

AROMATICITY AND THE TAUTOMERIC EQUILIBRIA
OF HETEROCYCLES*

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From a purely qualitative point of view, the characteristics of an aromatic compound can be determined rather simply. We call aromatic those cyclic compounds that have a high resonance energy and undergo predominantly substitution reactions rather than addition reactions. In other words, these are compounds that, as defined exactly by Robert Robinson, "revert to the original type," retaining the aromatic sextet of π electrons after the reaction. More precisely, aromatic compounds are characterized by the presence of $4n + 2 \pi$ electrons (the Hückel rule) and by diamagnetic properties of the ring current, which are readily detectable in the NMR spectrum. Comparatively recently it was established that, in addition to the usual classes of "aromatic" and "nonaromatic" compounds, one should also consider "antiaromatic" compounds; cyclic compounds that have $4n \pi$ electrons in the ring make up the latter class. The simplest method for the detection of "antiaromaticity" is NMR spectroscopy, since such compounds are characterized by paramagnetic properties of the ring current.

Difficulties arise when we attempt to render the concept of aromaticity more quantitative. These difficulties become particularly serious when there are heteroatoms present in the ring. Thus no one will deny that furan, thiophene, and pyrrole are aromatic systems. However, are they more or less aromatic than benzene? Some authors consider these compounds to be "superaromatic," since they extremely readily undergo the electrophilic substitution reactions so characteristic for benzene. In addition, a number of investigators consider these compounds (furan at least) to be "semiaromatic," for they also undergo addition reactions (for example, the Diels-Alder reaction), which to a certain extent is evidence for their diene character. One can cite another example: replacement of one CH group of the benzene ring by nitrogen gives pyridine. Does this substitution lead to an increase or decrease in the aromaticity? Of course, pyridine reacts with electrophilic agents with greater difficulty than benzene, but its reactions with nucleophiles proceed with greater ease than in the case of benzene. This is manifested even more acutely for a compound such as sym-triazine, which reacts very readily with nucleophiles but is absolutely inert in electrophilic substitution reactions involving the ring carbon atoms.

The difficulties that arise in an attempt to give a precise definition of aromaticity from a quantitative point of view have led some chemists to regard the entire concept of aromaticity as one that has become obsolete and old-fashioned. However, any chemist who has some experience in the teaching of chemistry and anyone who is studying it should imagine that the concept of aromaticity is the cornerstone of all of organic chemistry. It is precisely for this reason that many investigators have made considerable efforts to impart a more quantitative character to this concept. In my opinion, it is currently standard practice to characterize aromaticity by thermodynamic rather than kinetic criteria. In other words, an important quantitative parameter is the additional stabilization energy that the aromatic compound has as compared with a similar but cyclically unconjugated system. In particular, one should make a distinction between "empirical resonance energy" and "vertical resonance energy," as demonstrated in Scheme I [1]. The vertical resonance energy, i.e., the difference between the energies of the true structure and a hypothetical structure with localized double bonds and the same arrangement of atoms as in the real structure, is, theoretically speaking, probably a more important quantity. However, from the point of view of compre-

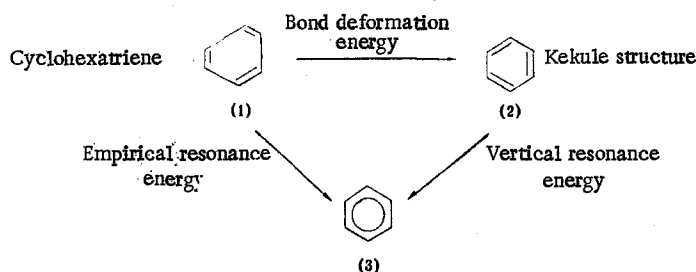
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Scheme I

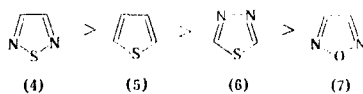
Vertical and empirical resonance energies



hension, the empirical resonance energy is certainly more convenient, and we will therefore deal precisely with it in the present paper.

The classical quantitative definition of aromaticity is based on heats of combustion. Some aromatic resonance energies obtained from the heats of combustion and hydrogenation are presented in Table 1. Both methods give extremely close results for benzene. However, one generally observes greater deviations, especially when heteroatoms are present. This is associated with the difficulty in determining the heats of combustion of compounds that contain nitrogen or sulfur and also with the fact that the resonance energy found by this method is a small difference between two large quantities. Furthermore, many heterocyclic compounds are difficult (and sometimes impossible) to hydrogenate quantitatively. A number of other methods for the quantitative evaluation of aromaticity have therefore been developed. Some of them will be examined briefly here.

a) Several groups of authors have compared the aromaticities of heterocycles using accurate data on bond lengths obtained by microwave spectroscopy [2,3]. This method established that, for example, the order of decrease in aromaticity is (4) > (5) > (6) > (7) [3].



b) Julg and Francois [4] have defined the so-called "aromaticity index" A by means of the following equation:

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

where n is the number of π electrons, d_{rs} is the distance between atoms r and s , and \bar{d} is the average bond length calculated from the formula

$$\bar{d} = \frac{1}{n} \sum_{(rs)} d_{rs}$$

Taking benzene as the standard ($A = 1$), the authors found that the aromaticity indexes for thiophene, pyrrole, and furan are, respectively, 0.93, 0.91, and 0.87.

