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HETEROCYCLIC AROMATICITY

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Abstract - The concept of aromaticity for heterocyclic compounds is summarized. The different methods available for calculating aromaticity are discussed. Overall conclusion are presented together with the outlook for further work.

Contents

1. Introduction

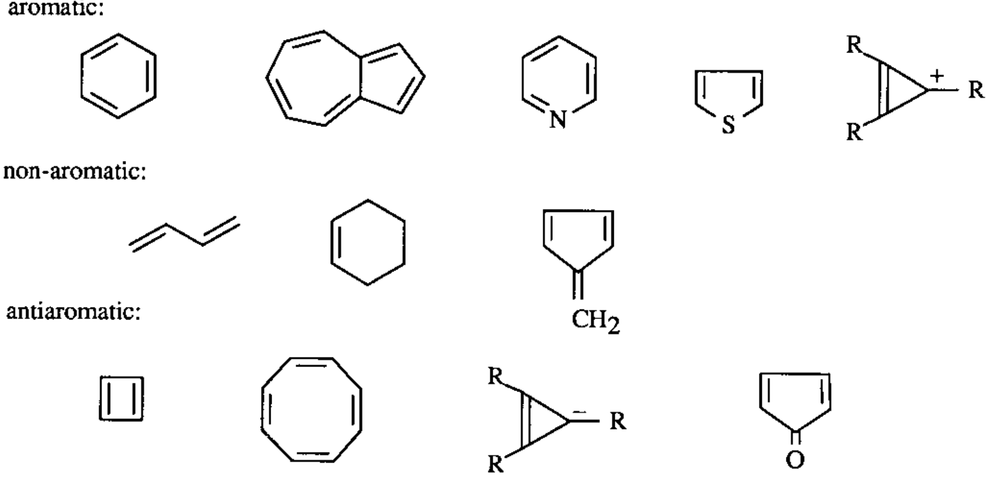
Aromaticity as a qualitative concept is very well established in teaching and research in organic, and particularly in heterocyclic chemistry.[1-8] The characteristics which distinguish aromatic from non-aromatic compounds have been realized for a very long time (Scheme 1), and it would be inconceivable to attempt to teach or practice heterocyclic chemistry without the use of the concept of aromaticity.

Scheme 1. Characteristics of an Aromatic Compound

1. Cyclic Compound with a Large Resonance Energy
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 support a Diamagnetic Ring Current

Cyclic compounds are now routinely divided into aromatic, non-aromatic, and anti-aromatic (Scheme 2),[5] and this qualitative distinction is quite clear.

Scheme 2. Aromatic, Non-Aromatic, and Antiaromatic Compounds



However, it is also well recognized that aromaticity is not only a qualitative but also a quantitative concept. Thus as shown in Scheme 3, some compounds are clearly more aromatic than others, and thus, quite obviously, a quantitative scale of aromaticity would be extremely useful.

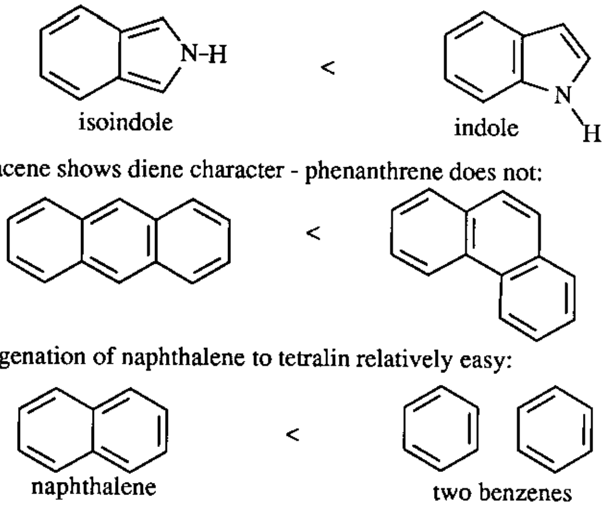
Scheme 3. Aromaticity: Some are More Equal Than Others

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

pronounced diene character of isoindole:

anthracene shows diene character - phenanthrene does not:

hydrogenation of naphthalene to tetralin relatively easy:



Hence a quantitative aromaticity scale would be useful

The methods that have been used to try to obtain a quantitative measure of aromaticity may be divided into three main groups (Scheme 4)[ref. 9 and references therein].

Scheme 4. Criteria for a Quantitative Measure of Aromaticity

1) Experimental methods to try to measure the energy (heat of formation) of the compound in question and to compare this with that of a hypothetical model compound without the cyclic conjugation.
2) Experimental methods which have looked in particular at the geometries and magnetic properties of aromatic compounds, and have compared them with non-aromatic analogs.
3) Molecular orbital calculations corresponding to both (1) and (2) above.

A great deal of effort has gone into the construction of such quantitative aromaticity scales, and some of this work will be summarized here. However, it is quite clear that there have been very considerable difficulties which have arisen for a variety of reasons some of which are given in Scheme 5.[7,8]

Scheme 5. Problems Encountered in the Definition of Quantitative Aromaticity Scales

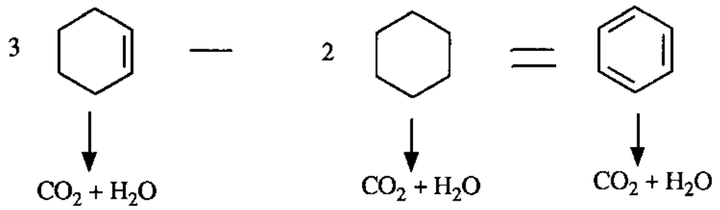
1. Differences Between the Electronic Structure of Heteroatoms and Carbon
2. Incompatibility of Different Physical and Chemical Molecular Characteristics
3. Comparison of Experimental Data Obtained in Different Media
4. Difficulties in Definition of Non-Aromatic Model to Compare with Aromatic Compound

2. Determination of Energy Scales of Aromaticity

a. *Aromatic Energies by Combustion or Hydrogenation*

Combustion was the first method used for the determination of aromatic stabilization energies. The principle is shown in Scheme 6 for benzene.[10]

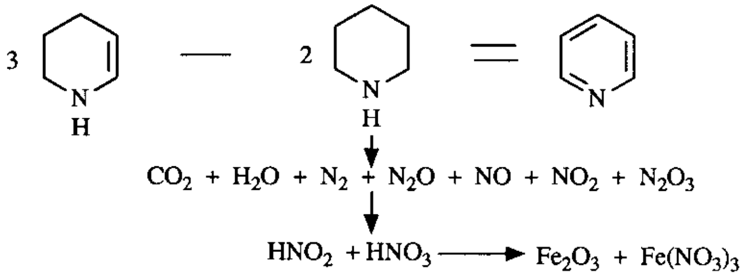
Scheme 6. Combustion Method for Determination of Aromacity for benzene



model for hypothetical cyclohexatriene

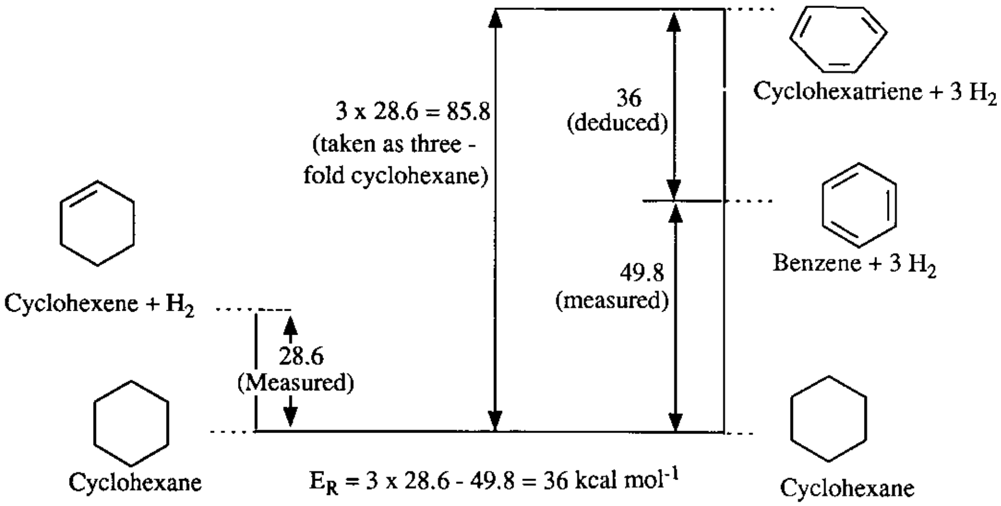
Unfortunately, application to heterocycles is more difficult as shown in Scheme 7.[9] On combustion, the presence of the nitrogen atom can form various N-oxides and oxyacids which can attack the material of the bomb used for the combustion. This leads to significant errors.

Scheme 7. Aromaticity of Pyridine by Combustion : Complications



The hydrogenation method for quantitative measurement of aromatic stabilization energies utilizes the principle shown in Scheme 8.[10] Again, application to heteroaromatic compounds is difficult because the presence of the nitrogen and sulfur often cause poisoning of the catalyst.

Scheme 8. Hydrogenation Method for Determination of Aromaticity



The results of such determinations of aromaticity by combustion and by hydrogenation[10] are gathered in Scheme 9. The combustion method has quite large errors.

Scheme 9. Quantitative Measurement of Aromaticity from Heats of Hydrogenation and Combustion

	Combustion	Hydrogenation
Benzene	36 - 37	36
Pyridine	23 - 43	-
Thiophene	24 - 31	29
Furan	16 - 23	22
Pyrrole	14 - 31	-

Large errors involved because of small differences between large quantities

b. Determination of Aromatic Stabilization Energies by Basicity Measurements Related to Proton Addition

In contrast to hydrogenation or combustion, which measure ΔH directly, methods depending on the study of equilibria measure ΔG. Hence a problem here is the conversion of ΔG values to ΔH values. Alternative methods for dealing with this problem are shown in Scheme 10.

Scheme 10. Methods for the Conversion of ΔG to ΔH

(i) By consideration of the temperature variation of measured K_T values

(ii) Using variable temperature determination of basicities

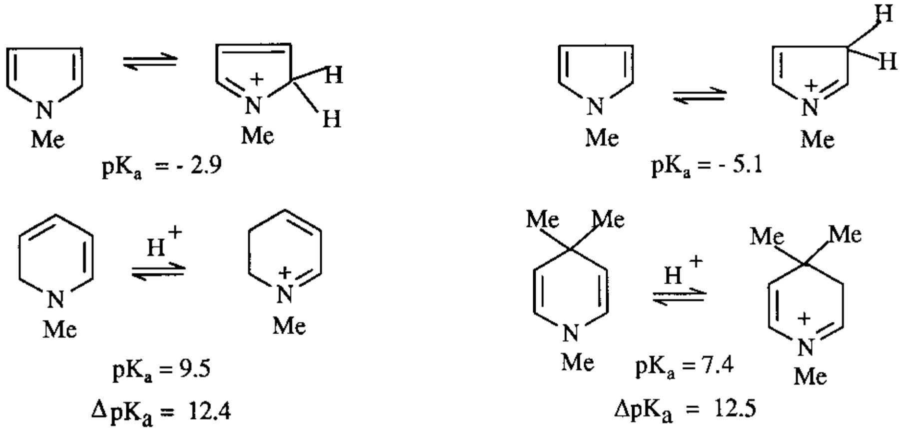
(iii) ΔG taken as an approximation for ΔH_{int} which excludes solvent interactions as suggested by Larson and Hepler [11]

(iv) A general consideration of the variation of acidity function with temperature which suggests [12] $\Delta H = 1.1 \Delta pKa$

Unfortunately, very few temperature variations of basicities, and still fewer of K_T are available which make impractical methods (i) and (ii). We have therefore used method (iv) of Scheme 10 to estimate ΔH values.

