm whereas for olefins S values are near to zero.

The S values decrease in the order pyrrole, thiophene, and furan. For pyrrole, the S value of 0.82 is higher than expected (anisotropy $\chi = 0.71$; benzene $= 1$), whereas for furan the S value of 0.42 is lower than expected, cf. $\chi = 0.65$. For pyrrole the result is interpreted in terms of a larger association constant, and for furan, the involvement of association at the periphery results in a deshielding contribution.

C. Nuclear Independent Chemical Shifts (NICS)

The ring current of π electrons in benzene and other aromatic compounds induced by an external magnetic field generates an induced magnetic field, which reinforces the applied field and deshields the outer protons. This displaces the chemical shift of the NMR absorption to lower applied field strength compared to the bare proton. With reference to the tetramethylsilane signal, the proton signal of aromatic compounds undergoes a large downfield shift of 6−8.5 ppm. This suggested the use of chemical shifts as a criterion for aromaticity. The ring current concept was used to explain the increased chemical shift of the benzene protons relative to those of ethylene.[202] Measured NMR chemical shifts for the outer and inner protons of aromatic [18]annulene were found to be positive and negative, respectively, whereas those of the antiaromatic [18]annulene dianion have the reverse pattern.[203−205] However, proton chemical shifts are not a general criterion.

They cannot be applied in systems without hydrogens and are misleading in bridged carbon cations, because abnormal chemical shifts cannot be associated with aromaticity.[206]

To improve the situation, Schleyer et al.[207] proposed "nucleus-independent chemical shifts" (NICS) as a new aromaticity index. They called it absolute magnetic shielding and computed it at the ring centers which are determined by the nonweighted mean of the heavy atom coordinates. The advantage is that they have a local criterion for each one of the rings in a polycyclic system. Aromatic systems are characterized by negative NICS, antiaromatic systems by positive NICS. A number of applications have been published.[103,208−212] A closer look at the results reveals several problems. First, the NICS are basis set dependent (the original authors recommend the 6-31+G* basis). Second, the size of the NICS does not provide an absolute measure of aromaticity. For instance, the value of (−15.1) for pyrrole is more negative than that for benzene (−9.7). Third, polycyclic rings also show anomalous behavior with the inner ring of anthracene, having again a more negative value (−13.3) than benzene, and the five-membered ring of azulene having a more negative value (−19.7) than that of cyclopentadienyl anion (−15.1). It is also disturbing that the NICS value for the Kekulé structure (−7.5) of benzene is not much different from that of benzene itself (−9.7).[17,213] Finally, NICS shares with some other aromaticity criteria the limitation that it is not an observable quantity.

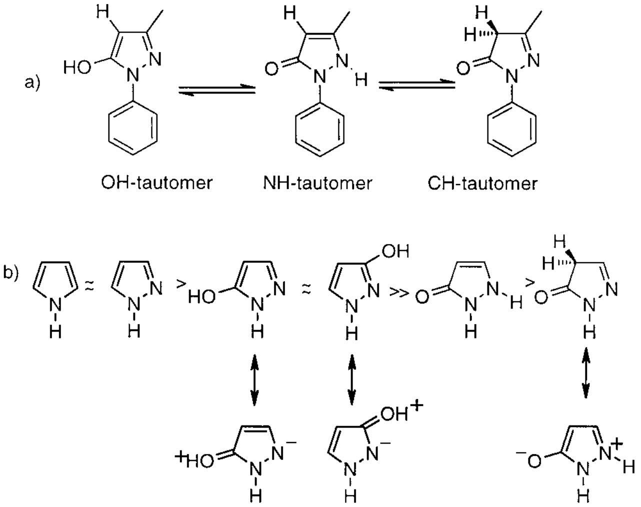
Jemmis and Kiran[214] studied the aromaticity of $X_3Y_3H_6$ (X = B, Al, Ga; Y= N, P, As), $X_3Z_3H_3$ (Z = O, S, Sc), and phosphazenes. They compared energetic and magnetic criteria by choosing aromatic stabilization energies (ASE), magnetic susceptibility exaltation (Λ), and NICS for their study. Aromatic stabilization energies were based on homodesmotic equations of the type

$$X_3Y_3H_6 + 3XYH_4 = 3X_2Y_2H_6 \tag{23}$$

The authors found that all these criteria can diverge quite strongly from each other. For example, despite equal aromatic stabilization energies, BNH_6 is not aromatic, but BPH_6 is substantially aromatic according to the Λ and NICS data. The Λ and NICS data also do not always parallel each other. Whereas their low NICS values indicate nonaromaticity of the $X_3Z_3H_6$ compounds, the Λ values indicate aromaticity.

The stability of the pyrazolinone tautomers was related to their scale of aromaticity.[16,215,216] Experimental values for the tautomerism of pyrazolinone derivatives were obtained by flash vacuum pyrolysis (FVP), which allowed the calculation of the effect of the temperature on the equilibrium between tautomers.[217] The variation of K_T with the temperature was determined by ^1H NMR in solution for the model compound 1-phenyl-3-methyl-2-pyrazolin-5-one (Scheme 25), showing that at 0 K the only tautomers present are either the NH or the OH ones. Temperature and solvent effects on the prototropic equilibrium of the model compound in solution showed that the percentage of the CH tautomer increases with the temperature and it is much larger in DMSO-d_6 than in methanol-d_4. The order of stability of the populations as determined by FVP and ab initio calculations at 298.15 K is described in Scheme 25.

Scheme 25. Tautomers of 1-Phenyl-3-methyl-2pyrazolin-5-one[217]



The fact that 3-hydroxypyrazoles are always predominant in the equilibria with their corresponding CH-tautomers is related to their aromaticity. Qualitative interpretations supported the hypothesis that the NH tautomer was less aromatic than the OH tautomer, and the CH tautomer was nonaromatic. Nuclear independent chemical shifts (NICS) values were calculated by using Schleyer's approach in order to determine the relative aromaticity of the pyrazole NH and OH tautomers using pyrrole as a reference. For pyrazole itself, the NICS value was close to pyrrole (−15.1 ppm). The NICS values were found to be −14.55 ppm for the 5-OH tautomer and −14.45 ppm for the 3-OH tautomer, indicating that the OH substituent does not alter the aromaticity of pyrazole and dipolar charges are not relevant. The NH tautomer has a NICS value of −6.75 ppm, intermediate between the OH tautomers and the nonaromatic CH tautomer, the latter with a NICS value of −0.25 ppm.

Very recently Juselius and Sundholm[218] studied the aromatic character of magnesium porphyrins by performing aromatic ring current shieldings (ARCS)[219] and NICS calculations. Although the NICS method cannot be applied to the molecule as a whole because of the location of the magnesium atom in the molecular center, they determined NICS values at the centers of the pyrrolic rings. This shows that NICS values can be used for the study of local aromaticity in polycyclic compounds.