TABLE 1. Resonance Energies from Heats of Combustion and Hydrogenation*

Compound	From heat of combustion, kcal/mole	From heat of hydrogenation, kcal/mole
Benzene	36-37	36
Pyridine	23-43	—
Thiophene	24-31	29
Furan	16-23	22
Pyrrole	14-31	—

* For example, see G. W. Wheland, *Resonance in Organic Chemistry*, New York (1955), pp. 98, 99, and many other studies.

c) Elvidge and Jackman have used the magnitudes of the chemical shifts induced by the ring current as a measure of aromaticity [5]. By measuring the chemical shifts of the protons bonded directly to the heterocycle or of the protons of the methyl groups bonded to the heterocycle and comparing these shifts with the shifts in model compounds, they estimated the degree of aromaticity of compounds (8)-(11) as compared with benzene, the aromaticity of which was taken as 100%.

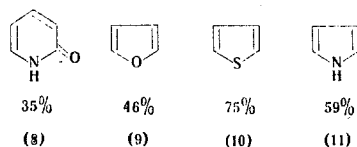
However, the accurate selection of model compounds is difficult in this method. Thus Abraham [6] has calculated that the ring currents in furan (9) and thiophene (10) are the same as in benzene; he feels that

TABLE 2. Methods for the Determination of Tautomeric Equilibrium Constants (K_T)*

Method	Characteristics of the method
NMR spectroscopy	Equilibrium is usually established rapidly on the NMR time scale
IR spectroscopy	Useful qualitative information
UV spectroscopy	Comparison of the labile system with fixed models – useful for many solvents but limited by the narrow range of the K_T values
pK_a measurements	Broad range of K_T values but applicable only to aqueous solutions

*See A. R. Katritzky and J. M. Lagowski, *Adv. Heterocycl. Chem.*, Vol. 1 (1963), p. 311, for details.

the ring current is unsuitable as a quantitative characteristic of aromaticity. On the basis of other measurements of the ring current, Wynberg [7] calculated that the aromaticities of furan (9) and thiophene (10) are, respectively, 61 and 75% of the aromaticity of benzene. The problem is obviously still a controversial one, but the use of ring currents as a measure of heteroaromaticity is not presently a generally accepted method.



d) A different approach was used by Balaban [8]. He introduced the "aromaticity constant" K , which is defined as $K = \sum k$. The k values in this expression characterize the tendency of the individual ring atoms to attract or repel the π electrons of the delocalized aromatic cloud and are defined by the equation

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

where m_π is the number of π electrons, r is the covalent radius in angstroms, and Z^* is the effective charge calculated from the formula

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

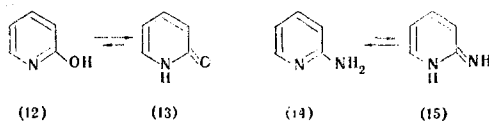
where Z_m is the nuclear charge, m_K is the number of electrons in the K shell, $m_{L,m}$ is the number of non-bonding L electrons, and $m_{L,b}$ is the number of bonding L electrons.

Taking benzene as the standard with $K = 0$, we obtain aromaticity constants of +23 for pyridine, +97 for the pyridinium ion, -1 for thiophene, -7 for phenol, and -100 for the cyclopentadienyl anion.

All of these methods are useful and give interesting information, but none of them associates aromaticity directly with readily accessible energy characteristics that can be obtained by investigating chemical equilibria. Our research also consisted in an attempt to find such relationships.

Tautomerism of Heteroaromatic Compounds

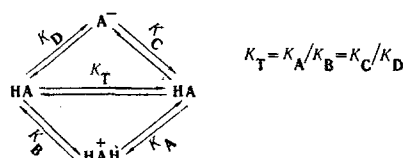
In connection with other problems, I have already emphasized that investigators doing research on the chemistry of heterocycles should depict and describe heteroaromatic compounds in the form in which they really exist – in other words, "call things by their proper names" [9-11]. Thus, in my opinion, we should ascribe precisely the 2-pyridone (13) structure to 2-pyridone rather than the 2-hydroxypyridone structure (12), the fraction of which in equilibrium between these two substances is only one thousandth. Similarly, we should speak of 2-aminopyridine (14) rather than of 2-pyridonimine (15), since the fraction of imine (15) in the (14) \rightleftharpoons (15) equilibrium is only one millionth.



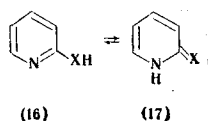
Physical methods are the most reliable methods for the study of tautomeric equilibria. The characteristics of the most common of them are presented in Table 2. The method of pK_a values is particularly valuable, since it can be used for the determination of very large or very small tautomeric equilibrium constants. The principle of this method is demonstrated in Scheme II.

Scheme II

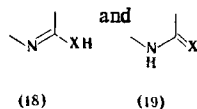
pK_a method for the determination of K_T



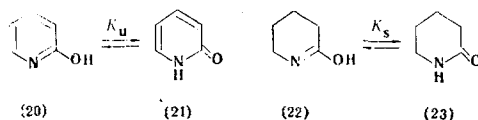
If two tautomeric compounds, HA and AH, form a common cation, HAH^+ , the tautomeric equilibrium constant (K_T) is then associated with the basicity constants K_B and K_A of HA and AH by the ratio $K_T = K_A / K_B$. Although K_A and K_B cannot be measured directly, they can be estimated from the pK_a values of fixed methylated tautomers CH_3A and ACH_3 .



We will now consider factors that affect the position of a tautomeric equilibrium of the (16) \rightleftharpoons (17) type. One should make a distinction between external (such as the polarity of the solvent and the possibility of the formation of hydrogen bonds) and internal factors. Of the latter, two are important: first, the stability peculiar to both tautomeric functional groups, in this case to groups (18) and (19); second, the relative stabilization energies of delocalization of the six- π -electron systems in the rings of (16) and (17).



If we can take into account the difference in the stabilities peculiar to each of the two tautomeric functional groups and determine the difference in the energies between the two tautomers, we are then in a position to also determine such differences in the energies of aromatic delocalization of the two tautomers. For this, we compare two alternative tautomeric systems (20) \rightleftharpoons (21) and (22) \rightleftharpoons (23).