It is well known that pyrrole is a very weak base, the reason being that it coordinates at the α-carbon atom with loss of the aromatic resonance energy. The somewhat similar compounds 1,2- and 1,4-dihydropyridines are much stronger bases as shown in Scheme 11.[13]

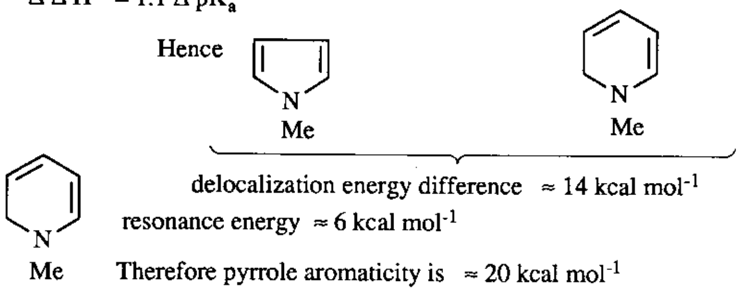
Scheme 11. Basicity of Pyrrole



This difference in the basicities of pyrrole and model compounds can be used to calculate the aromatic stabilization energy of pyrrole. The principle used is shown in Scheme 12.[13,14]

Scheme 12. Aromaticity of Pyrrole

$\Delta \Delta H^0 = 1.1 \Delta pK_a$



delocalization energy difference ≈ 14 kcal mol^{-1}

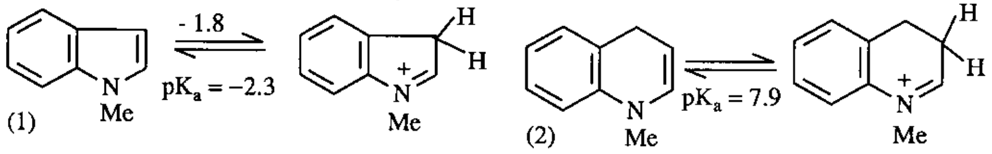
resonance energy ≈ 6 kcal mol^{-1}

Therefore pyrrole aromaticity is ≈ 20 kcal mol^{-1}

Similar methods have been used to determine the aromaticity of other heteroaromatics. The comparisons used for indole are shown in Scheme 13 for carbazole in Scheme 14 and for indolizidine in Scheme 15.[14]

Scheme 13. Aromaticity of Indole

ΔH_o for hemi-protonation

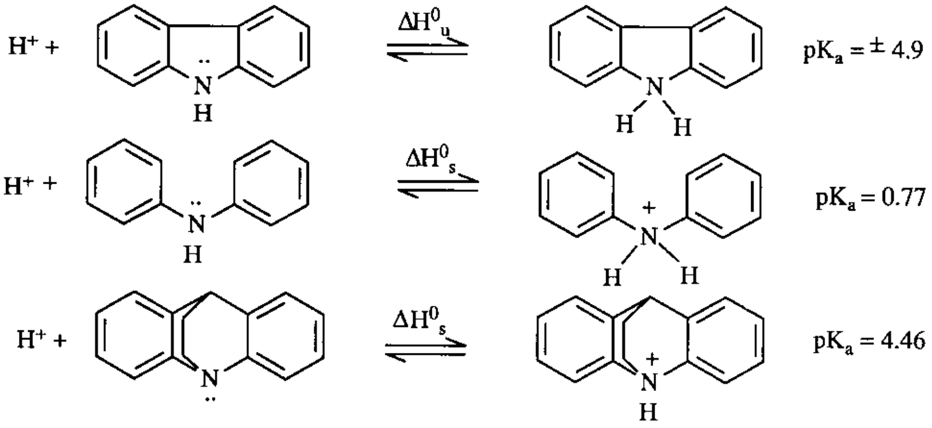


$\Delta pK_a = 10.2$ corresponds to ΔH° of 11

Resonance Energy of (2) is 36 (Benzene) + 6 kcal mol^{-1}

Hence Resonance Energy of Indole ≈ 53 kcal mol^{-1}

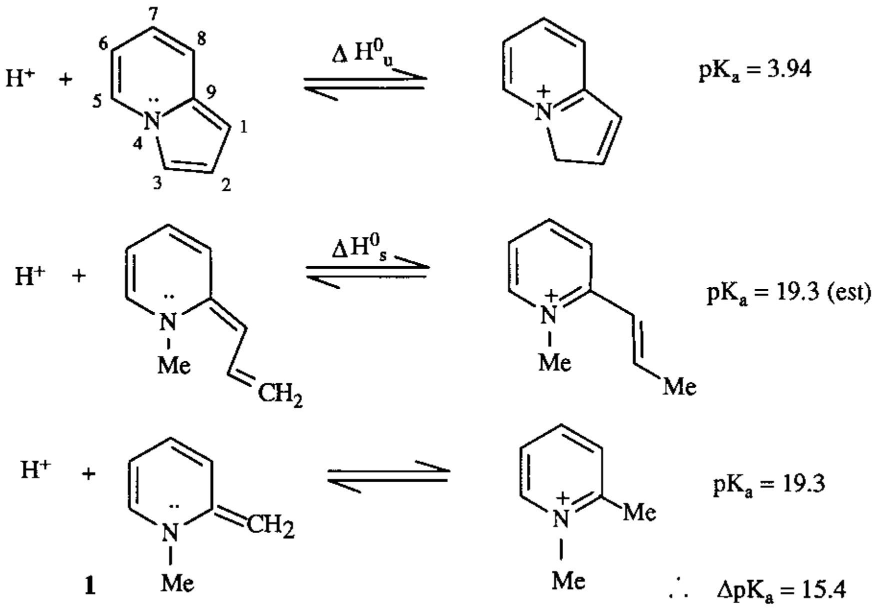
Scheme 14. Aromaticity of Carbazole



$$\therefore A_{\text{carbazole}} = A_{\text{PhNHPh}} + 5 = 78 + 5 = 83 \text{ kcal mol}^{-1}$$

$$\text{or } A_{\text{carbazole}} = 2A_{\text{benzene}} + 12 = 72 + 12 = 84 \text{ kcal mol}^{-1}$$

Scheme 15. Aromaticity of Indolizidine

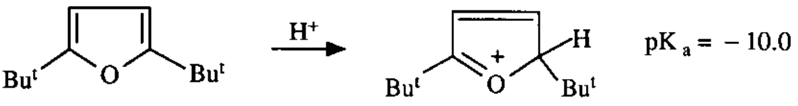


$$A_{\text{indolizidine}} = A_{\text{pyridine}} - A(1) + 17 \text{ kcal mol}^{-1}$$

$$= 32 - 14 + 17 = 35 \text{ kcal mol}^{-1}$$

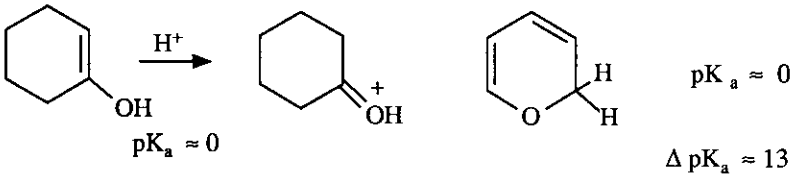
The application of this method to furan is more difficult because this compound is still less basic and one has to grapple with the additional difficulty of the definition of acidity functions in the strongly acidic regions needed - see Scheme 16.[14]

Scheme 16. Aromaticity of Furans



Estimating for effect of di-t-butyl given for furan $pK_a = -13$

From estimate



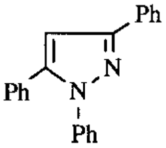
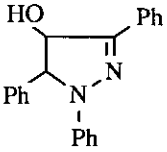
Hence, aromaticity of furan 14 + stabilization of dieneol thus

furan ≈ 18 kcal mol^{-1}

c. Determination of Aromatic Stabilization Energy from Heats of Dehydration

An alternate method for the estimation of aromaticity is the determination of heats of dehydration.[15] This has been carried out for pyrazole and isoxazole as shown in Schemes 17 and 18 respectively. Whereas pyrazole has quite a high stabilization, that found for isoxazole is very low.

Scheme 17. Resonance Energy of Pyrazole from Heat of Dehydration

		Crystal to		Estimate of Vapors to H_2SO_4
		H_2SO_4	$CHCl_3$	
	**1**	-16.4	3.3	-19.7
H_2O		-	-	-8.2
	**2**	-47.6	5.0	-52.6

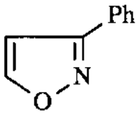
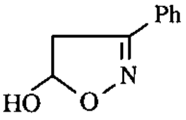
Hence

2 $\longrightarrow$ **1** + H_2O + 24.7 kcal mol^{-1}

Resonance Energy of Pyrazole = $24.7 + 4^{*} - 3^{\neq}$; ie $\approx$ 26 kcal mol^{-1}

* N - N = C resonance in **2** ≠ 5-Ph / ring resonance in **1**

Scheme 18. Resonance Energy of Isoxazole from Heat of Dehydration

		Crystal to		Estimate of Vapors to H_2SO_4
		H_2SO_4	$CHCl_3$	
	**1**	-22.7	4.0	-26.7
H_2O		-	-	-8.2
	**2**	-15.5	-0.9	-14.6

Hence

2 $\longrightarrow$ **1** + H_2O + 3.9 kcal mol^{-1}

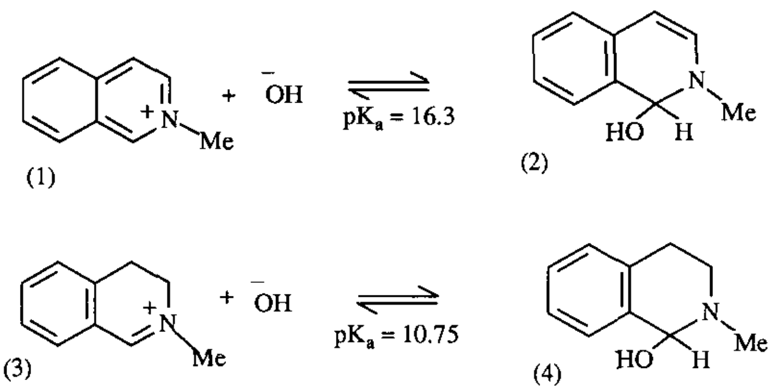
Resonance Energy of Isoxazole = $3.9 + 4^{*}$; ie $\approx$ 8 kcal mol^{-1}

* O - N = C resonance in **2**

d. Aromatic Stabilization Energies for 6-Membered Rings Using Pseudo-Base Equilibria

It is clearly not possible to gain a measure of the aromaticity of a six-membered ring compound such as pyridine by simply measuring the basicity towards proton addition, because aromaticity is retained in the protonated cation. However, it is possible to gain insight into the aromatic stabilization energy by considering the basicities of pseudo-bases derived from N-methylheteroaromatic cations and corresponding model compounds. The principle is shown in Scheme 19 for isoquinoline. The model taken here is 2-methyl-3,4-dihydroisoquinolinium cation. Corrections have to be made for the conjugation energies in the fragments (shown in Scheme 19 second part) and when this is done, a value can be derived.[16]

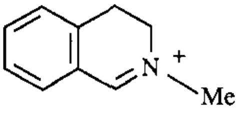
Scheme 19. Aromaticity and Pseudo-base Equilibria



$\Delta pK_a = 5.5$; $\Delta\Delta H^0 = 6$ kcal mol^{-1}

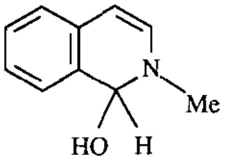
Hence: $A_{isoquin} = A_{benzene} + 6 + X + Y$

Where: Conj. energy X



≈ 2 (cf. styrene)

Conj. energy Y



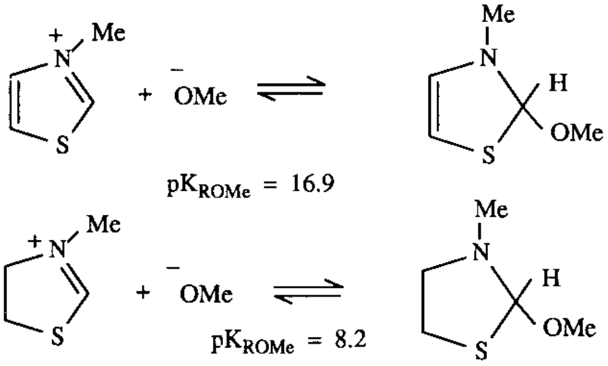
greater resonance energy over benzene of this compound

= 4 (for enamine) + 2 (for styrene) = 6

Hence $A_{isoquin} = 36 + 6 + 2 + 6 = 50$ kcal mol^{-1}

This method can be extended to pseudo bases derived from the azoles as illustrated for thiazole (Scheme 20).[17]