V. Other Quantitative Measures of Aromaticity

Further criteria that are related to energetic, structural, or magnetic properties have been proposed. Binsch introduced the criterion of double-bond fixation.[220,221] He defined a π electron system as aromatic if it shows neither strong first-order nor second-order double-bond fixation. The author was interested in the tendency of π electrons to cluster in certain bonds. The difference in lengths between adjacent bonds is a measure of first-order double bond fixation. The second-order double bond fixation is related to an analysis of the Hessian matrix of the π electrons. Here he considered the matrix of the second derivatives of the π electron energy with respect to the bond lengths of a ring system. The lowest eigenvalue of this matrix is compared with a reference value and can serve as a criterion whether strong bond alternation is to be expected in a ring system. Binsch studied a number of polycyclic hydrocarbons and found that the ring current criterion[164] may give a different answer. Whereas the ring current criterion classified some of the compounds as aromatic, the second-order double bond fixation criterion would classify them as antiaromatic. The explanation of the author for these cases was that the ring current criterion did not account for configuration interaction, when it was relevant. This criterion is a combined energetic and structural criterion. It was abandoned, because it was mainly defined on the π electron level and not generalized to systems with heteroatoms.

Another category of aromaticity criteria that has not yet been mentioned is the reactivity criteria, which go back to the 19th century.[222] It is well-known that benzene does not easily undergo addition reactions but is more susceptible to substitution reactions.[223] The problem with such a criterion is that it depends on the difference of the free energy of the ground state of the molecule and the transition state of the reaction. In this sense it is not easy to quantify, because it does not depend on the ground state alone and may vary with the choice of the reagent.

Reactivity and aromaticity are directly related only when the energy level of the transition state remains constant, which is usually not the case. Only for a series of compounds where the changes in the energy of ground state and transition state are proportional would a reactivity criterion be straightforward.[224]

The competition between thermodynamic and kinetic stability may lead to different answers with respect to the question of aromaticity. There are exceptions to the rule that aromatic compounds undergo electrophilic substitution rather than addition reactions.[206,225] There is an increasing tendency to addition within the series naphthalene, anthracene, tetracene, and pentacene. For anthracene and tetracene, 1,4-addition becomes more important and it is dominant in pentacene.[17]

Conflicting thermodynamic and kinetic answers are particularly striking in the case of aniline. This compound is thermodynamically stable with a resonance energy similar to benzene,[225,226] but it is kinetically unstable with a high reactivity due to the possibility of an easy electron-transfer reaction to oxygen. Reactivity is related to the HOMO and LUMO energies. Bird[227] showed that the hardness of a molecule that is half of the HOMO−LUMO gap is related to the REPE.

A most recent attempt to use reactivity as a criterion for aromaticity was given for borazine.[228,229] The gas-phase reactivity of selected ionic species with borazine and borazine-derived ions with selected neutral molecules has been studied by FT-ICR and ab initio calculations. Evidence for an electrophilic substitution on the borazine ring was found in the alkylation by gaseous Me_2F^+, Me_2CH^+, and Me_3C^+ that led to neutral substitution products, as a result of an N-alkylation.[228] Further studies on the protonation, alkylation, and nitration of neutral borazine have been compared with the corresponding reactions of benzene, and it was shown that the cyclic $B_3N_3H_5^+$ reacts similarly to the phenylium cation $C_6H_5^+$.[229] In this sense, borazine shows a remarkable similarity to benzene.

An excellent correlation in terms of the order of aromaticity was reported for five-membered and benzo-fused five-membered heterocyclic compounds between heats of combustion and computed data on stability and reactivity.[230] Highly accurate experimental values for the energies and geometries of thiophene, pyrrole, and furan have been obtained by microwave spectroscopy. Experimental data are correlated with those calculated with the ab initio density functional theory method using the GAUSSIAN 94 package (B3LYP/6-31G* calculational level). The approach was further extended to the benzo[*b*] and benzo[*c*] fused five-membered heterocycles, for whom there are no thermodynamical data available. Calculations of the benzene C−C ring distortions were performed with the assumption that the aromaticity for benzene in fused heterocycles is high if the bond distances of the benzene ring do not deviate from benzene itself. Calculations of the benzene C−C bond distance were used to further compute magnetic susceptibility anisotropies and relative energies for the benzene ring in the fused heterocycles studied. Results show that the energy differences between the [*b*]- and [*c*]-fused benzofurans are high, with benzo[*b*]furan very stable (in agreement with its chemical behavior). Calculations for benzopyrroles show similar aromaticity, while benzo[*c*]thiophene is less aromatic than the corresponding benzo[*b*] isomer.

VI. Comparisons of Quantitative Measures of Aromaticity

A. Introduction

A great deal of effort has gone into the construction of quantitative aromaticity scales, as summarized above. However, it is quite clear that there have been very considerable difficulties, which have arisen for a variety of reasons that include the following:

(1) differences between the electronic structure of heteroatoms and carbon;

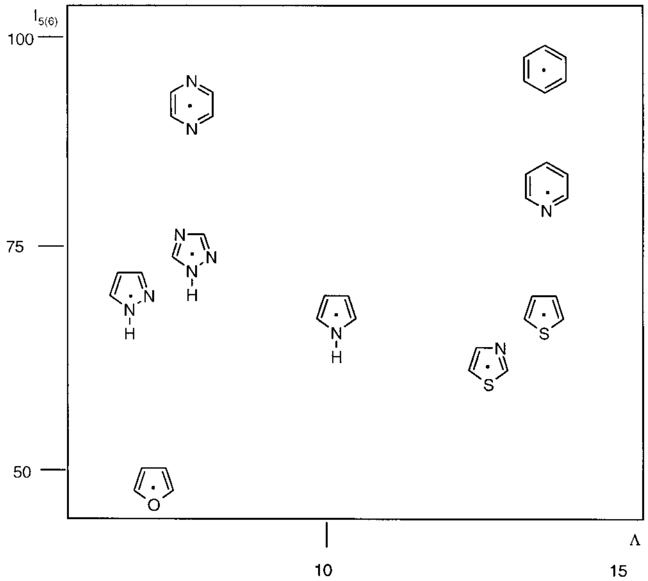
(2) incompatibility of different physical and chemical molecular characteristics;

(3) comparison of experimental data obtained in different media;

(4) difficulties in the definition of nonaromatic models to compare with aromatic compounds.

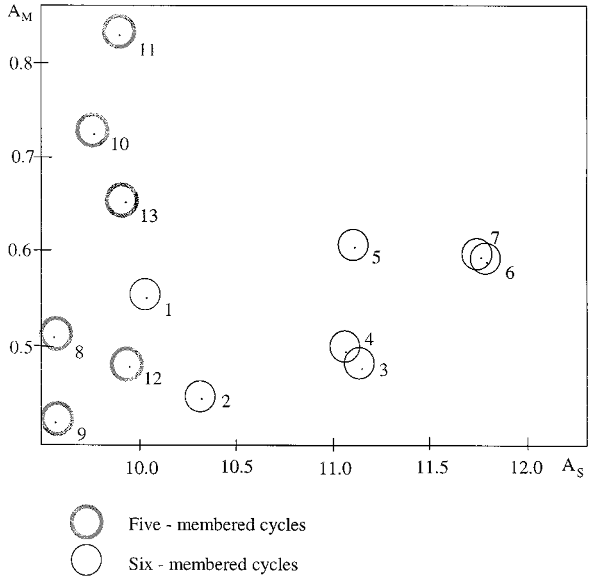
Although very useful insight is obtained regarding the aromatic stabilization of a variety of compounds from the work just described, the overall picture is nevertheless one of confusion and complexity. In particular, the different measures do not tie up with each other. Thus, the plot in Scheme 26 of the aromaticities deduced from Bird aromaticity indices against those for the same compounds from molar magnetic susceptibility shows absolutely no correlation.