We can then set up Eqs. (1) and (2):

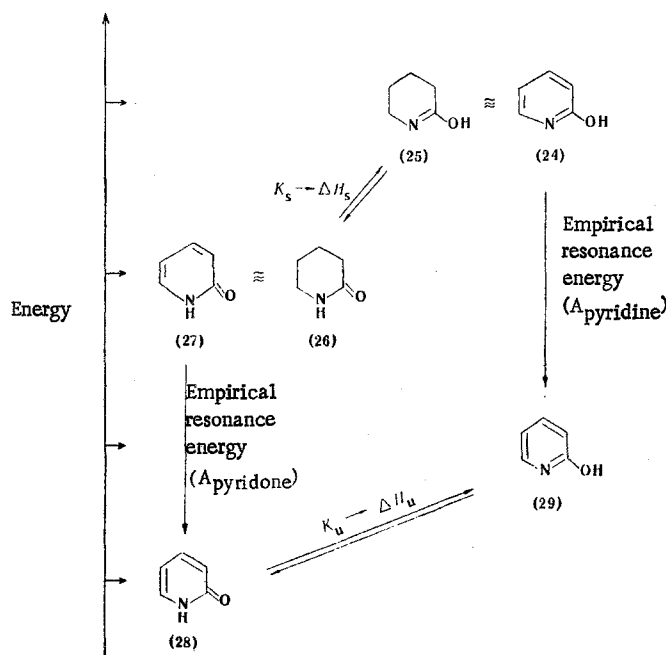
$$\Delta H_u = [A_{\text{pyridone}} + (\text{NH/CO}) \text{ interaction}] - [A_{\text{pyridine}} + (\text{N/OH}) \text{ interaction}] \quad (1)$$

$$\Delta H_s = (\text{NH/CO}) \text{ interaction} - (\text{N/OH}) \text{ interaction} \quad (2)$$

We will assume that the interactions between NH and the carbonyl group in (21) and (23) are identical; the admissibility of this assumption is confirmed, for example, by the dipole moments [12]. We will also assume that the interactions between the nitrogen atom and the OH group in (20) and (22) are also identical. Then, subtracting Eq. (1) from Eq. (2), we obtain Eq. (3):

$$\Delta H_s - \Delta H_u = A_{\text{pyridine}} - A_{\text{pyridone}} \quad (3)$$

Scheme III



The measured tautomeric equilibrium constants are associated with ΔH_u of Eq. (3) by expression (4):

$$\Delta H_u = \Delta G_u + T\Delta S_u = -RT \ln K_u + T\Delta S_u. \quad (4)$$

Thus, to determine the difference in the aromatic resonance energy, it is necessary to know not only the constants of both tautomeric equilibria but also the difference in entropies [Eq. (5)]:

$$A_{\text{pyridine}} - A_{\text{pyridone}} = RT \ln K_u/K_s + T(\Delta S_s - \Delta S_u). \quad (5)$$

As we will see below, there are different methods to take the difference in entropies into account. However, we will initially examine in greater detail the approximations that were assumed when we took the saturated system (22) \rightleftharpoons (23) as the model for the description of the interaction between the nitrogen and oxygen atoms in unsaturated system (20) \rightleftharpoons (21). In this connection, let us turn to the energy diagram presented in Scheme III. We will equate the difference in energies between pyridone, with localized double bonds (27), and 2-hydroxypyridine, with localized double bonds (24), to the difference in energies between piperidone (26) and 2-hydroxytetrahydropyridine (25). This sort of approximation probably does not give rise to serious misgivings, as is apparent from a comparison of the data presented in Scheme IV.

Scheme IV

Approximation of a saturated model

$C_6H_5NHCOC_6H_5$	$C_6H_5N=C(C_6H_5)OC_6H_5$	
$pK_a -2.50$ [13]	$pK_a 3.4^*$	$\Delta pK_a 5.9$
$(CH_3)_2NCOCH_3$	$CH_3N=C(CH_3)OC_2H_5$	
$pK_a -0.19$ [14]	$pK_a 7.5$ [15]	$\Delta pK_a 7.7$

* Estimated from data for $CH_3N=C(CH_3)OC_2H_5$, $pK_a 7.5$; $C_6H_5N=C(CH_3)OC_2H_5$, 5.06; $HN=C(C_6H_5)OC_2H_5$, 5.80.

5.80.

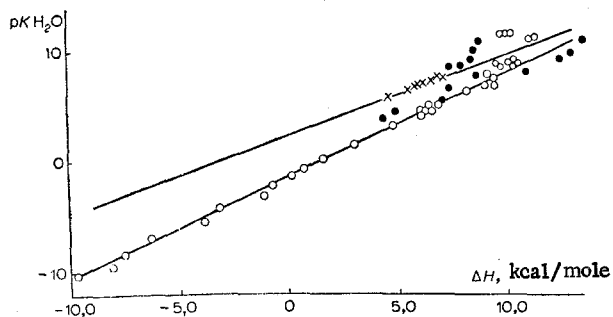


Fig. 1. Dependence of the pK on ΔH for protonation of the bases: ○) primary aromatic amines; ×) pyridines; ●) various other bases.