Scheme 20. Thiazolium Pseudo-bases



$pK_{ROMe} = 16.9$

$pK_{ROMe} = 8.2$

Assuming $\Delta H° = 1.1\,\Delta pK_a$

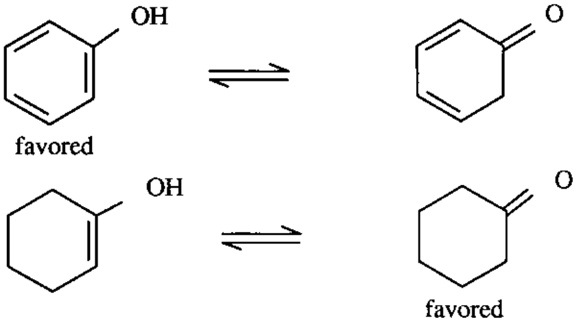
$A_{thiazolium} = 1.1\,(16.9 - 8.2) + 10^* \approx 20$ kcal mol^{-1}

* rough estimate of resonance interactions in thiazolium pseudo-base

e. Deduction of the Aromatic Stabilization Energy of Benzene from Tautomeric Equilibrium

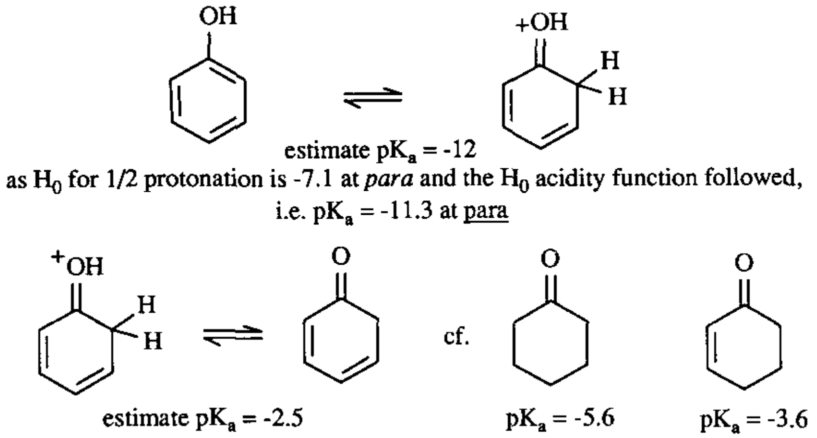
It is very well recognized that phenol exists as such in the hydroxy form and not as cylcohexadienone whereas cyclohexenol does exist predominantly as the carbonyl form, cyclohexanone. The reason for the different behavior is clearly the aromaticity in phenol. By comparing the tautomeric equilibrium constants, it should be possible to derive a measure of this stabilization energy (Scheme 21).

Scheme 21. Aromaticity of Benzene and Tautomeric Equilibria



In some cases direct measurements of the tautomeric equilibrium constants in solution are not available. The ways in which they have been estimated are summarized in Schemes 22 and 23, which leads to the result of Scheme 24.

Scheme 22. Tautomeric Equilibrium Constants of Phenol and Cyclohexanone



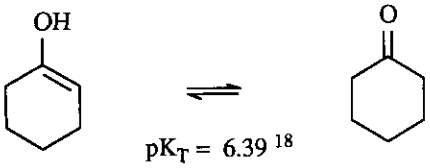
estimate $pK_a = -12$

as H_0 for 1/2 protonation is -7.1 at *para* and the H_0 acidity function followed,
i.e. $pK_a = -11.3$ at para

estimate $pK_a = -2.5$ $pK_a = -5.6$ $pK_a = -3.6$

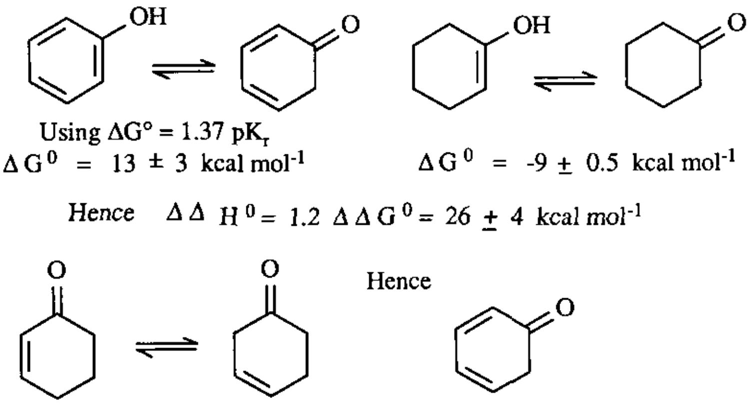
Hence $pK_T \approx 9.5$

Scheme 23. Keto-Enol Equilibrium Constant of Cylclohexanone.



$pK_T = 6.39$ [18]

Scheme 24. Calculation of the Aromaticity Resonance Energy of Benzene from Tautomeric Equilibria Data



Using $\Delta G° = 1.37\ pK_T$

$\Delta G^0 = 13 \pm 3$ kcal mol^{-1} $\Delta G^0 = -9 \pm 0.5$ kcal mol^{-1}

Hence $\Delta\Delta H^0 = 1.2\ \Delta\Delta G^0 = 26 \pm 4$ kcal mol^{-1}

Hence

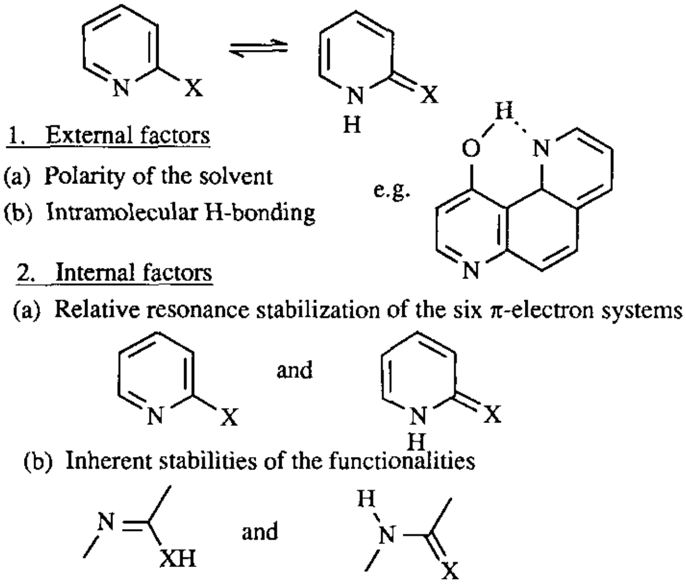
$\Delta G^0 = 3.2$ kcal mol^{-1} resonance $\Delta H^0 = 6 \pm 1$ kcal mol^{-1}

So aromaticity of benzene = 32 ± 5 kcal mol^{-1}

f. Estimation of Aromatic Stabilization Energies of Pyridones from Tautomeric Equilibrium

The factors which influence the tautomeric equilibria of a compound such as 2-pyridone are of two types: external factors and internal factors (Scheme 25).[19]

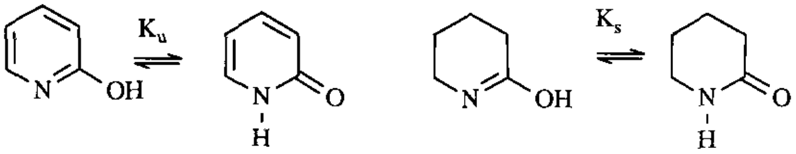
Scheme 25. Factors Influencing Tautomeric Equilibria of Heterocycles



1. External factors
   - (a) Polarity of the solvent
   - (b) Intramolecular H-bonding
2. Internal factors
   - (a) Relative resonance stabilization of the six π-electron systems
   - (b) Inherent stabilities of the functionalities

Once again, by a comparison of the tautomeric equilibrium constants in a compound such as 2-pyridone with a model derivative such as tetrahydro-2-pyridone, it is possible to obtain an estimate of the difference in the aromatic stabilization energies of 2-hydroxypyridine and of 2-pyridone. The calculation method used is shown in Scheme 26 and the respective energy diagram in Scheme 27.[20] It should be noted that the tautomeric equilibria of pyridones and analogous compounds are highly dependent on the medium: this implies that aromatic stability also depends on the medium. All the data given in the present section refer to aqueous solution.

Scheme 26. The Aromaticity of 2-Pyridone as Estimated on the Basis of Tautomeric Equilibrium Constants



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

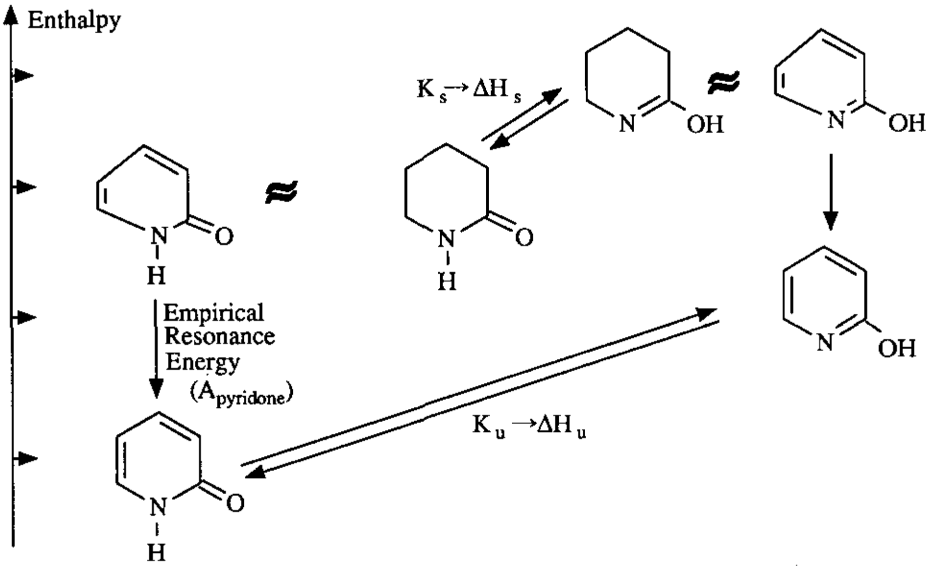
$$\Delta H_s = \text{Interact (NH/CO)} - \text{Interact (N/OH)}$$

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

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

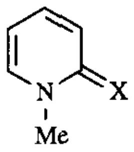
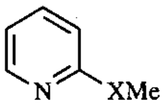
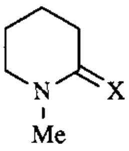
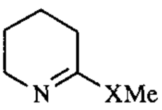
$$A_{\text{pyridine}} - A_{\text{pyridone}} = RT\ln(K_u/K_s) + T(\Delta S_s - \Delta S_u)$$

Scheme 27. The Enthalpy of Tautomeric Equilibria for the Resonance Energy Calculation of 2- Pyridone.