Scheme 26. Plot of Bird Aromaticity Parameters $I_{5(6)}$ against Molar Susceptibility Exaltation Λ, Showing No Correlation[14]



There is no common relationship between the A_S and A_M parameters, calculated by the same quantum-chemical method (AM1 SCF LCAO MO) (Scheme 27).[14] However, the five- and six-membered rings can be separated into two groups, which have a slight dependence between those parameters. Notably, the five-membered rings are more sensitive toward the "magnetic" A_M parameter whereas the six-membered rings have larger dispersion of "structural" A_S parameters.

Scheme 27. Plot of AM1 Calculated A_M Aromaticity Parameters against AM1 Calculated A_S Parameters[14]



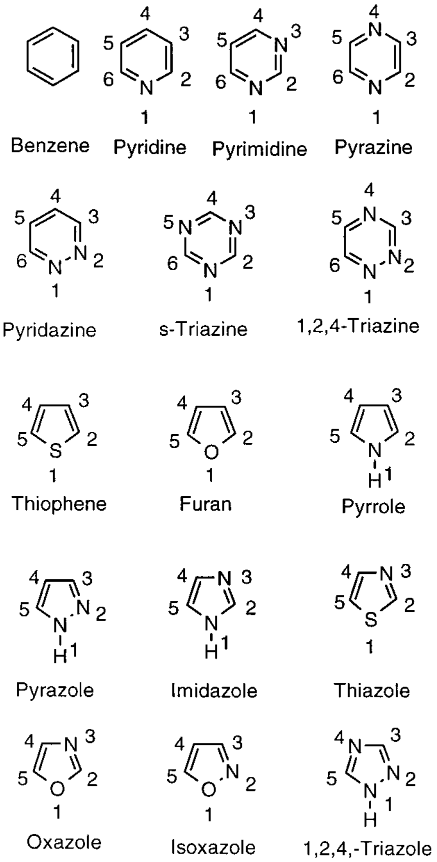
Several attempts have been made to clarify and rationalize the relationships between the different quantitative measures of aromaticity.

B. Katritzky Principal Component Treatment

i. Familiar Monocyclic Aromatics

In 1989, a new approach[16] was taken by applying the principal component (PC) analysis to all data then available. Initially, a set of 16 familiar monocyclic aromatics was chosen (Scheme 28). A total of 12 variables were treated by the SIMCA method. Of the variables, four were 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 were 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 were magnetic (molar magnetic susceptibility, diamagnetic susceptibility exaltation, and the average ^{15}N chemical shift).[16] The data set for the 12 characteristics and 16 compounds used is given in Scheme 29.

Scheme 28. Model Set of 16 Familiar Monocyclic Aromatic Compounds[16]



To determine the number of statistically significant eigenvectors, the method of cross-validation is used.

Scheme 29. Data Set for Familiar Monocyclic Compounds[16]

Compounds	1	2	3	4	5	6	7	8	9	10	11	12
	I_x	I_x'	RC	ΔN	DRE	DRE'	HRSE	ΔH_f	ΔH_{fcal}	χ_M	Λ	^{15}N
1 Benzene	100.0	100.0	1.774	0.0	3.77	3.84	0.065	19.8	22.0	54.8	17.9	---
2 Pyridine	85.7	84.1	1.571	0.10	3.85	4.12	0.058	34.6	32.0	49.2	18.3	-63.5
3 Pyrimidine	84.3	82.4	1.498	0.13	3.37	3.60	0.050	47.0	46.8	43.1	18.2	-84.5
4 Pyrazine	88.8	90.8	1.561	0.06	2.85	4.00	0.049	46.9	44.4	37.6	12.7	-46.1
5 Pyridazine	78.9	73.4	1.468	0.18	---	---	---	66.4	55.4	40.5	8.7	20.2
6 s-Triazine	100.0	100.0	1.483	0.0	---	3.33	0.040	54.0	60.1	37.9	19.0	-98.5
7 1,2,4-Triazine	86.1	71.9	1.398	0.19	---	---	---	52.4	69.5	---	---	-6.7
8 Thiophene	66.0	67.7	1.533	0.25	1.08	0.96	0.032	27.6	40.1	57.4	17.8	---
9 Furan	43.0	35.2	1.105	0.47	0.72	0.63	0.007	-8.3	3.0	43.1	13.9	---
10 Pyrrole	59.0	66.5	1.344	0.24	1.40	2.15	0.039	25.9	40.1	47.6	14.5	-224.6
11 Pyrazole	73.0	74.2	1.316	0.18	---	---	0.055	43.3	66.5	42.6	15.5	-126.5
12 Imidazole	64.0	68.0	1.306	0.21	2.57	3.34	0.042	30.6	51.0	44.3	17.2	-169.0
13 Thiazole	64.0	59.4	1.283	0.32	1.87	1.32	0.034	37.0	49.9	50.6	17.0	-57.4
14 Oxazole	38.0	37.8	1.075	0.40	---	2.07	0.007	-3.7	12.6	39.2	16.0	-127.0
15 Isoxazole	47.0	48.1	1.042	0.36	---	---	---	18.8	44.4	37.5	14.3	2.7
16 1,2,4-Triazole	81.0	74.7	1.273	0.17	---	---	0.050	46.3	74.0	---	---	-13

Scheme 30. Results of PC Analysis on 12 Objects[231]

Principal Component(s)	Percentage of Variance Accounted For
t_1	48.4
$t_1 + t_2$	65.2 (48.4 + 16.8)
$t_1 + t_2 + t_3$	73.7 (48.4 + 16.8 + 8.5)

The number of principal components is selected as three. The results on the PC analysis are given in Scheme 30. It is seen that two principal components account for 65% and three for 74% of the variance.

The first PC eigenvector accounts for 48.4% of the total variance in the data set and is dominant for I_X, I'_X and ΔN. Characteristics DRE, DRE′, HSRE, RC, and ΔH_f also depend moderately on the first eigenvector. For $\Delta H_{f\ (AM1)}$ low relevance and for χ_M, Λ, and ^{15}N zero dependence on the first PC (zero modeling power) were observed. For the second PC, four variables (I_{SC}, I'_{SC}, RC, and ΔN) are highly relevant, and those remaining have moderate modeling powers. For the third PC, the geometrical and energetic variables have similar, high utility in the model, with the magnetic variables having somewhat lower utility.