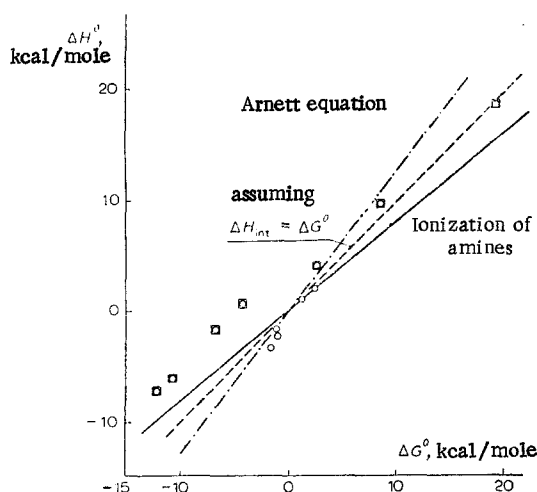


Fig. 2. Relationship between ΔH° and ΔG° for tautomeric equilibria.

line for primary aromatic amines is presently reliable for a broad range of pK values [18, 19]. Unfortunately, the specific correlations for other types of bases do not come through as distinctly, although pyridines apparently lie on the line.

The dependence between ΔH and ΔG for tautomeric equilibria is presented in Fig. 2. The ΔH value can be obtained directly only if the position of the tautomeric equilibrium is determined at different temperatures, and this is possible only under the condition that it is not shifted too markedly to one or the other side. The data were taken primarily from the studies of Soviet authors [20]; they are designated by circles and are compared with three theoretical lines obtained by various other methods. Points obtained on the basis of the assumption that the ionization of substituted pyridine corresponds to the line for pyridines that is presented in Fig. 1 are noted by squares in the graph, while the ionization of the second tautomer corresponds to the line for anilines in Fig. 1. The Arnett line is also presented. The slopes of all of the lines in Fig. 2 do not differ markedly from one another.

Determination of the Resonance Energy for 2-Pyridone and Its Analogs

The results obtained for 2-pyridone and its analogs are presented in Table 3. Some of the compounds necessary for the pK_a measurements were inaccessible, and pK_a values of similarly constructed compounds were therefore used (Table 4). Some of the pK_a values presented in the literature are incorrect, while some of the other values have not been determined. Thus, for example, we found the pK_a values for 1-methyl-2-pyridone imine (13.0) and 1-methyl-2-pyridone methide (19.3).

Stronger perturbations of the NHCO and N=C(OH) systems might have been expected if they were bonded to phenyl groups (as in Scheme IV) rather than to "unconjugated double bonds." The ΔpK value when the methyl groups are replaced by phenyl groups in the equilibrium of methylacetamide (Scheme IV) is 1.8 pK units. The difference in the ΔpK value caused by the introduction of unconjugated double bonds would certainly be considerably less than this, and the error associated with this approximation is consequently less than 1 pK unit.

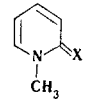
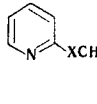
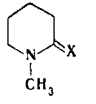
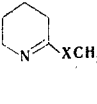
Methods for Transition from ΔG Values to ΔH Values

The following methods were used for transition from ΔG values obtained on the basis of the tautomeric equilibrium constants to ΔH values:

- 1) Disregarding the interaction with the solvent, one can assume that ΔG is approximately equal to ΔH , in accordance with the work of Larsen and Hepler [16];
- 2) One can correct the pK_a values taken for the calculation of the individual K_T values: a) the Arnett [17] correlation between the ΔH values determined by a calorimetric method and the ΔG values measured for ionization ($\Delta H = 1.3\Delta G$) is used; b) the pK_a values can also be corrected by using their dependence on temperature;
- 3) The temperature dependence of the measured K_T values can be used.

The relationship between the measured ΔH values for the protonation of the bases and the corresponding pK_a values is shown in Fig. 1. The straight

TABLE 3. Results for 2-Pyridone and Related Compounds

X	pK _a		ΔG_{a} , kcal/ mole	pK _a		ΔG_{g} , kcal/ mole	$\Delta G_{\text{a}} - \Delta G_{\text{g}}$, kcal/mole
	 (30)	 (31)		 (32)	 (33)		
S	-1,22 ^a	3,62 ^a	-6,7	-1,76 ^f	6,9 ^f	-12,0	5,3
O	0,32 ^b	3,28 ^b	-4,1	0,19 ^f	7,5 ^f	-10,6	6,5
NH	13,02 ^c	6,86 ^d	8,5	11,4 ^g	9,43 ^g	0,00	8,5
CH ₂	19,8 ^c	5,97 ^e	19,0	11,4 ^f	9,43 ^h	2,7	16,3

^aA. Albert and G. B. Barlin, *J. Chem. Soc.*, 2384 (1959). ^bA. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956). ^cResults of the present investigation. ^dA. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948). ^eH. C. Brown and X. R. Mihm, *J. Am. Chem. Soc.*, 77, 1723 (1965). ^fSee the references in Table 4. ^gAssumed to be equal.

TABLE 4. Model Compounds for pK_a Measurements

"Best" model	Model used	pK _a	Literature
1-Methylpiperidine-2-thione	CH ₃ C(S)NH ₂	-1,76	a
2-Methylthio-3,4,5,6-tetrahydropyridine	CH ₃ C(=NH)SC ₂ H ₅	+6,9	b
1-Methyl-2-piperidone	CH ₃ CON(CH ₃) ₂	-0,19	c
2-Methoxy-3,4,5,6-tetrahydropyridine	CH ₃ COC ₂ H ₅ N-CH ₃	+7,5	d
2-Methyl-3,4,5,6-tetrahydropyridine	N-Methylcyclohexanone imine	+9,43	e
1-Methyl-2-piperidone methide	1,2-Dimethyl-1,4,5,6-tetrahydropyridine	+11,4	f

^aRosenthal and T. I. Taylor, *J. Am. Chem. Soc.*, 79, 2684 (1957).

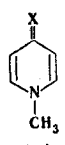
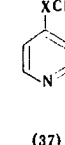
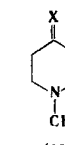
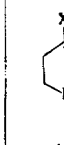
^bR. W. Chaturvedi, A. E. MacMahon, and G. L. Schmir, *J. Am. Chem. Soc.*, 89, 6984 (1967). ^cSee [14]. ^dSee [15]. ^eM. Brezina and P. Zuman, *Chem. Listy*, 47, 975 (1953). ^fR. Adams and J. E. Mahan, *J. Am. Chem. Soc.*, 64, 2588 (1942).