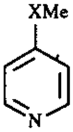
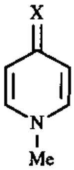
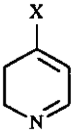
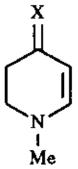
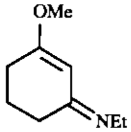
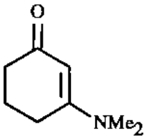
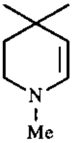
The results for 2-pyridone and related compounds are given in Scheme 28 in detail.[21]

Scheme 28. Results for the Aromaticity Calculations of 2-Pyridone and Related Compounds

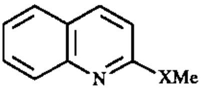
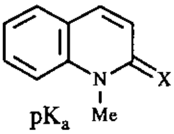
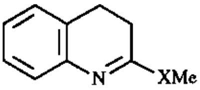
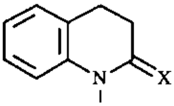
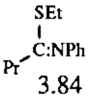
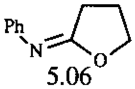
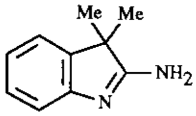
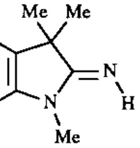
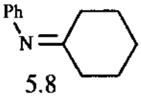
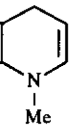
X	 pKa	 pKa	ΔG_u kcal mol^{-1}	 pKa	 pKa	ΔG_S kcal mol^{-1}	$\Delta G_u - \Delta G_S$ kcal mol^{-1}
S	-1.22	3.62	-6.7	-1.76	6.9	-12.0	5.3
O	0.32	3.28	-4.1	0.19	7.5	-10.0	6.5
NH	13.02	6.86	8.5	assumed equal by symmetry		0.0	8.5
CH_2	19.8	5.97	19.0	11.4	9.43	2.7	16.3

We have summarized results for 4-pyridone, 2-quinolone, and 1-isoquinolone compounds in Schemes 29, 30 and 31.[13,21,22]

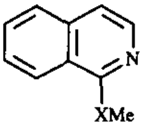
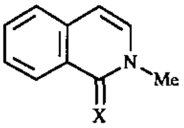
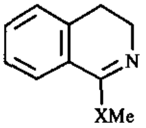
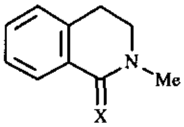
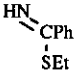
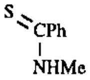
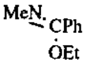
Scheme 29. Aromatic Resonance Energy for 4-Pyridone and Its Analogs

X	 pK_a	 pK_a	 estimated pK_a	 estimated pK_a	4-series A_{py} - A_X kcal mol^{-1}	2-series A_{py} - A_X kcal mol^{-1}
S	5.97	1.30	N/A	N/A	—	6.0
O	6.66	3.33	11.9 	3.1 	7.7	7.5
NH	9.66	15.75	assumed equal by symmetry		10.4	9.6
CH_2	6.02	21.3	7.4 p-$MeC_6H_4CH{=}N$-Bu^t	est. 9.45 c.f. 10.45 	20.2	18

Scheme 30. Aromatic Resonance Energy for 2-Quinolone and Its Analogs

X	 pK_a	 pK_a	 estimated pK_a	 estimated pK_a	A_q-A_x kcal mol^{-1}
S	3.71	-1.40	 $PrC(SEt){:}NPh$ 3.84	PhNMeCSMe -3.34	2.9
O	3.17	-0.71	 5.06	PhNMeCOMe	2.0
NH	7.34	11.58	 8.15	9.25 	5.0
CH_2	5.41	15.0	 5.8	10.0 	7.5

Scheme 31. Aromatic Resonance Energy for 1-Isoquinolone and Its Analogs

X	 pK$_a$	 pK$_a$	 estimated pK$_a$	 estimated pK$_a$	A$_q$-A$_x$ kcal mol^{-1}
S	3.93	-2.13	6.04  $HN{=}C(SEt)Ph$	-2.61  $S{=}C(NHMe)Ph$	4.3
O	3.05	-1.80	6.20  $MeN{=}C(OEt)Ph$	PhCONMe -1.62	4.1
NH	7.62	11.38	assumed equal by symmetry		6.0
CH_2	6.42	15.62	8.30	13.06	7.0

Using the results described above for the aromatic stabilization energies of the parent pyridine, quinoline and isoquinoline molecules, we can now give the differences in the aromatic resonance stabilizations for these pyridone-like compounds compared to the parent heterocycle in Scheme 32.[23]

Scheme 32. Comparison of Aromatic Resonance Energy Differences for Different Heterocycles (kcal mol^{-1})

X	A$_{pyridine}$ - A$_{pyridone}$ 2 - series	A$_{pyridine}$ - A$_{pyridone}$ 4 - series	A$_{quinoline}$ - A$_{quinolone}$	A$_{isoquinoline}$ - A$_{isoquinolone}$
S	6	-	3	4
O	7.5	8	2	4
NH	10	10	5	6
CH_2	18	20	7.5	7

g. Aromatic Resonance Energies from MO Calculations

Two of the best known calculated energy criteria are: a)the Hess-Schaad resonance energy[24,25] and b) the Dewar resonance energy,[26] (Schemes 33 and 34).

Scheme 33. Hess - Schaad Resonance Energy Definition

$$HSRE = E_{HMO} - E_{LOC}$$

E_{HMO} - HMO π - system energy

E_{LOC} - Empirical isolated π -bond energies

Scheme 34. Dewar Resonance Energy Definition

$$E_R = \Delta H_f - n_H E_{CH} - n'_C E_{C-C} - n''_C E_{C=C}$$

ΔH_f – heat of formation
n_H – number of CH bonds with energy E_{CH}
n'_C – number of single CC bonds with energy E_{C-C}
n''_C – number of double CC bonds with energy $E_{C=C}$

Compound	E_R (eV)
Benzene	0.97
Naphthalene	1.46
Anthracene	1.78
Naphthacene	2.03
Phenanthrene	2.13
Perylene	2.89
Azulene	0.30

An alternative Dewar resonance energy DRE′ can be calculated using AM1 heats of formation (Scheme 35).[27]

Scheme 35. Dewar Resonance Energy Definition (DRE′)

$$DRE' = n\,(E_{CX}(s) - E'_{CX}) + m\,(E_{CX}(d) - E''_{CX}) + E_{\pi b}$$
$$X = C, N, O, S$$

n - total number of C-C and C-X bonds
m - total number of C=C and C=X bonds
$E_{CX}(s)$ - σ- bond energy of "single" bond in acyclic polyene
$E_{CX}(d)$ - σ- bond energy of "double" bond in acyclic polyene
E'_{CX} - σ- bond energy of "single" bond in cyclic polyene
E''_{CX} - σ- bond energy of "double" bond in cyclic polyene
$E_{\pi b}$ - π- bonding energy

The respective values of different theoretical resonance energies of aromatic compounds are given in Scheme 36.[24,25,28,29]

Scheme 36. Calculated Resonance Energies of Some Aromatic Compounds

Compound	DRE (kcal mol^{-1})	HSRE (kcal mol^{-1})
Benzene	22.6	9.0
Pyridine	23.1	8.0
Pyrimidine	20.2	6.8
Pyrazine	17.1	6.8
Thiophene	6.5	4.5
Furan	4.3	1.0
Pyrrole	5.3	5.3
Imidazole	15.4	5.8

The Dewar resonance energy in its original form cannot be calculated for compounds containing N-N single bonds, N-N double bonds N-O bonds or N-S bonds as the polyene bond energies are not available for these compounds. Similarly, the Hess-Schaad resonance energy cannot be calculated for any compounds containing N-N double bonds, N-O single bonds or N-S single bonds as Huckel π-bond energies are not available.

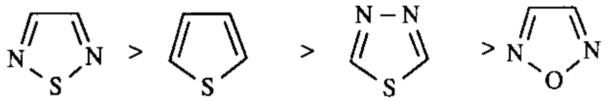
3. Non-Energetic Criteria of Aromaticity

a. Geometrical Criteria for Heteroaromaticity

It has long been suggested that the geometry of a ring can be used as a criterium for the degree of aromaticity. Thus, Bak *et al.*[30] pointed out that the order of decreasing aromaticity of Scheme 37 could be inferred from microwave-derived bondings. Julg sought to make this approach quantitative with his aromaticity index (Scheme 37).[31]

Scheme 37. Quantitative Geometrical Aromaticity Index

(a) According to bond order data, aromaticity decreases [30]



(b) Aromaticity index $\underline{A}$

$$\underline{A} = \frac{1 - 225}{n} \sum_{(rs)} \frac{(1 - d_{rs})^2}{\bar{d}}$$

where:

n = no. of π - electrons

$$d_{rs} = \text{bond length} / \bar{d} \quad = \frac{1}{n} \sum_{(rs)} d_{rs}$$

i.e. deviation of bonds from equal lengths

Benzene	$\underline{A}$ = 1	Furan	$\underline{A}$ = 0.87
Thiophene	$\underline{A}$ = 0.93	Fulvene	$\underline{A}$ = 0.62
Pyrrole	$\underline{A}$ = 0.91		

Other quantitative measures derived from geometry or similar sources are Pozharskii's index (Scheme 38)[32] and the Berezin coefficient of influence[33] and Balaban's aromaticity constant[34] (Scheme 39).

Scheme 38. Pozharskii's Aromaticity Index Definition

$$\overline{\Delta N} = \frac{\sum_i \Delta N}{n}$$

ΔN - difference in bond order

n - number of bonds

Scheme 39. Other Quantitative Measures of Aromaticity

"Coefficients of Influence" (V. I. Berezin)

Σ_r = sum of the internal angles of a 6 membered aromatic ring.

Benzene Σ_r =	2. 130	Pyridine	1. 987
Pyrazine	2. 046	s-Tetrazine	1. 666

"Aromaticity constant" $K = \Sigma\ k$, where k values express the tendency of an atom to release or attract π-electrons from the delocalized aromatic cloud. (Balaban)

$$k = (0.478\ \frac{Z^*}{r} - 1.01 - m_\pi)\ 100$$

$$Z^* = Z_m - 0.85\ m_k - 0.525\ m_{L,m} - 0.175\ m_{L,b}$$

Z = nuclear charge

Z* = effective charge

r = covalent radius A^0

m_k = number of electrons in the K shell

$m_{L,m}$ = number of nonbonding L electrons

$m_{L,b}$ = number of bonding L electrons

m_π = number of π electrons

Benzene	0	Thiophen	- 1	Pyrrole	- 26
Pyridine	+ 23	Furan	- 3	Pyrrole anion	- 77
Pyridinium	+ 97	Phenol	- 7	Cyclopentadienyl anion	-100

This approach has been expanded most recently by Bird to give the Bird aromaticity indicies (Scheme 40).[35,36]

Scheme 40. Definition of Bird Aromaticity Indicies

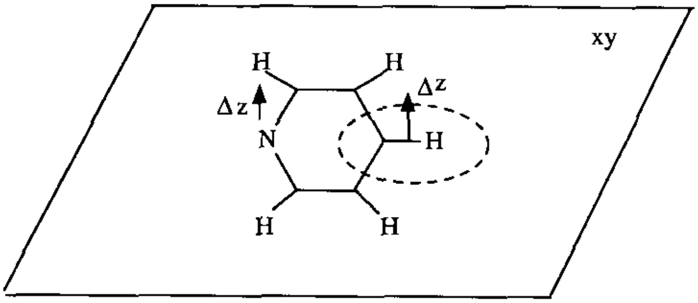
$$I_{5(6)} = 100\left[1 - \frac{V}{V_K}\right] \quad \text{where} \quad V = \frac{100}{N_0}\sqrt{\frac{\Sigma\,(N - N_0)^2}{n}}$$

$$V_K = \begin{cases} 35 & \text{for a five - membered heterocycle} \\ 33.3 & \text{for a six - membered heterocycle} \end{cases}$$

N is the bond order $N_0 = \frac{\frac{\Sigma\ N}{n}}{n}$ n is the number of bonds in cycle

Another "geometrical" aromacity parameter A_s can be defined on the basis of the quantum-chemically calculated harmonic force constants for "out-of-plane" vibrations of ring atoms in cyclic systems (Scheme 41).[37] This parameter is also an energetic measure of the rigidity of an aromatic π-system towards spatial distortions.