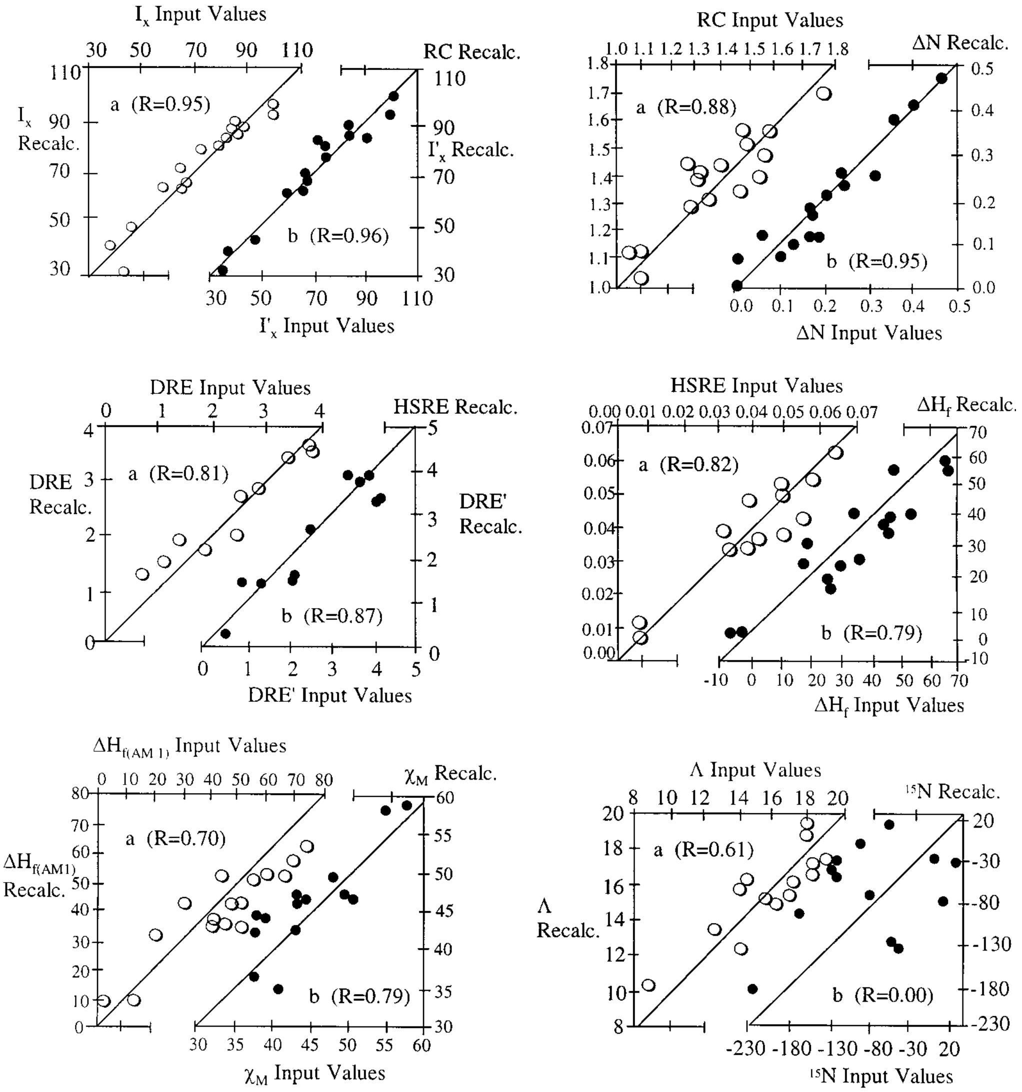
To assess the predictive power, the data matrix containing *i* objects and *k* independent variables per object was treated as follows: each data point, x_{ik}, was omitted successively one at a time, and a PC analysis was carried out in each case on the remaining set of data. A new value for the data point omitted was then recalculated using the new values of the scores and the new values of the loadings. These recalculated values, when compared with the input values, demonstrate the predictive power of the model. They are plotted against the input values, and R^2 is determined for the 1:1 line to determine a measure of fit. The results of the PC analysis are shown in Scheme 31.

The PC scores for all 16 compounds are plotted graphically in Scheme 32,[231] with the principal component scores t_1 and t_2 as the ordinate and abscissa, respectively, and the score t_3 for the third PC shown within the circle.

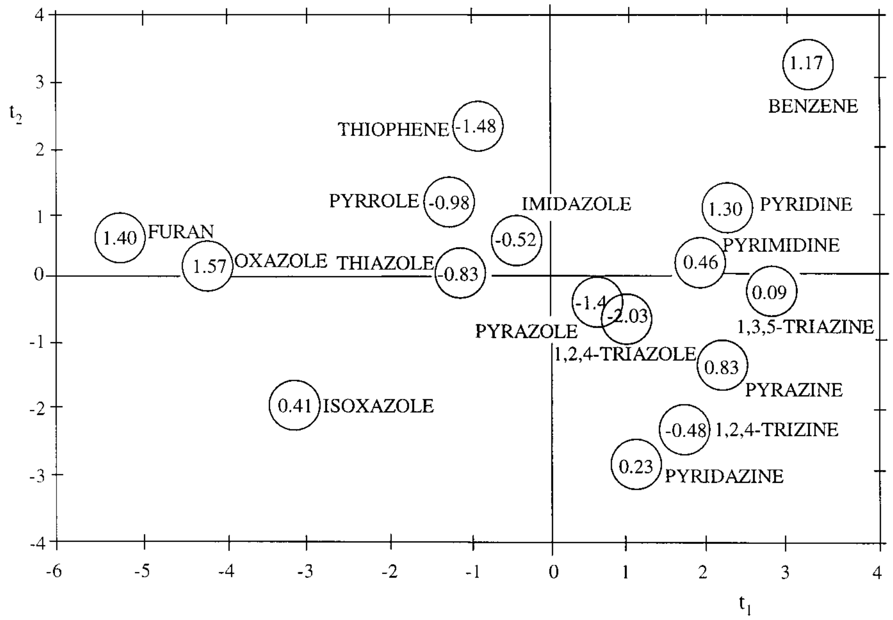
Scheme 32 shows that in the three-dimensional space defined by their principal component scores t_1, t_2, and t_3, the compounds **1**−**16** can be divided into four or five groups. Benzene and pyridine have all three t_1, t_2, and t_3 values positive. Di- and triazines are placed in another quartile with only t_2 negative. Azines and azoles with two nitrogen atoms in adjacent positions in the ring form a separate group with t_1 positive and both t_2 and t_3 negative. The final group contains five-membered rings with nitrogen and/or sulfur heteroatoms (moderately negative t_1, t_2 positive, and t_3 negative).