TABLE 5. Differential Aromatic Resonance Energies (kcal/mole)

X	Method					Weighted mean value
	1	2a	2b	3	4	
S	5,3	4,3	5,5	6,8	6,9	6 ± 1
O	6,5	5,3	6,8	8,4	8,6	7,5 ± 1
NH	8,5	7,0		11,0	11,1	10 ± 2
CH ₂	16,3	13,4	14,6	21,1	21,4	18 ± 3

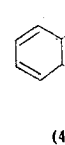
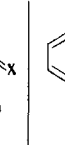
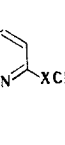
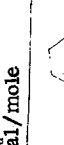
$$A_{\text{py}} - A_{\text{x}} = \begin{matrix} 1 & 1,37 \sum pK_{\text{a}} \\ 2\text{a} & 1,13 \sum pK_{\text{a}} \\ 2\text{b} & 1,13 [\Delta pK] - 1,48 [\Delta pK'] \\ 3 & 1,78 \sum pK_{\text{a}} \\ 4 & 1,81 \sum pK_{\text{a}} \end{matrix}$$

TABLE 6. Aromatic Resonance Energies of 4-Pyridone and Its Analogs

X	pK _a				4-Pyridone derivatives	2-Pyridone derivatives
	 (36)	 (37)	 (38)	 (39)	A _{py} -A _x (difference), kcal/mole	A _{py} -A _x (difference), kcal/mole
S	1,30 ^a	5,97 ^a	f	f	—	5,3
O	3,33 ^b	6,62 ^b	3,1 ^g	11,2 ^h	6,6	6,5
NH	15,75 ^c	9,12 ^d	h	i	9,1	8,5
CH ₂	21,3 ^c	6,02 ^e	f	f	—	16,3

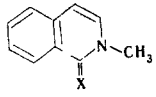
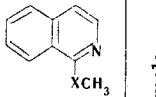
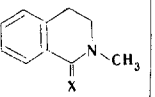
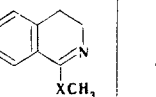
^aA. Albert and G. B. Barlin, *J. Chem. Soc.*, 2384 (1969). ^bA. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956). ^cResults of this investigation. ^dA. Fischer, W. J. Galloway, and J. Vaughan, *J. Chem. Soc.*, 3591 (1964). ^eH. C. Brown and X. R. Mihm, *J. Am. Chem. Soc.*, 77, 1723 (1955). ^fThis compound has not yet been obtained. ^gJ. V. Greenhill, *J. Chem. Soc. (B)*, 29 (1969). This is the value for 3-ethylaminocyclohex-2-enone. ^hSee note g; this is the value for N-(3-methoxy-2-cyclohexenylidene)ethylamine. ⁱThe values were assumed to be equal because of symmetry.

TABLE 7. Aromatic Resonance Energies of 2-Quinolone and Its Analogs

X	pK _a		$\Delta G_{\text{res}}^{\circ}$ kcal/mole	pK _a		$\Delta G_{\text{res}}^{\circ}$ kcal/mole	$\Delta G_{\text{res}}^{\circ}$ kcal/mole
	 (40)	 (41)		 (42)	 (43)		
S	-1,6 ^a	3,71 ^a	-7,3	—	3,84 ^h	—	—
O	-0,71 ^b	3,17 ^b	-5,3	-0,50 ^f	4,63 ⁱ	-7,0	1,7
NH	11,68 ^c	7,34 ^d	5,9	9,25 ^g	8,15 ^j	1,5	4,4
CH ₂	15,01 ^c	5,80 ^e	13,1	—	—	—	—

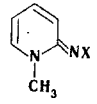
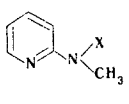
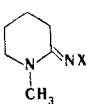
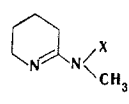
^aA. Albert and G. B. Barlin, *J. Chem. Soc.*, 2384 (1959). ^bS. F. Mason, *J. Chem. Soc.*, 674 (1958). ^cResults of this investigation. ^dA. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948). ^eC. Golumbic and M. Orchin, *J. Am. Chem. Soc.*, 72, 4145 (1950). ^fC. A. Streuli, *Anal. Chem.*, 31, 1652 (1959). This is the value for N-methylacetanilide. ^gJ. Kebrle and K. Hoffmann, *Helv. Chim. Acta*, 39, 116 (1956). This is the value for 1,3,3-trimethyl-2-iminoindoline. ^hR. K. Chaturvedi, A. E. MacMahon, and G. L. Schmir, *J. Am. Chem. Soc.*, 89, 6984 (1967). This is the value for ethyl N-phenylthio-butylimidate. ⁱR. K. Chaturvedi and G. L. Schmir, *J. Am. Chem. Soc.*, 90, 4413 (1968). This is the value for ethyl N-phenylacetimidate. ^jSee note g; this is the value for 2-aminoindolenine.