Scheme 41. Aromatic π - System Rigidity Parameter



$$k_h = \frac{\Delta E}{\Delta z^2}$$

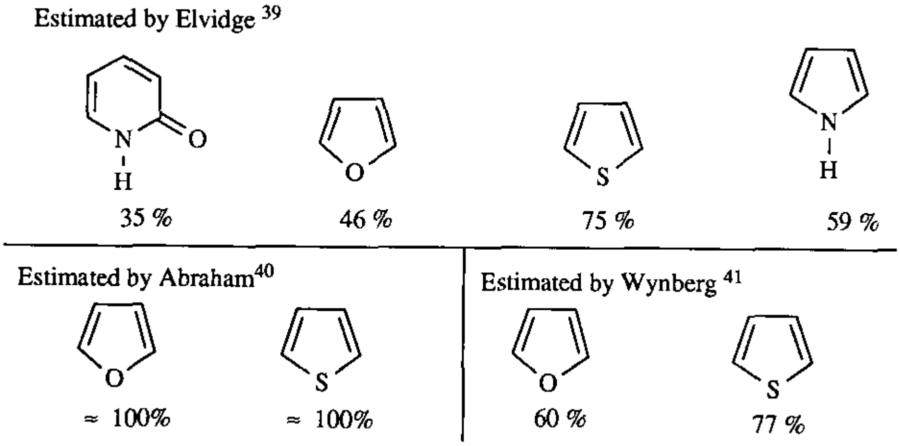
Aromaticity = Geometric mean of k_w

$$A_s = \underset{n}{\Pi k_h}$$

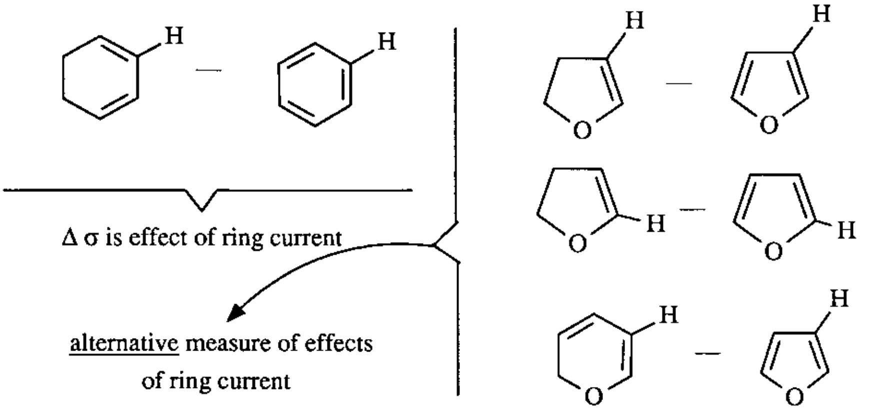
b. Magnetic Criteria for Heteroaromaticity

It has long been known that the ring current in an aromatic compound exerts a deshielding effect on atoms outside the ring and a shielding effect on atoms inside the ring. Numerous attempts have been made to apply this in a qualitative way. However, it has been extremely difficult to get the correct model compounds and make the right corrections. As is shown in Scheme 42, different workers have come to quite different results using this method. Some of the difficulties are illustrated in Scheme 43.[38]

Scheme 42. Quantitative Measurement of Aromaticity by Nmr Ring Currents



Scheme 43. Nmr_ Ring Current Method for Aromaticity



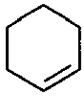
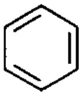
The molar diamagnetic susceptibility exaltation has been widely proposed as a criterion of aromaticity (Scheme 44).[42-44]

Scheme 44. Molar Susceptibility As a Criterion of Aromaticity

Susceptibility Exaltation (van Vleck, 1932)

(Ring Current Increases Magnetic Susceptibility)

$$\lambda = \chi_m(\text{obs}) - \chi_m(\text{calc})$$

	χ_m (obs)	λ
 Cyclohexene	57.5	-0.8
 Benzene	54.8	13.7

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 (Scheme 45).[37]

Scheme 45. Aromaticity Index by Ring Current Intensity

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

Where n is the number of ring atoms; the summation is taken of the (2n + 1)th π-orbital over all the ring atoms.

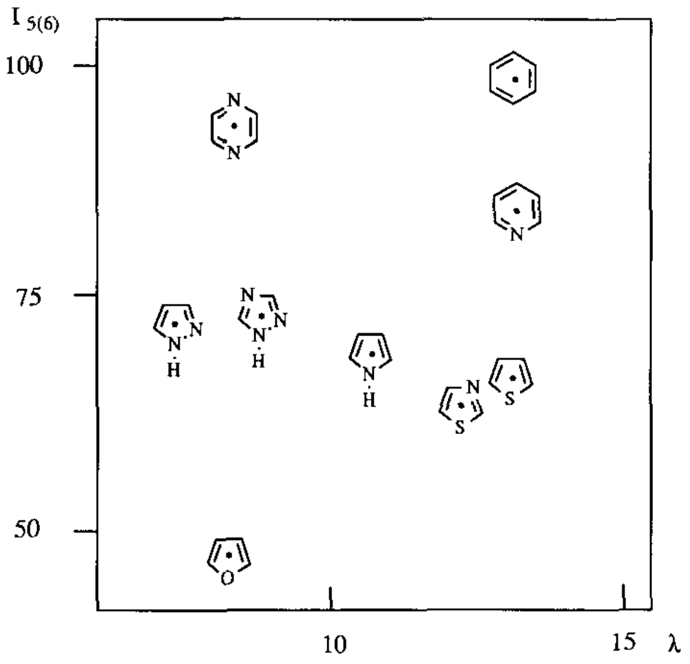
c is the MO coefficients at the 2n + 1 "aromatic" π-orbital.

4. Statistical Approach to Aromaticity

a. *Summary of Classical Approaches to Heteroaromaticity and Need for a New Approach*

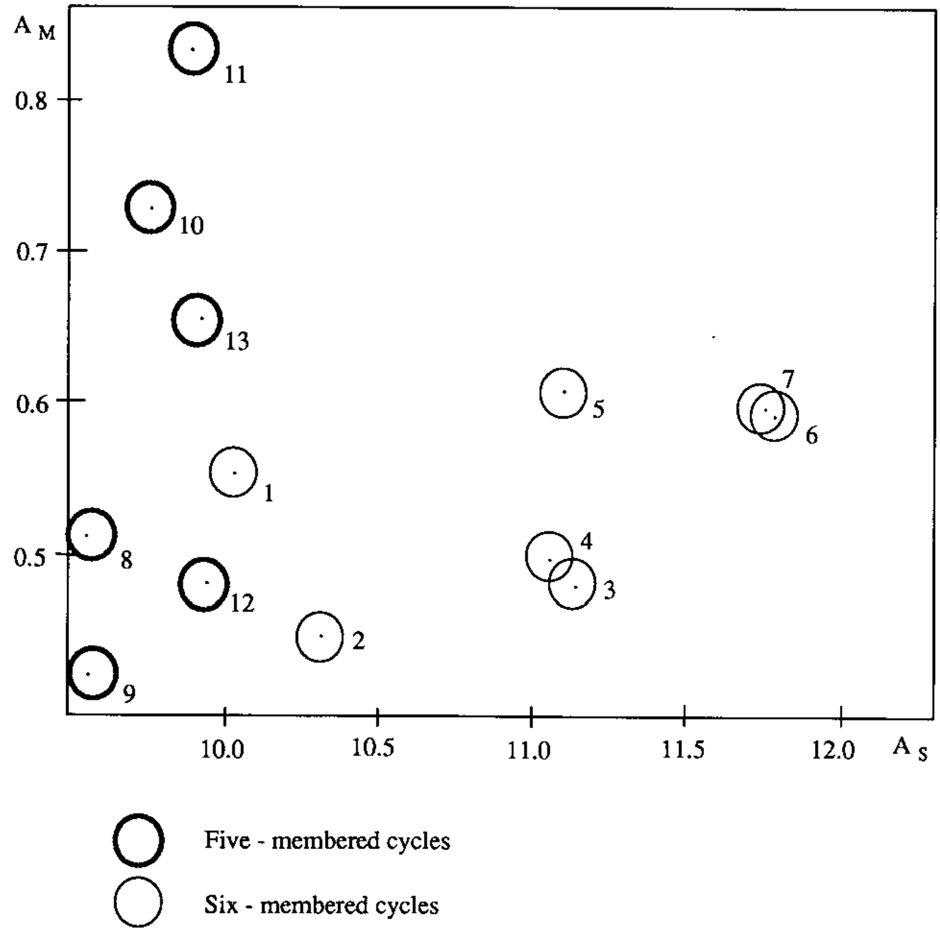
Although very useful insight is obtained regarding the aromatic stabilization of a variety of compounds from the work just described, the overall picture is nevertheless one of confusion and complication. In particular, the different measures do not tie up with each other. Thus in Scheme 46, a plot of the aromaticities deduced from the Bird aromaticity indices with those from molar magnetic susceptibility shows absolutely no correlation.

Scheme 46. Plot of Bird Aromaticity Parameters $I_{(5,6)}$ Against Molar Susceptibility Exaltation, λ



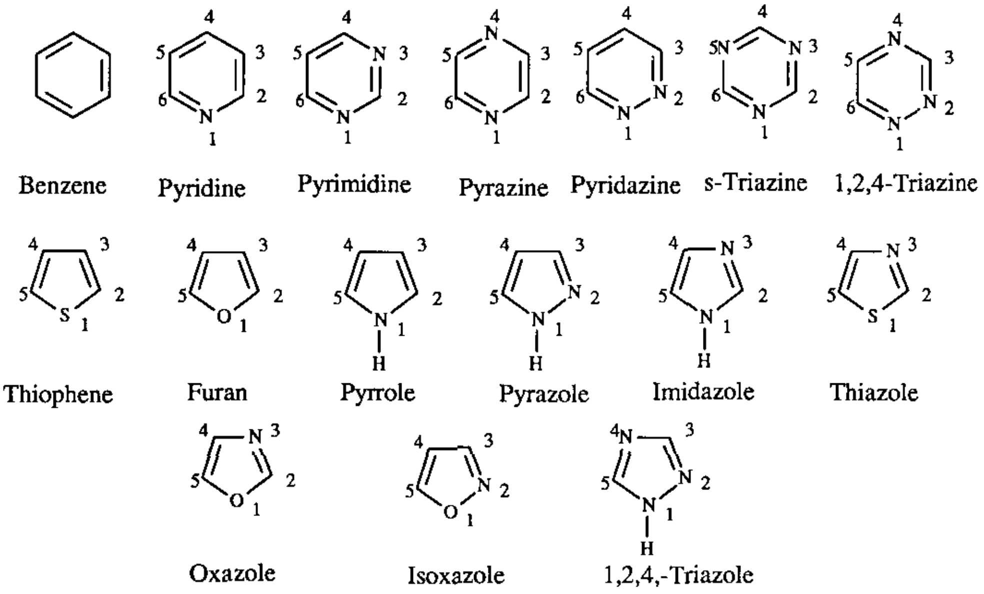
There is no common relationship between the A_s and A_m, parameters, calculated by the same quantum-chemical method (AM1 SCF LCAO MO) (Scheme 47).[37] However, the five- and six-membered rings can be separated into two groups, which have a slight dependence between those parameters. Notably, the five-membered rings are more sensitive towards the "magnetic" A_M parameter whereas the six-membered rings have larger dispersion of "structural" A_s parameters.

Scheme 47. Plot of AM1 Calculated A_M Aromaticity Parameters Against AM1 Calculated A_S Parameters



In this situation, a new approach was required, and we decided to apply the method of Principal Component Analysis to all available data. In our initial approach, we chose a set of 16 familiar monocyclic aromatics (Scheme 48).

Scheme 48. A Model Set of Sixteen Familiar Monocyclic Aromatic Compounds



We treated by the SIMCA method, a total of 12 variables of which 4 were geometric (the Bird indices derived from experimental data, the Bird indicies derived from AM1 calculated ring geometries, the Julg measure of ring current, and the Pozharskii indicies), 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).[9] The data set of 12 characteristics and 16 compounds used is shown in Scheme 49.

To determine the number of statistically significant eigenvectors, the method of cross-validation is used. The number of principal components is selected as three. The results on the PC analysis are given in Scheme 50. It is seen that two Principal Components account for 74% and three for 87% of the variance.

With 48.4% of the total variance in the data set, eigenvector number one is comprised predominantly of I_x, I'_x and ΔN. Characteristics DRE, DRE′, HSRE, RC, and ΔH_f are also moderately relevant. For $\Delta H_{f(AM1)}$ low utility and for χ_M, Λ, and ^{15}N zero utility in the model (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 third PC, the geometrical and energetic variables have similar, high utility in the model, with the magnetic variables having somewhat lower utility.