The PC loadings for the 12 characteristics are given in Scheme 33.[231] In the three-dimensional space defined by their PC loadings, the characteristics can

Scheme 31. Plots of Recalculated vs Original Data for Monocyclic Aromatic Compounds[16]

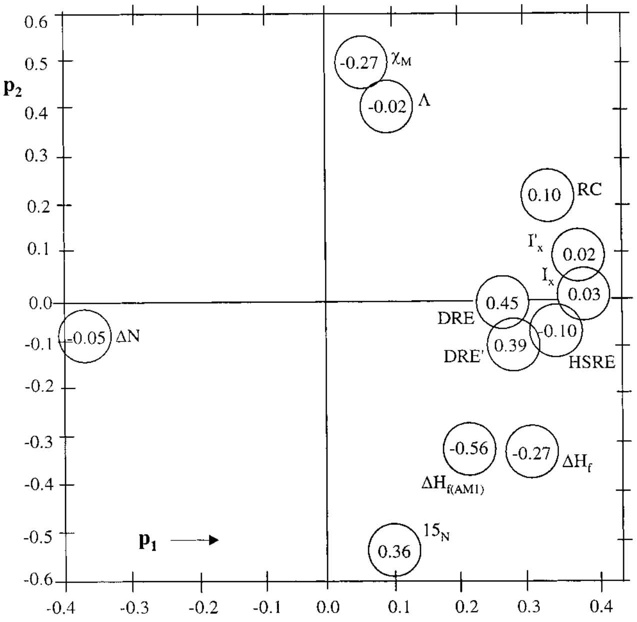


Scheme 32. Scores of t_1 vs t_2 for Monocyclic Compounds with t_3 Indicated[231]



be divided into three main groups: group A is dominated by the p_1 PC loadings (I_X, I'_X, ΔN, DRE, DRE′, HSRE) and with small p_2 and p_3 loadings; the second group (B) is comprised of the magnetic pa-

Scheme 33. Loadings Plot p_1 vs p_2 for Monocyclic Compounds with p_3 Indicated[231]



rameters χ_M, Λ, and ^{15}N and is marked by a very small p_1 component but large positive p_2 and variable p_3 components; the remaining characteristics form the third group. Two of these groups, A and B, are almost orthogonal to each other and can be related to the concepts of "classical" and "magnetic" aromaticity.

ii. Bicyclic Heteroaromatics

An extension to bicyclic compounds[232] is shown in Scheme 34, and the corresponding data set is shown in Scheme 35. PC analysis gave two significant PCs: t_1 accounted for 38%, while t_1 and t_2 together explain 63% of the variance. The PC analysis results are given in Scheme 36, and the PC loadings and PC scores are plotted in Schemes 37 and 38, respectively.

Although the monocyclic and bicyclic compounds form two completely independent data sets, highly significant correlations between the two sets were found both for the loadings and for the scores. The close correspondence of the loadings for mono- and bicyclic derivatives is depicted in Scheme 39. Similarly, Scheme 40 compares the scores for the benzoheterocycles with those for the corresponding monoheterocycles and again demonstrates a very good agreement.

Scheme 41 shows plots of the individual p_1 and p_2 for bicyclic versus monocyclic compounds, and gives the correlation coefficients. Scheme 42 shows the plots for individual t_1 and t_2 for bicyclic versus monocyclic compounds.

iii. Less Familiar Monocyclic Heteroaromatics

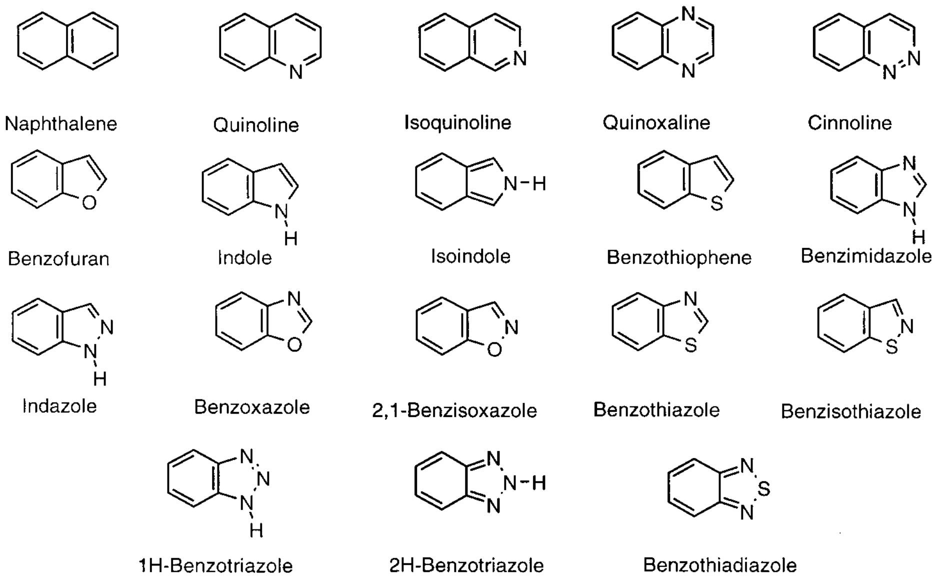
A further extension to a set of 23 less-familiar monoheterocycles (Scheme 43) was made in which available characteristics were treated by PC analysis using the loadings derived from the 16 standard monoheterocycles, already described, to give the scores of the new heterocycles.[233]

The scores for the total set for 16 + 23 = 39 monoheterocycles are shown in Scheme 44. The dominant influence on t_1 is the size of the ring and the nature of the heteroatoms present, whereas the dominant influence on t_2 is the number of heteroatoms present.

It is concluded that pyridine-like nitrogen atoms have relatively little effect on classical aromaticity: five-membered rings are less aromatic than six-membered, the presence of an oxygen atom has a particular aromaticity-reducing effect, whereas the effect of sulfur is much less than oxygen and only a little more than nitrogen. The predictive power for the present compounds is limited by the relative paucity of, and some problems with, the input data, but succeeds well for I_X, ΔN, and ΔH_f.

This work resolves, to a considerable extent, the apparent impasse between classical and magnetic aromaticity and provides a firm basis for the consideration of aromaticity as a quantitative concept. It demonstrates that there are at least two types of

Scheme 34. Bicycles Studied[232]



Scheme 35. Data Set for Bicyclic Compounds[232]