TABLE 8. Aromatic Resonance Energies of 1-Isoquinolone and Its Analogs

X	pK _a		ΔG _v ^o kcal/mole	pK _a		ΔG _v ^o kcal/mole	ΔG _v ^o - ΔG _v ^o kcal/mole
							
S	-2,13 ^a	3,93 ^a	-8,3	—	6,04 ^h	—	—
O	-1,80 ^b	3,05 ^b	-6,6	-1,62 ^e	5,7 ⁱ	-10,2	3,6
NH	—	7,62 ^d	—	—	—	0	—
CH ₂	15,62 ^c	—	—	13,06 ^g	8,30 ^j	6,5	—

^aA. Albert and G. B. Barlin, *J. Chem. Soc.*, 2384 (1959). ^bA. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956). ^cResults of the present investigation. ^dA. Albert, R. Goldacre, and J. N. Phillips, *J. Chem. Soc.*, 2240 (1948). ^eJ. T. Edward, H. S. Chang, K. Yates, and R. Stewart, *Can. J. Chem.*, **38**, 1518 (1960). ^fAssumed to be equal. ^gResults of this investigation; this is the value for N-methyl-1,2,3,4-tetrahydroisoquinoline 1-methide. ^hR. K. Chaturvedi, A. E. MacMahon, and G. L. Schmir, *J. Am. Chem. Soc.*, **89**, 6984 (1967). This is the value for ethyl thiobenzimidate. ⁱJ. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2009 (1957). This is the value for methyl benzimidate. ^jResults of this investigation; this is the value for 3,4-dihydro-1-methylisoquinoline.

TABLE 9. Aromatic Resonance Energies of Substituted 2-Aminopyridines

X	pK _a				Δpyridine - Δpyridone ^o kcal/mole
					
H	13,02 ^a	6,86 ^a	—	—	8,5
C ₆ H ₅	10,17 ^b	5,84 ^b	8,15 ^f	—	7,4
COCH ₃	7,12 ^c	4,09 ^c	—	9,25 ^g	—
SO ₂ CH ₃	-0,33 ^d	1,10 ^d	—	—	—

^aSee the footnote in Table 3. ^bResults of this investigation. ^cR. A. Jones and A. R. Katritzky, *J. Chem. Soc.*, 1317 (1959). ^dR. A. Jones and A. R. Katritzky, *J. Chem. Soc.*, 378 (1961). ^eAssumed to be equal. ^fJ. Kebrle and K. Hoffmann, *Helv. Chim. Acta*, **39**, 116 (1956). This is the value for 2-aminoindolenine. ^gSee note f; this is the value for 1,3,3-trimethyl-2-iminoindoline.

The data in Table 3 served as a basis for the conclusions presented in Table 5. The difference (in kilocalories per mole) between the resonance energies of the pyridinoid (34) and pyridonoid (35) forms, obtained by various methods, is also presented in Table 5 along with the weighted mean values. The results obtained by method 2a were not taken into account in the determination of the latter values, since they are less accurate than the data obtained by other methods. One can be easily convinced that the deviations in the resonance energies are not very large, and all of these compounds have considerable aromaticity.

In particular, we arrive at the conclusion that 2-pyridone (35, X = O) and pyridine-2-thione (35, X = S) are to a considerable degree aromatic compounds. Their delocalization energy is apparently about 25 kcal/mole, while the most reliable estimate [21] of the aromatic resonance energy of pyridine itself gives 32 kcal/mole. The aromaticity of 2-pyridone imine (35, X = NH) is substantially lower, while the aromaticity of the corresponding methide (35, X = CH₂) is only about half that of pyridine.

Aromatic Resonance Energies of 4-Pyridone,

Its Analogs, and Compounds with Condensed Benzene Rings

The corresponding data for 4-pyridone and its analogs (see [36]) are presented in Table 6. Although the results are still incomplete, it can still be stated at the present time that all of these compounds are extremely similar to the members of the 2-pyridone series of derivatives and have considerable aromaticity.

The aromatic resonance energies for compounds of the 2-quinolone and 1-isoquinolone series are presented in Tables 7 and 8, respectively. In these cases, the difference in aromaticity between the quinolinoid and quinolonoid forms is even less than for monocyclic compounds. This might have been expected, since the heteroring makes a smaller contribution to the aromatic character of these compounds than to the monocyclic series.

Effect of Substitution in Methyl or Amino Groups

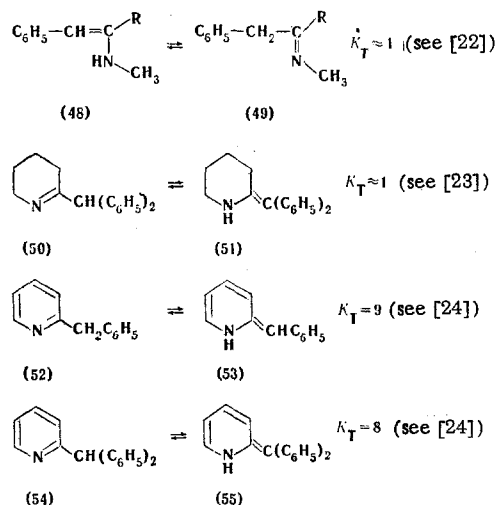
A study of the effect of replacement of the hydrogen atoms in methyl or amino groups by various substituents also seems of interest, since it is known that in some cases this sort of substitution has a substantial effect on the position of the tautomeric equilibrium. The (48) \rightleftharpoons (49) and (52) \rightleftharpoons (53) equilibria and the (50) \rightleftharpoons (51) and (54) \rightleftharpoons (55) equilibria are compared in Scheme V. It is apparent that the difference in the aromatic resonance energies between 2-benzylpyridine (52) and its methide (53) is about about 12 kcal/mole, in contrast to 18 kcal/mole, found above for 2-methylpyridine. The introduction of yet another phenyl group reduces the difference in the case of compounds (54) and (55) by about 1 kcal/mole. Data for a number of substituents in amino groups are presented in Table 9.