Scheme 49. Data Set for Familiar Monocyclic Compounds

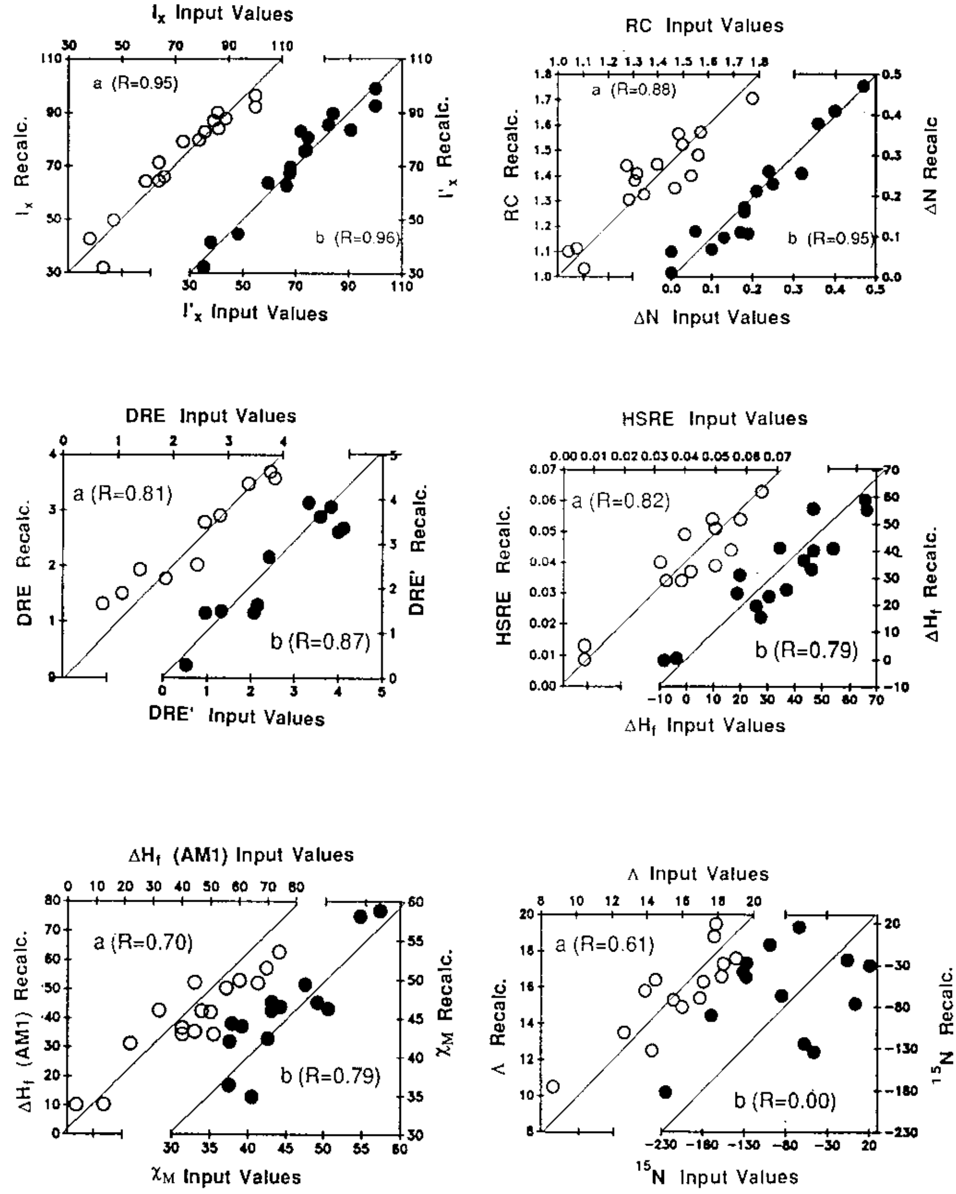
	Variables											
Compounds	1	2	3	4	5	6	7	8	9	10	11	12
	I_x	I_x'	RC	ΔN	DRE	DRE′	HRSE	ΔH_f	ΔH_{fcal}	χ_M	Λ	15_N
1 Benzene	100.0	100.0	1.774	0.0	3.77	3.84	0.065	19.8	22.0	54.8	17.9	—
2 Pyridine	85.7	84.1	1.571	0.10	3.85	4.12	0.058	34.6	32.0	49.2	18.3	-63.5
3 Pyrimidine	84.3	82.4	1.498	0.13	3.37	3.60	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 50. Results of PC Analysis on Sixteen Objects

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)

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 resulting plots are shown in Scheme 51.

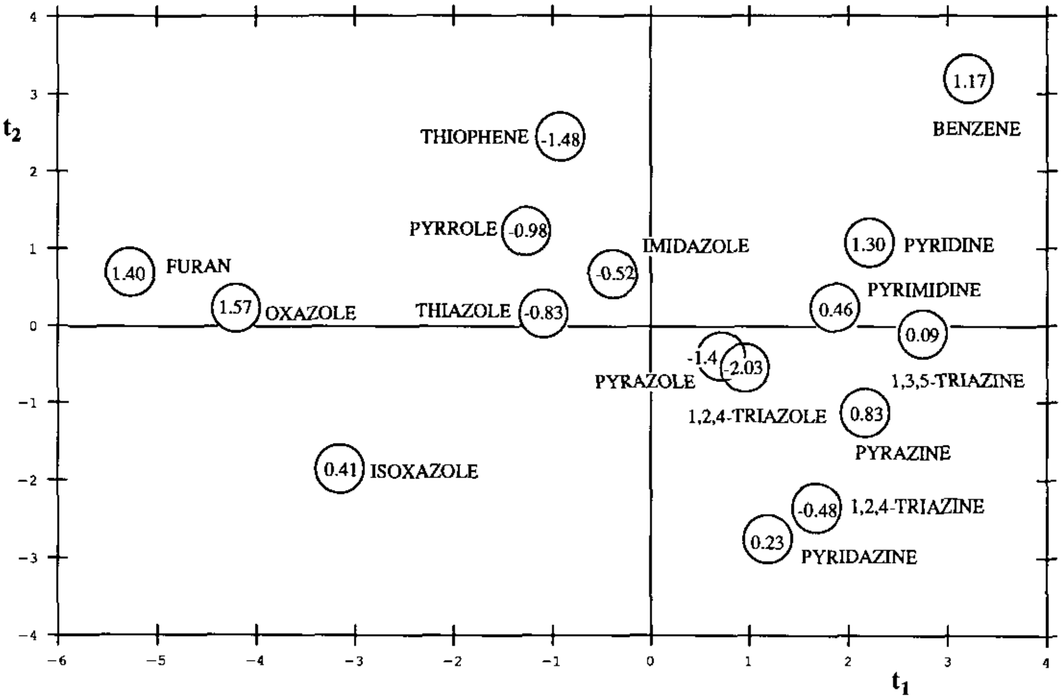
Scheme 51. Plots of Recalculated vs. Original Data for Monocyclic Aromatic Compounds



The PC scores for all 16 compounds are plotted graphically in Scheme 52, with the Principal Component scores t_1 and t_2 as the ordinate and absicca, respectively, and the score t_3 for the third PC shown within the circle.

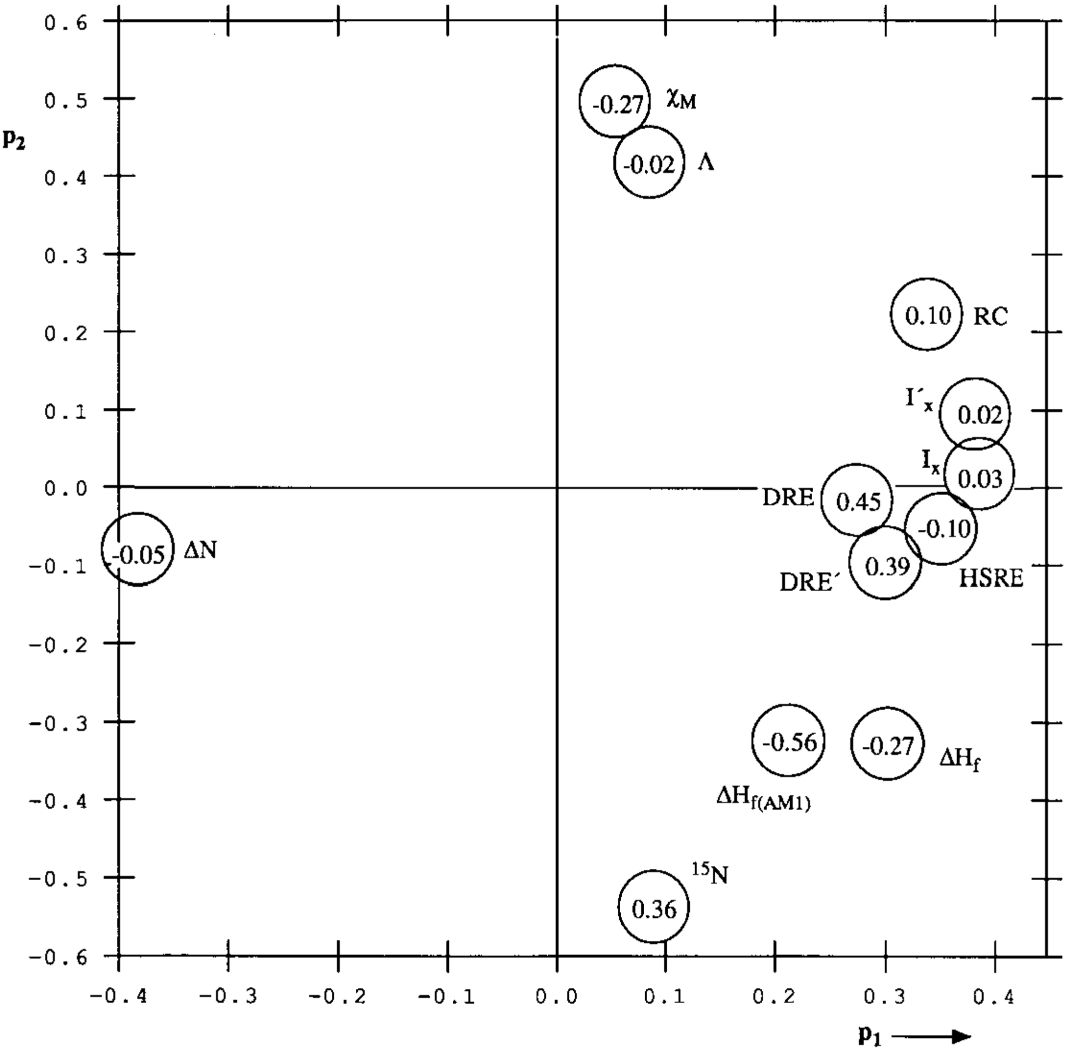
Scheme 52 shows that in the three-dimensional space defined by their principal components scores t_1, t_2, and t_3, the compounds 1-16 can be divided into four or five groups. Benzene and pyridine have all three t_1, t_2, and t_3 values positive. Di- and triazines are placed in another quartile with only t_2 negative. Azines and azoles with two nitrogen atoms in adjacent positions in the ring form a separate group with both t_2 and t_3 negative. The final group contains five-membered rings with nitrogen and/or sulfur heteroatoms (moderately negative t_1 negative and t_3 positive).

Scheme 52. Scores Plot of t_1 vs. t_2 for Monocyclic Compounds with t_3 Indicated



The PC loadings for the 12 characteristics are given in Scheme 53. In the three-dimensional space defined by their PC loadings, the characteristics can be divided into three main groups: those (Group A) dominated by the p_1 GC 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 parameters 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.

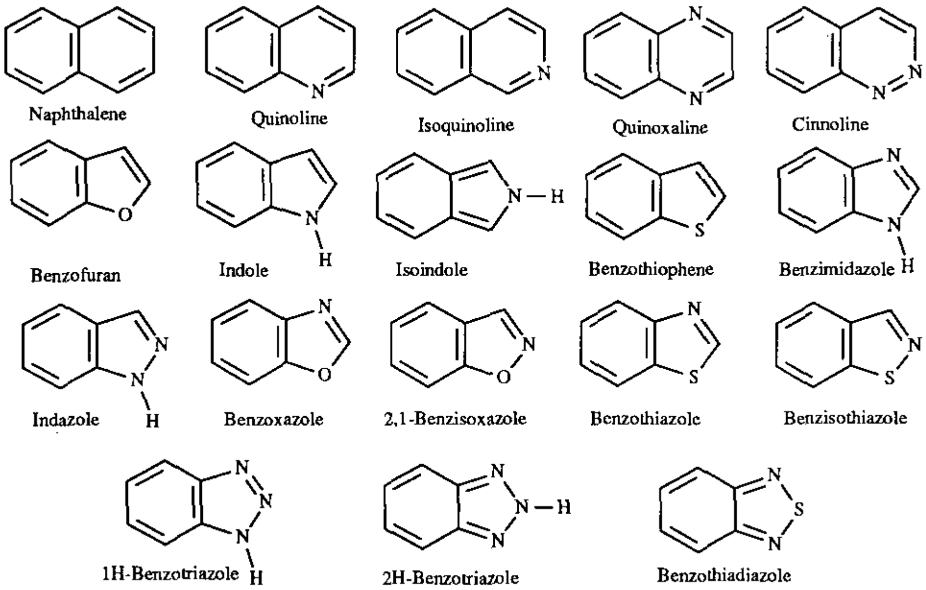
Scheme 53. Loadings Plot of p_1 vs. p_2 for Monocyclic Compounds with p_3 Indicated



c. Bicyclic Heteroaromaticity

We have extended this work to bicyclic compounds.[45] The bicycles studied are shown in Scheme 54, and the corresponding data set in Scheme 55.