Compounds	Variables											
	1	2	3	4	5	6	7	8	9	10	11	12
	I_x	I_x'	RC	ΔN	DRE	DRE'	HRSE	ΔH_f	$\Delta H_{f(AM1)}$	χ_M	Λ	^{15}N
1 Naphthalene	77.3	76.9	1.648	0.18	3.36	3.35	0.055	36.1	40.8	91.9	36.2	---
2 Quinoline	73.0	73.9	1.383	0.18	3.30	3.38	0.052	50.0	52.1	86.0	36.3	-67.5
3 Isoquinoline	72.1	78.2	1.447	0.14	3.41	3.65	0.051	50.0	50.2	83.9	34.2	-69.3
4 Quinoxaline	71.9	70.5	1.368	0.21	2.81	3.20	0.048	63.0	65.6	---	---	-50.1
5 Cinnoline	70.8	61.3	1.268	0.27	---	---	---	81.0	74.3	---	---	42.9
6 Benzofuran	45.4	56.6	1.059	0.33	2.03	0.76	0.036	6.5	20.8	79.8	31.8	---
7 Indole	70.0	66.5	1.311	0.23	2.38	1.47	0.047	44.6	55.2	85.0	33.1	-253.6
8 Isoindole	72.0	68.9	1.378	0.22	1.16	0.76	0.029	56.0	61.7	---	---	-218.0
9 Benzothiophene	57.0	76.1	1.515	0.18	2.48	1.18	0.044	40.0	53.9	93.3	34.9	---
10 Benzimidazole	71.0	65.3	1.255	0.28	3.09	1.39	0.050	43.4	67.1	71.9	26.0	-186.4
11 Indazole	68.9	70.8	1.292	0.23	---	---	0.056	60.7	82.3	72.7	26.8	-130.7
12 Benzoxazole	38.0	44.8	1.100	0.35	---	0.90	0.031	---	31.3	74.4	32.4	-131.5
13 2,1-Benzisoxazole	54.0	54.3	1.084	0.30	---	---	---	---	69.4	71.6	29.6	-7.5
14 Benzothiazole	57.0	65.7	1.223	0.23	---	1.35	0.047	---	64.1	88.5	36.1	-64.7
15 Benzisothiazole	68.0	69.6	1.280	0.20	---	---	---	---	73.1	85.1	32.7	-76.0
16 1H-Benzotriazole	67.0	58.9	1.178	0.28	---	---	---	83.0	104.2	---	---	-67.9
17 2H-Benzotriazole	73.0	68.6	1.417	0.26	---	---	0.067	---	117.0	---	---	-80.7
18 Benzothiadiazole	56.2	46.4	1.072	0.36	---	---	---	---	93.1	---	---	51.9

Scheme 36. Results of PC Analysis for Bicyclic Compounds[232]

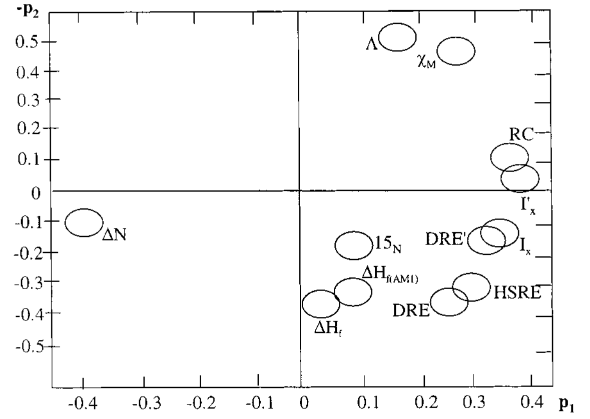
Principal Component(s)	Percentage of Variance Accounted For
t_1	37.5
$t_1 + t_2$	63 (37.5 + 25.5)

aromaticity. A good measure of classical aromaticity is provided by the Bird I_5 and I_6 parameter, which correlates well for ΔN and for DRE. The second type is magnetic aromaticity, which is measured by the molar magnetic susceptibility χ_M. These two types of aromaticity, classical and magnetic, are found to be orthogonal in this analysis. Other aromatic characteristics are inferred by both "classical" and by "magnetic" aromaticity to varying extents.

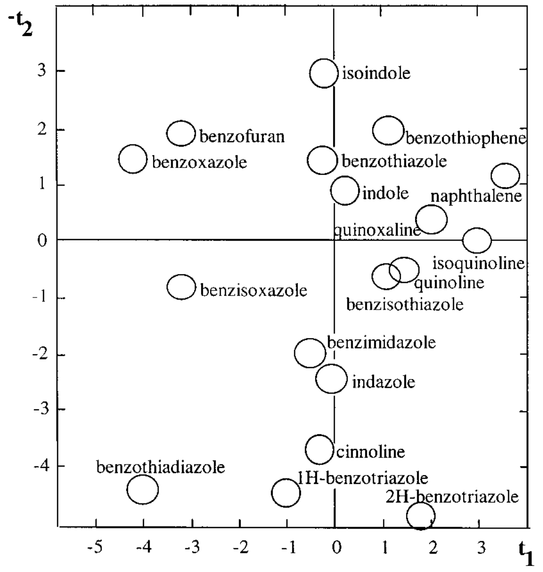
C. Jug Principal Component Treatment

Following the classification by Katritzky et al.,[9] the aromaticity criteria were grouped by Jug and Köster[234] in three classes: geometric, energetic, and magnetic. It was pointed out that the geometric criteria frequently do not use geometry directly but indirectly via bond orders. These are approximately related to bond lengths and are more suitable than bond lengths for comparison of heterocylic rings. In Jug and Köster's study, the criteria by Bird[118] and Pozharskii[140] were excluded because they predict perfect aromaticity for rings without bond alternation: these criteria suggest the same degree of aromaticity for benzene and borazine, a prediction

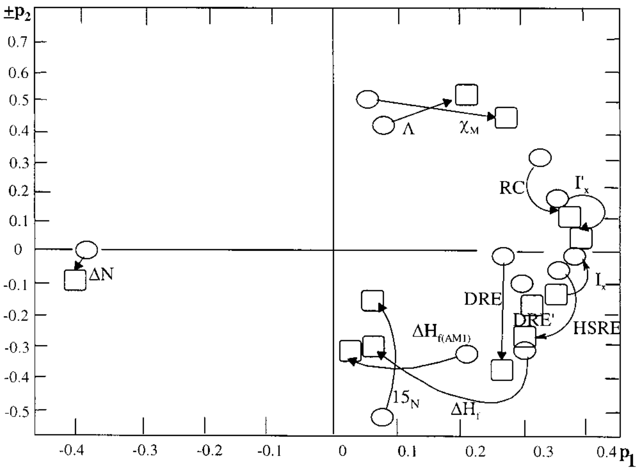
Scheme 37. Loading Plot of p_1 vs $-p_2$ for Bicyclic Compounds[232]



Scheme 38. Scores Plot of t_1 vs $-t_2$ for Bicyclic Compounds[232]



Scheme 39. Loadings of Bicycles Compared to Monocycles—Plot[232]



not supported by chemical intuition. The ring current criterion RC[83] does not suffer from this drawback. To enhance the number of aromaticity criteria, a similar ring current criterion RC_v was introduced, which uses bond valence rather than bond orders for the description of bonding between atoms.[235−237] Compared with bond order, which is linear in density matrix elements, bond valence is quadratic in density matrix elements. The RC and RC_v values were calculated for 29 monocyclic three-, four-, five-, and six-membered rings without and with heteroatoms. The RC versus RC_v plot shows a substantial scattering.

Three energetic criteria were included. Besides the DRE[238,239] and the HSRE,[62,63] a new energy criterion $\Delta E/E$ was introduced based on the distortion of equilibrium structures to Kekulé structures.[134] Here, ΔE is the energy difference between the Kekulé and equilibrium structures, and E is the energy of the equilibrium structure.