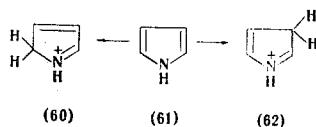
Aromaticity of Pyrrole

One can draw a conclusion relative to the aromaticity of pyrrole from its basicity. 1-Methylpyrrole is a weak base that is half protonated with an H₀ value of -2.9 [25]. This corresponds to a pK_a of -3.4 on the H_{R'} scale [26]. It is known that protonation occurs predominantly in the α position; however, the β position is also protonated to a certain degree, and the H₀ value for half protonation is $\sim -5^\circ$ [25]. Assuming that correspondence with the H_{R'} scale is observed in this case, it can be concluded that the pK_a is ~ -5.5 . The

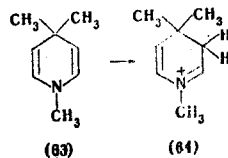
Scheme V

Effect of substituents in the methyl group



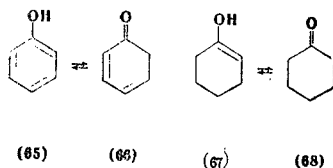


protonation of the β position of pyrrole can be compared with the protonation of 1,4-dihydropyridine in the β position [(63) \rightleftharpoons (64)], for which the pK_a is 7.4 [27]. The pK_a is consequently 12.9, which corresponds to a delocalization energy of about 22 kcal/mole for pyrrole.

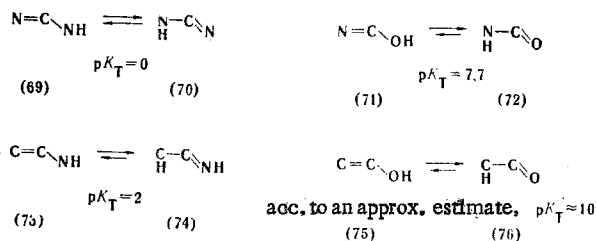


Aromaticity of Benzene

To obtain values that characterize the aromaticity of benzene, we will compare the phenol-cyclohexadienone and cyclohexenol-cyclohexanone equilibria. Unfortunately, accurate data on these equilibria are not available. We will attempt to make an approximate evaluation of the K_T values for these two equilibria. It should be emphasized that the error in this sort of estimate is rather large, but the order of magnitude can nevertheless be estimated correctly.



Different results relative to the enol concentration in cyclohexanone are presented in the literature: 1.2% according to Gero [28], 0.02% according to Schwarzenbach [29], and $4 \cdot 10^{-6}$ according to the recent data of Bell [30]. However, all of these results may still be too high, since the accurate determination of small concentrations of enol involves certain difficulties. The constants of the following tautomeric equilibria can be compared:

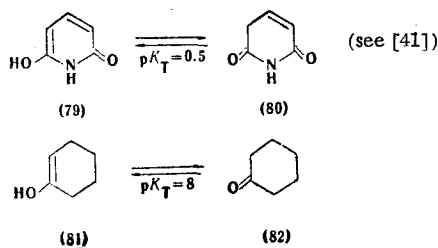


This comparison gives a pK_T value of about 10 for the equilibrium enol-ketone mixture. This value, however, seems too high, since it supposes an improbably high basicity of 1-cyclohexenol for cyclohexanone's pK_a of -5.6 [31]. We will therefore take a pK_T of 8, which corresponds to ΔG° of 11 kcal/mole (this is in agreement with the difference ΔH° for the ketone-enol equilibrium of acetone, which was obtained from the heats of hydrogenation of acetone and 2-ethoxypropene [32] and is equal to 11.6 kcal/mole), as the most reliable estimate.

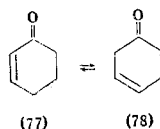
To estimate the phenol-cyclohexadienone equilibrium, we will attempt to estimate the pK values for the protonation of phenol in the o position and of cyclohexadienone at the oxygen atom. For phenol, the H_0 value for half protonation in the 4 [33] position is -7.04 [34]; however, this protonation apparently corresponds to the H_C acidity function rather than to H_0 [35], and the corresponding pK_a is therefore -11.3 . The pK_a value for protonation of phenol in the 2 position should be lower, since compounds protonated in the 2 position are not detected in the NMR spectrum. However, it is apparently not much lower, since the rates of acid-catalyzed exchange of protons in the 2 and 4 positions are comparable (see the discussion in [36]). We will therefore take a pK_a of -12 for the protonation of phenol in the 2 position. The pK_a for 2,4-cyclohexa-

Scheme VI

Aromaticity of 2-pyridone



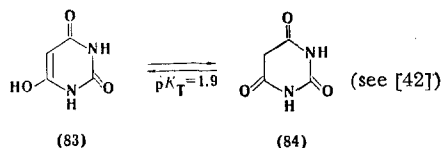
dienone can be estimated at -2.5 from the following data [37]: cyclohexanone, H_0 for half protonation -7.1 ,* $pK_a -5.6$ (without making assumptions regarding the character of the acidity function) [31]; cyclohexenone (H_A acidity function) [39], $pK_a -3.6$ [39]. Hence, for the phenol-2,4-cyclohexadienone equilibrium we obtain a pK_T of 9.5, which corresponds to a ΔG° of 13 kcal/mole, and ΔH° is consequently approximately equal to 29 kcal/mole for the difference in the delocalization energies of phenol and 2,4-cyclohexadienone. The (77) \rightleftharpoons (78) equilibrium, for which $\Delta G^\circ = 3.2$ kcal/mole [40], makes it possible to estimate the delocalization energy of 2,4-cyclohexadienone at about 5 kcal/mole. We then obtain 34 kcal/mole for the delocalization energy of benzene.

Aromaticity of 2-Pyridone and Uracil

The preceding method, in which tautomerism of different hydroxy compounds with the corresponding nonaromatic derivatives was used, can also be applied to 2-pyridone (Scheme VI).

A comparison of the (79) \rightleftharpoons (80) equilibrium with the equilibrium for cyclohexenol [(81) \rightleftharpoons (82)] demonstrates that the delocalization energy of compound (79) is 17 kcal/mole higher than for compound (80).