Scheme 54. Bicycles Studied



Scheme 55. Data Set for Bicyclic Compounds

	Variables											
Compounds	1	2	3	4	5	6	7	8	9	10	11	12
	I_x	I'_x	RC	ΔN	DRE	DRE′	HSRE	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

The results of PC analysis are given in Scheme 56. Here, two significant PCs are found, which together explain 63% of the variance.

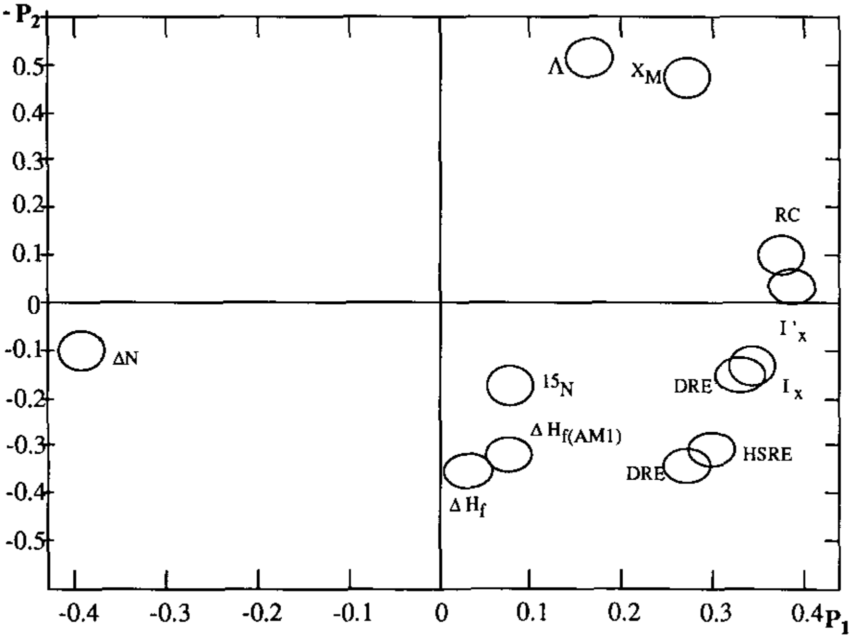
Scheme 56. Results of PC Analysis for Bicyclic Compounds

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

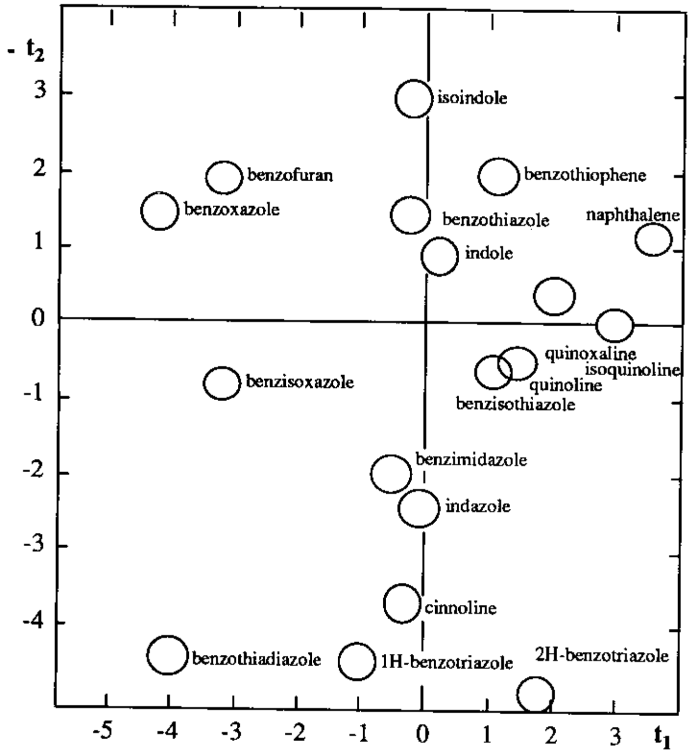
The PC loadings and PC scores are plotted in Schemes 57 and 58, respectively.

Although the monocyclic and bicyclic compounds form two completely independent data sets, we find most significant correlations between both the loadings and the scores of the two sets. Scheme 59 compares the loadings for mono and bicyclic derivatives: a close correspondence is found.

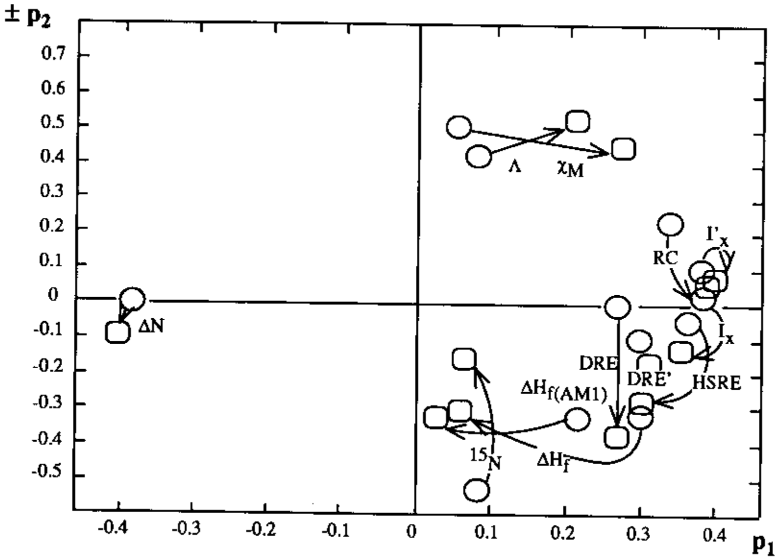
Scheme 57. Loadings Plot of p_1 vs. $-p_2$ for Bicyclic Compounds



Scheme 58. Scores plot of t_1 vs. $-t_2$ for Bicyclic Compounds

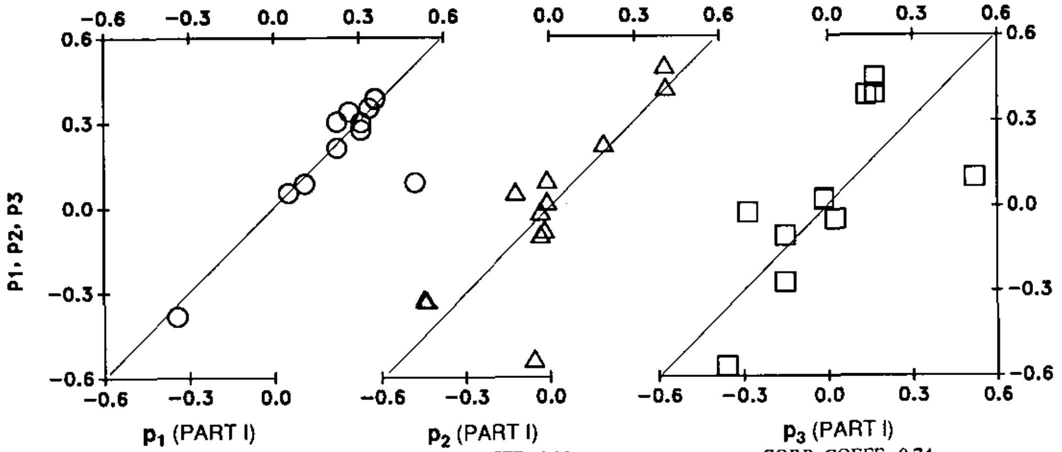


Scheme 59. Loadings of Bicycles Compared to Monocycles -- Plot



Scheme 60 shows plots of the individual p_1 and p_2 for bicyclic vs. monocyclic compounds, and gives the correlation coefficients.

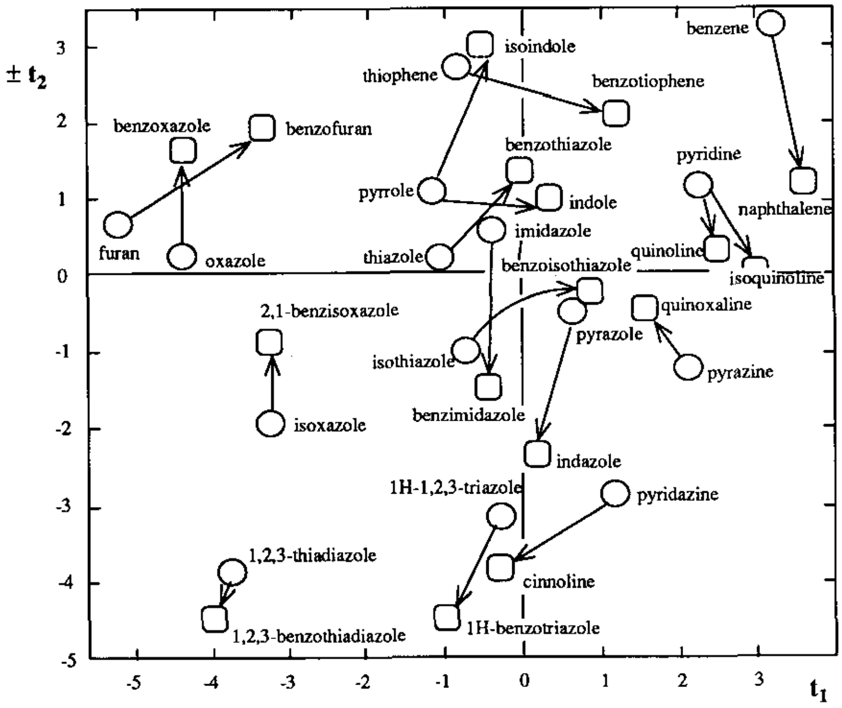
Scheme 60. Loadings of Bicycles Compared to Monocycles -- Correlation Coefficients



CORR. COEFF.: 0.98
CORR. COEFF.: 0.93
CORR. COEFF.: 0.74

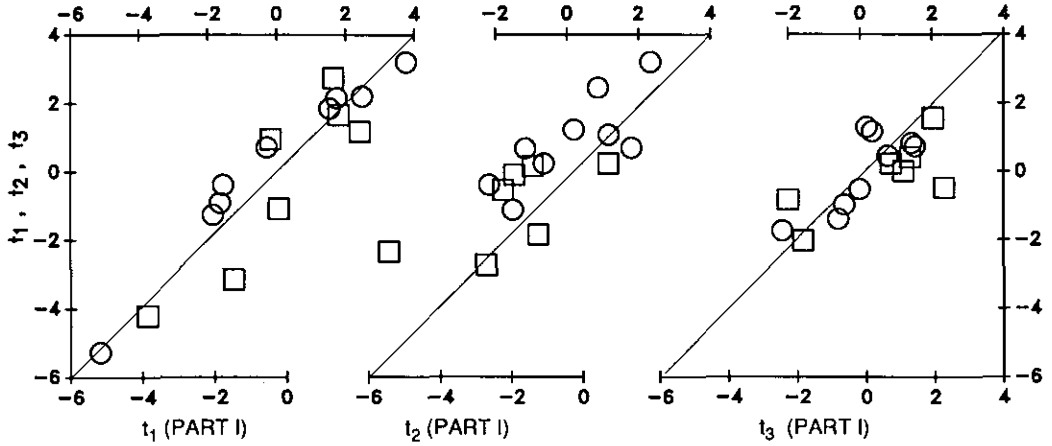
In Scheme 61, the scores for the benzoheterocycles are compared with those for the corresponding monoheterocycles. Very good agreement is again found.

Scheme 61. Scores of Bicycles Compared to Monocycles -- Plot



Scheme 62 shows the plots for individual t_1 and t_2 for bicyclic vs. monocyclic compounds.