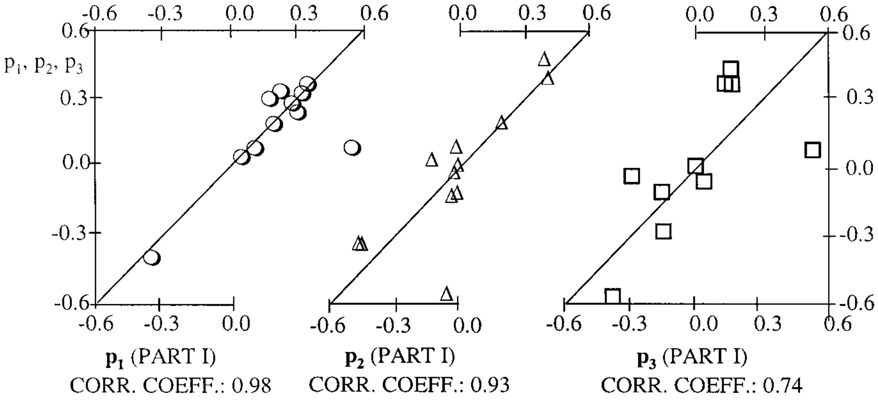
Three magnetic criteria were used. From the literature were taken molar susceptibility χ_M and the index Λ, which is defined as the difference between the measured and calculated molar susceptibilities.[240] As a new index, the normalized zz component of the diamagnetic susceptibility tensor for the π electrons was introduced and labeled $\chi_{zz}{}^{\pi}/n_{\pi}$.

These eight criteria were applied to 12 monocyclic five- and six-membered rings, and the data were subjected to a principal component analysis. The first two components p_1 and p_2 comprise 75% of the variance of all variables. The location of the eight methods in the two-dimensional plane showed that the energetic, geometric, and magnetic criteria are separated in groups. The geometric criteria are characterized by a large p_1 and a small p_2, whereas the energetic criteria have a small p_1 and a large p_2. The magnetic criteria have similar p_1 and p_2 values and are therefore located between the geometric and energetic criteria. The results support the finding by Katritzky et al.[9] that aromaticity is at least a two-dimensional phenomenon. Different from Katritzky is the grouping of the criteria. Here, energetic and geometric criteria are orthogonal whereas magnetic criteria are not orthogonal to one of the others. This means that the results of a principal component analysis depend on the methods used and the compounds included. Orthogonality has therefore not an absolute, but only a relative, meaning.

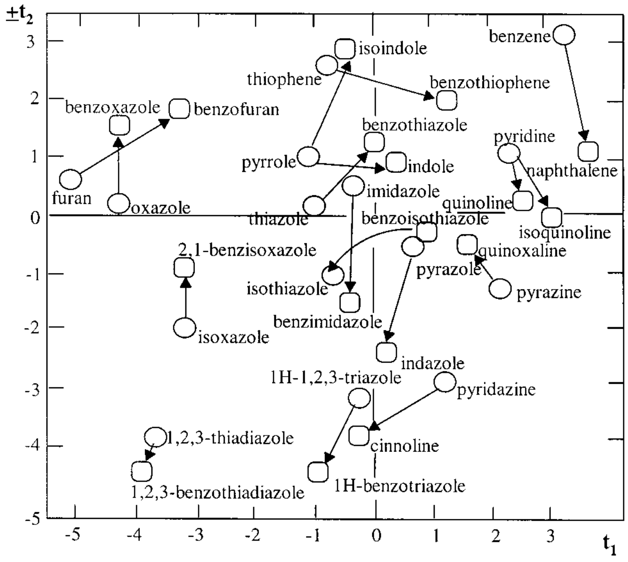
D. Krygowski Treatment

Stimulated by the first studies applying principal component analysis to aromaticity scales,[9,234] Krygowski et al.[241] studied 32 polybenzenoid compounds with five different aromaticity indices. Included as

Scheme 40. Loadings of Bicycles Compared to Monocycles—Correlation Coefficient[232]



Scheme 41. Scores of Bicycles Compared to Monocycles—Plot[232]



geometrical criteria were the I_6 index by Bird,[117] the HOMA index,[98,100] and the RC index by Jug[83] in a modified form where the smallest bond order was replaced by the largest bond length, and the index was called LB. Following Binsch and Heilbronner,[242] the double-bond fixation theory was used, and a new geometrical index was introduced. The bond alternation coefficient (BAC) was defined as

$$\mathrm{BAC} = \sum_i (R_i - R_{i+1})^2 \tag{24}$$

where R_i and R_{i+1} are consecutive bond lengths in the ring, and the summation runs over all bonds of the molecule or the fragment under study, which was the benzene rings in all different possible environment of the selected compounds. Altogether, 154 benzene rings were studied. The authors point out that this bond difference criterion is reminiscent of Pozharskii's ΔN index.[140] Finally, an energetic criterion, the bond energy BE of the molecular fragment, was introduced

$$\mathrm{BE\ (molecule\ or\ fragment)} = \sum_i \mathrm{BE}_i \tag{25}$$

where BE_i is given as

$$\mathrm{BE}_i = E(1)\exp[\alpha\{R(1) - R(i)\}] \tag{26}$$

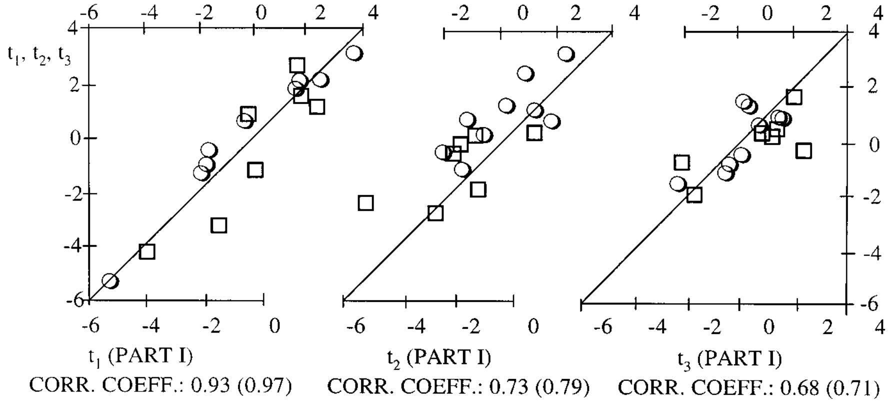
Here $E(1)$ and $R(1)$ are the bond energy and bond length, respectively, of a single bond, and $R(i)$ is the bond length of the bond in question. The structures were taken from the Cambridge Structural Database.[101,243]

The regression analysis reveals that the indices are not equivalent even for such a homogeneous sample as the benzene rings differing only in their environment in polybenzenoid hydrocarbons. This is qualitatively in line with the earlier conclusions.[9,234] Krygowski et al.[241] have plotted the values of the five criteria pairwise, thus generating 10 plots. The best-correlated pairs are I_6 and BAC (−0.937), and HOMA and LB (−0.909), but both with negative correlation coefficients. The worst scattering is observed for BE and I_6 or BAC. The factor analysis reveals that only two factors are needed to explain 95.8% of the total variation of the data. The first factor accounts for 70%.