The same approach is possible in the case of 1,3-dioxypyrimidines (uracils). A comparison of the (83) \rightleftharpoons (84) and (81) \rightleftharpoons (82) equilibria indicates that the delocalization energy of compound (83) is 10 kcal/mole higher than the delocalization energy of compound (84).



The method described above is quite general and can be applied to most heteroaromatic systems.

I would like to express my special thanks to Doctor P. Linda (Perugia University) and Doctor M. J. Kuku for the substantial role that they played in this research and to Bachelor of Sciences R. D. Taku and Master of Sciences S. O. Chua for their great amount of experimental work.

LITERATURE CITED

1. G. M. Badger, *Aromatic Character and Aromaticity*, Cambridge University Press, Cambridge (1969), p. 43.
2. N. N. Magdesieva, *Adv. Heterocycl. Chem.*, **12**, 5 (1970).
3. L. M. Weinstock and P. I. Pollak, *Adv. Heterocycl. Chem.*, **9**, 149 (1968).
4. A. Julg and P. Francois, *Theor. Chim. Acta*, **8**, 249 (1967).
5. J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 859 (1961).

*We note that the pK_a for 4,4-dimethylcyclohexa-2,5-dienone is -2.37 [37].

6. R. J. Abraham, R. C. Sheppard, W. A. Thomas, and S. Turner, *Chem. Comm.*, 43 (1965).
7. H. A. P. DeJonge and H. Wynberg, *Tetrahedron*, 21, 515 (1965).
8. A. T. Balaban and Z. Simon, *Tetrahedron*, 18, 315 (1962).
9. A. R. Katritzky, *Chimia*, 24, 134 (1970).
10. A. R. Katritzky, *Chem. Ind.*, 331 (1965).
11. A. R. Katritzky and J. M. Lagowski, *Adv. Heterocycl. Chem.*, 1, 311, 339 (1963); 2, 1, 27 (1964).
12. H. Lumbroso and D. M. Bertin, *Bull. Soc. Chim. France*, 1728 (1970).
13. E. M. Arnett, *Progr. Phys. Org. Chem.*, Vol. 1 (1963), p. 342.
14. A. R. Goldfarb, A. Mele, and N. Gutstein, *J. Am. Chem. Soc.*, 77, 6194 (1955).
15. T. C. Pletcher, S. Koehler, and E. H. Cordes, *J. Am. Chem. Soc.*, 90, 7072 (1968).
16. J. W. Larsen and L. G. Hepler, in: *Solute-Solvent Interactions*, J. F. Coetzee and C. D. Ritchie (editors), Dekker, New York (1969), p. 1.
17. E. M. Arnett, R. P. Quirk, and J. J. Burke, *J. Am. Chem. Soc.*, 92, 1260 (1970).
18. P. D. Bolton and F. M. Hall, *J. Chem. Soc. (B)*, 259 (1969); 1247 (1970).
19. P. D. Bolton, C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Am. Chem. Soc.*, 2, 1567 (1970).
20. Yu. N. Sheinker, E. M. Peresleni, I. S. Rezhikova, and N. P. Zosimova, *Dokl. Akad. Nauk SSSR*, 192, 1295 (1970).
21. A. R. Bedford, A. E. Beezer, and C. T. Mortimer, *J. Chem. Soc.*, 2039 (1963).
22. H. Ahlbrecht, J. Blecher, and F. Kröhnke, *Tetrahedron Lett.*, 439 (1969).
23. E. Sury and K. Hoffmann, *Helv. Chim. Acta*, 38, 728 (1955).
24. Unpublished data obtained in the author's laboratory.
25. Y. Chiang and E. B. Whipple, *J. Am. Chem. Soc.*, 85, 2763 (1963).
26. Y. Chiang, R. L. Hinman, S. Theodoropoulos, and E. B. Whipple, *Tetrahedron*, 23, 745 (1967).
27. E. M. Kosower and T. S. Sorensen, *J. Org. Chem.*, 27, 3764 (1962).
28. A. Gero, *J. Org. Chem.*, 26, 3156 (1961).
29. G. Schwarzenbach and C. Wittwer, *Helv. Chim. Acta*, 30, 669 (1947).
30. R. P. Bell and P. W. Smith, *J. Chem. Soc. (B)*, 241 (1966).
31. E. M. Arnett, R. P. Quirk, and J. W. Larsen, *J. Am. Chem. Soc.*, 92, 3977 (1970).
32. M. A. Dolliver, T. L. Gresham, E. B. Kistiakowsky, E. A. Smith, and W. E. Vaughan, *J. Am. Chem. Soc.*, 60, 440 (1938).
33. T. Birchall, A. N. Bourns, R. J. Gillespie, and P. J. Smith, *Can. J. Chem.*, 42, 1433 (1964).
34. E. M. Arnett and C. Y. Wu, *J. Am. Chem. Soc.*, 82, 5660 (1960).
35. M. T. Reagan, *J. Am. Chem. Soc.*, 91, 5506 (1969).
36. M. Russell and S. Olsson, *Arkiv Kemi*, 31, 455 (1970).
37. K. L. Cook and A. J. Waring, *Tetrahedron Lett.*, 1675 (1971).
38. H. J. Campbell and J. T. Edward, *Can. J. Chem.*, 38, 2109 (1960).
39. R. I. Zalewski and G. E. Dunn, *Can. J. Chem.*, 47, 2263 (1969).
40. N. Heap and G. H. Whitham, *J. Chem. Soc. (B)*, 164 (1966).
41. A. R. Katritzky, F. D. Popp, and J. D. Rowe, *J. Chem. Soc. (B)*, 562 (1966).
42. M. Eigen, G. Ilgenfritz, and W. Kruse, *Ber.*, 98, 1623 (1965).