Scheme 62. Scores of Bicycles Compared to Monocycles -- Correlation Coefficient

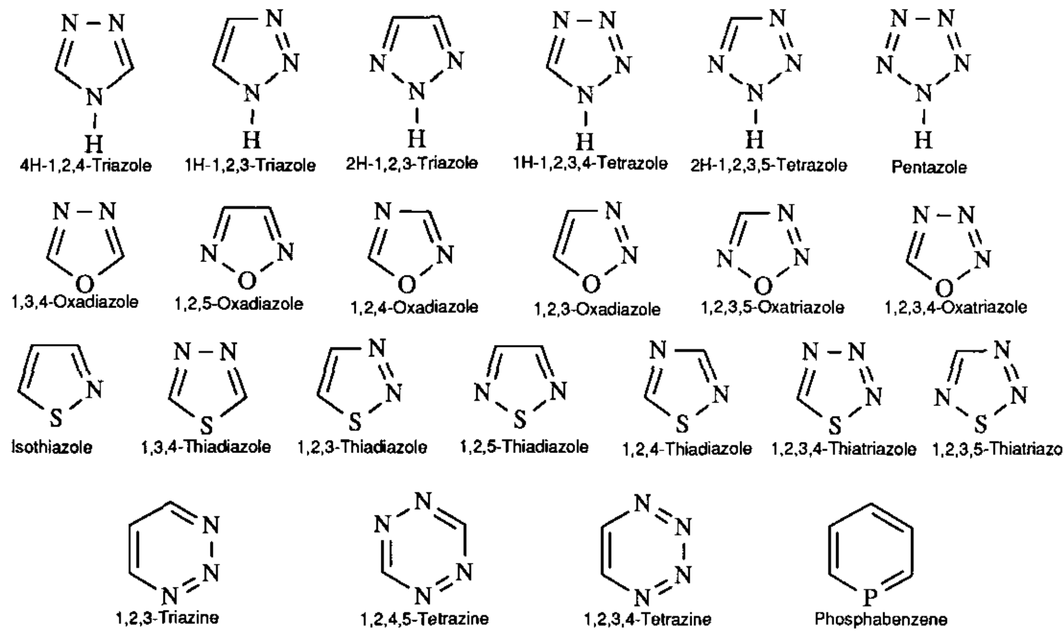


CORR. COEFF.: 0.93 (0.97) CORR. COEFF.: 0.73 (0.79) CORR. COEFF.: 0.68 (0.71)

c. Less Familiar Monocyclic Heteroaromatics

This work has been extended to a further set of 23 less-familiar monoheterocycles (Scheme 63). The 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.

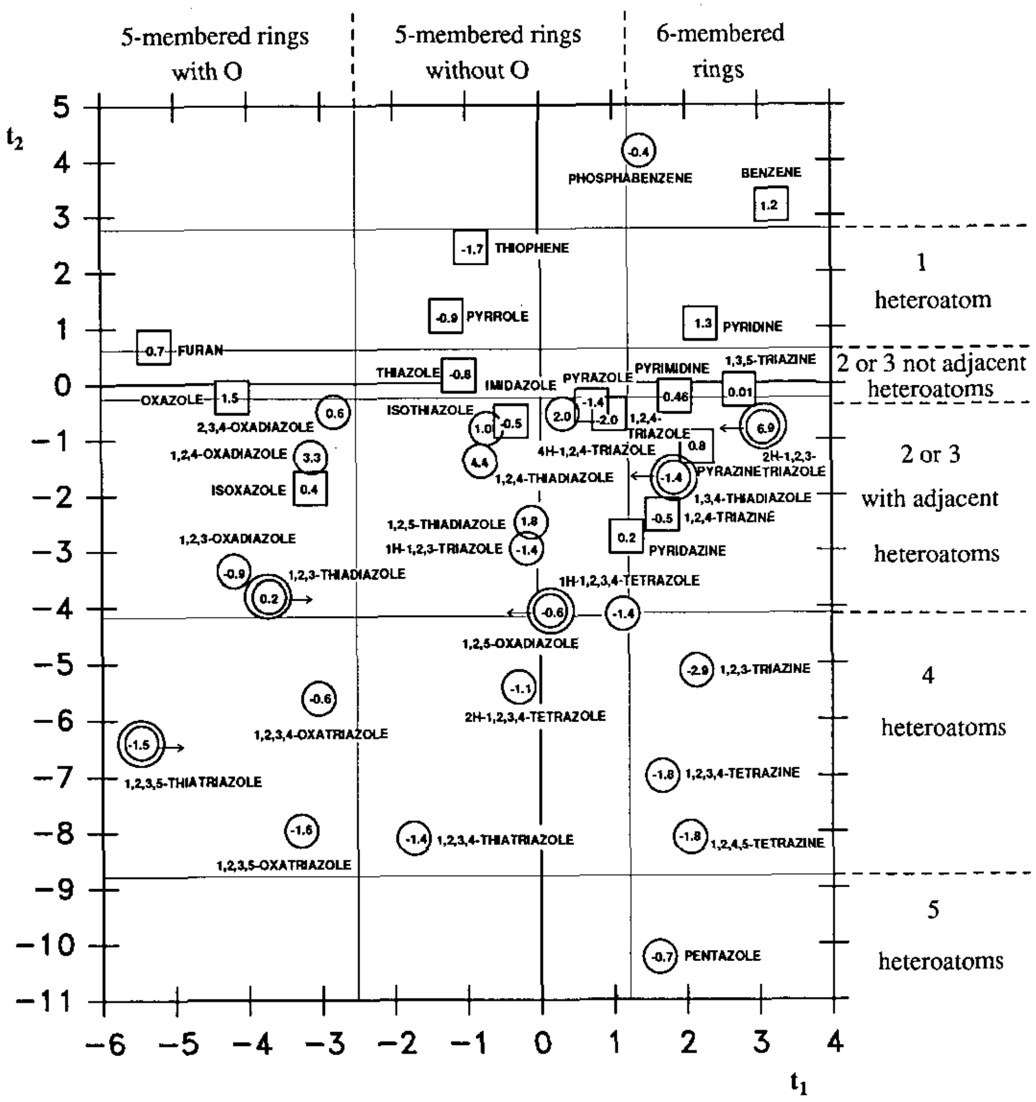
Scheme 63. Additional Monoheterocycles Studied



The scores for the total set for 16 + 23 = 39 monoheterocycles are shown in Scheme 64. 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 particularly 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.

Scheme 64. Scores for the Total Set of Monocyclic Heteroaromatics



In conclusion, we believe that in this work, we have been able to a considerable extent to resolve the apparent impasse between classical and magnetic aromaticity and to provide a firm basis for the consideration of aromaticity as a quantitative concept. In fact, there are at least two types of aromaticity. The best available measure of classical aromaticity is provided by the Bird-I-5-6 parameter, and this correlates well for ΔN and for DRE. The second type is magnetic aromaticity, which is best measured by the molar magnetic susceptibility χ_M. These two types of aromaticity, classical and magnetic, are orthogonal. Other aromatic characteristics are inferred by both "classical" and by "magnetic" aromaticity to varying extents. Hence, we believe that there are at least two quantitative aromaticity scales.

5. References

1 R. Breslow, Pure Appl. Chem., 1971, **28**, 111.

2 F. Gerson, Pure Appl. Chem., 1971, **28**, 131.

3 K. Hafner, Pure Appl. Chem., 1971, **28**, 153.

4 R. Hoffmann, Pure Appl. Chem., 1971, **28**, 181.

5 E. D. Bergmann and B. Pullman (Eds.), Aromaticity, Pseudoaromaticity, Antiaromaticity, Jerusalem Symposia on Quantum Chemistry and Biochemistry, Vol. III, Acad. Press, New York, 1971.

6 I. Agranat, Organic Chemistry, Series One, Vol. 3, Chapter 5, Butterworths, London, 1973.

7 M. J. Cook, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem.*, Academic Press, New York, 1974, **17**, 255.

8 A. R. Katritzky, "Handbook of Heterocyclic Chemistry", Pergamon Press, Oxford, 1985.

9 A. R. Katritzky, P. Barczynski, G. Musumarra, D. Pisano, and M. Szafran, *J. Am. Chem. Soc.*, 1989, **111**, 7.

10 D. Lewis and D. Peeters, "Facts and Theories of Aromaticity", The MacMillan Press Ltd., London, 1975.

11 J. W. Larsen and L. G. Hepler, "Solute Solvent Interactions", eds. by J. F. Coetzee and C. D. Ritchie, M. Dekker, New York, 1969, p. 1.

12 M. J. Cook, N. L. Dassanyake, C. D. Johnson, A. R. Katritzky, and T. W. Toone, *J. Chem. Soc., Perkin Trans. 2,* 1974, 1069.

13 M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *J. Chem. Soc., Perkin Trans. 2,* 1972, 1295.

14 M. P. Carmody, M. J. Cook, N. L. Dassanayane, A. R. Katritzky, P. Linda, and R. D. Tack, *Tetrahedron*, 1976, **32**, 1767.

15 A. V. Chapman, M. J. Cook, A. R. Katritzky, M. H. Abraham, A. F. Danil de Namor, L. Dumont, and J. Reisse, *Tetrahedron,* 1978, **34**, 1571.

16 M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *Tetrahedron Lett.,* 1972, 5019.

17 M. J. Cook, A. R. Katritzky, A. D. Page, R. D. Tack, and H. Witek, *Tetrahedron,* 1976, **32**, 1773.

18 A. J. Kresge, *Acc. Chem. Res.*, 1990, *23*, 43.

19 J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem., Suppl. 1,* 1975, Academic Press, New York, 1976.

20 M. J. Cook, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem.*, Academic Press, New York, 1974, **17**, 268.

21 M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1080.

22 M. J.Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *Chem. Commun.*, 1971, 510.

23 M. J. Cook, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem.*, Pergamon Press, Oxford, 1974, **17**, 269.

24 B. S. Hess, Jr., L. J. Schaad, and C. W. Holyoke, *Tetrahedron*, 1975, **31**, 295.

25 B. A. Hess, Jr. and L. J. Schaad, *J. Am. Chem. Soc.*, 1973, **95**, 3907.

26 M. J. S. Dewar, "Aromaticity", Chem. Soc. Spec. Publ., 1967, **21**, 177.

27 M. J. S. Dewar, A. I. Harget, and N. Trinajstic, *J. Am. Chem. Soc.*, 1969, **91**, 6321.

28 M. J. S. Dewar, A. J. Harget, N. Trinajstic, and S. D. Worley, *Tetrahedron,* 1970, **26**, 4505.

29 M. J. S. Dewar and N. Trinajstic, *Theor. Chim. Acta,* 1970, **17**, 235.

30 B. Bak, L. Nygaard, E. J. Pedersen, and L. Rastrup-Andersen, *J. Mol. Spectrosc.*, 1966, **19**, 283.

31 A. Julg and P. Francois, *Theor. Chim. Acta*, 1967, **7**, 249.

32 A. F. Pozharskii, *Chem. Heterocycl. Comp.*, 1985, **21**, 717.

33 V. I. Berezin, *Dokl. Phys. Chem.*, 1964, **155**, 305.

34 A. T. Balaban and Z. Simon, *Tetrahedron,* 1962, **18**, 315.

35 C. W. Bird, *Tetrahedron,* 1985, **41**, 1409.

36 C. W. Bird, *Tetrahedron*, 1986, **42**, 89.

37 A. R. Katritzky and M. Karelson, (In preparation).

38 R. B. Mallion, *Pure Appl. Chem.*, 1980, **52**, 1541.

39 J.A. Elvidge, *J. Chem. Soc., Chem. Commun.*,1965, 160.

40 R. J. Abraham, R. C. Sheppard, W. A. Thomas, and S. Turner, *J. Chem. Soc., Chem. Commun.*, 1965, 43.

41 H. A. P. De Jongh and H. Wynberg, *Tetrahedron,* 1965, **21**, 515.

42 M. H. Palmer, R. H. Findlay, W. Moyes, and A. J. Gaskell, *J. Chem. Soc., Perkin Trans. 2,* 1975, 841.

43 M. H. Palmer and R. H. Findlay, *Tetrahedron Lett.*, 1974, 253.

44 J. H. van Vleck, "The Theory of Electric and Magnetic Suceptibilities", Oxford Univ. Press, London, 1932.

45 a) A. R. Katritzky, V. Feygelman, G. Musumarra, P. Barczynski, and M. Szafran, *J. Fuer Prak. Chem.* 1991 (In Press).
b) A. R. Katritzky, V. Feygelman, G. Musumarra, P. Barczynski, and M. Szafran, *J. Fuer Prak. Chem.* 1991 (In Press).
c) A. R. Katritzky and P. Barczynski, *J. Fuer Prak. Chem.* 1991 (In Press).

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