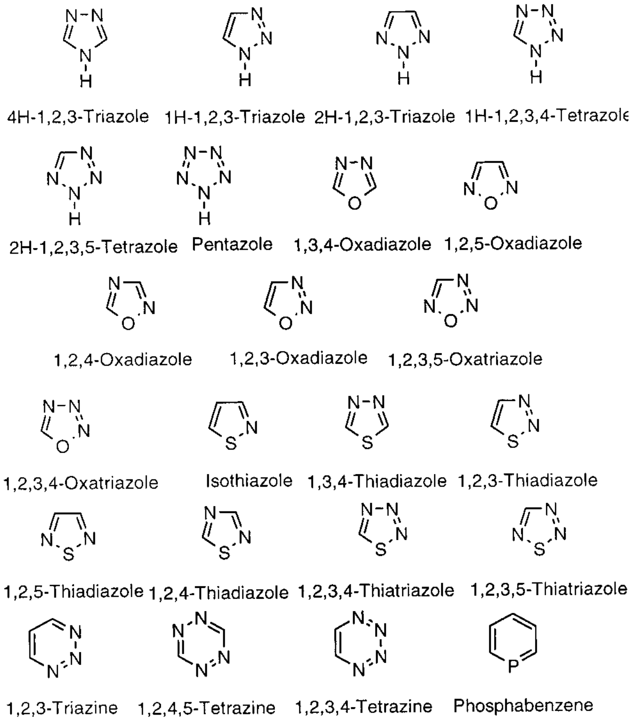
This result differs from earlier results where more factors (three) were needed to explain a smaller fraction of the total variation. This can be explained by the heterogeneous nature of the π electron systems in the preceding studies.[9,231] When the sample is more homogeneous, the multidimensional character of aromaticity becomes less pronounced. Finally, Krygowski et al.[241] compare the indices HOMA, BAC, I_6, and LB with a graph theoretical index,[244,245] which relates the similarity of a given benzene ring in a benzenoid hydrocarbon to the isolated benzene ring. It is found that this graph theoretical index by Randić correlates well with BE (0.91) and HOMA (0.88), less well with LB (−0.82), and poorly with BAC (−0.77) and I_6 (0.64).

More recently, Krygowski, Katritzky, and co-workers[17] have reviewed this question. They point out again that mutual relationships between aromaticity scales depend strongly on the selection of molecules in the sample.[216,246,247] Schleyer et al.[216] found a collinearity between NICS and the aromatic stabilization energy (ASE) as well as ASE and the diamagnetic susceptibity exaltation Λ for a limited set of monocyclic five-membered rings with one heteroatom.

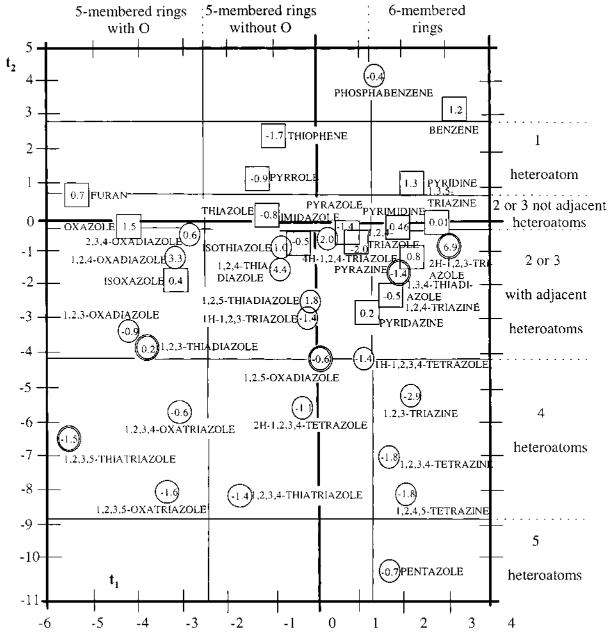
Scheme 42. Scores of Bicycles Compared to Monocycles—Correlation Coefficient[232]



Scheme 43. Additional Monoheterocycles Studied[233]



Scheme 44. Scores for the Total Set of Monocyclic Heteroaromatics[233]



In the case of porphyrins, the magnetic index NICS and the geometric index HOMA change monotonically. Similarly, 18 independent rings in nine benzenoid hydrocarbons showed a good collinearity between HOMA and NICS.[248]

It has also been shown that for a series of benzene rings in paracyclophanes[114] and in benzenoid hydrocarbons,[116] a very good correlation exists between the geometry-based index HOMA and the Hartree–Fock energy (HF) at the 6-31G** level of theory. It is clear that in all these cases the selection process favors a projection from a multidimensional space to a lower subspace. However, it may not be possible, in principle, to find a good correlation between indices. Scatter plots for NICS, HOMA, EN, and GEO versus HF show that only the first three have high correlation coefficients, whereas the bond alternation contribution GEO shows a highly scattered pattern versus HF.

VII. Conclusions

For over a century the concept of aromaticity has proven to be a fascinating and useful idea for the characterization of an important class of chemical compounds. Starting with the recognition of the properties of benzene, it was only natural to seek and develop quantitative measures of aromaticity for the characterization of other compounds and to relate their properties to those of benzene on a quantitative scale. What makes benzene so special are its stability, reactivity, structure, and diamagnetic properties. Therefore, criteria were developed along these lines both from theory and experiment. A particular boost came from the famous $4n + 2$ rule by Hückel and the resonance energy and ring current ideas advanced by Pauling. From the many aromaticity criteria that were developed over the years, some were abandoned and some survived. The presently accepted and used aromaticity criteria can be broadly subdivided in three groups: energetic, geometric, and magnetic criteria. They serve to describe the properties of ring systems with π electrons. Among these, the heteroaromatic ring systems are the most interesting. For long it was the expectation and the goal of chemists to achieve a characterization of ring compounds in a simple way, namely with a single scale. This would be possible if all adopted aromaticity criteria would more or less lead to the same ordering of compounds. This view was recently challenged by our groups[16,234] in systematic studies of five- and six-membered heterocyclic compounds. Principal component analysis revealed that, in general, aromatic compounds cannot be characterized by a single scale, but that a multidimensional character has to be accepted for aromaticity as a basic feature of this concept. From the analyses, the energetic, geometric, and magnetic criteria emerged as characteristics that can be related or unrelated to each other. It became clear that at least two substantial components exist which are orthogonal to each other and therefore can lead to different results for the degree of aromaticity in ring compounds. Of course, for certain subsets of compounds and aromaticity criteria, approximate linear relationships between two or more aromaticity scales can be found. However, the general multidimensional character of aromaticity has been recently reconfirmed.[246] This proves that different physical properties described by corresponding aromaticity criteria will, in general, not lead to the same classification of compounds and that the notion of a single index to characterize the properties of aromatic compounds has to be abandoned.

VIII. References

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