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AROMATICITY AND TAUTOMERISM—V[1]

THE BASICITY AND AROMATICITY OF PYRROLE, FURAN, THIOPHEN AND THEIR BENZO DERIVATIVES

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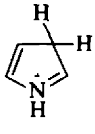
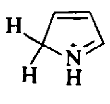
Abstract—Furans and thiophens are considerably weaker bases than pyrroles; the same applies to the benzo derivatives. The H_c function is obeyed by many of these compounds. Aromatic resonance energies are deduced for pyrrole, furan, and benzopyrroles by comparison of their basicities with those for model nonaromatic compounds.

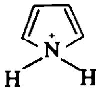
The low basicity of pyrrole compared to that of enamines generally,[2] is a consequence of the loss of the pyrrole aromaticity in all the alternative tautomeric forms (**1a–c**) of the cation.



1a



1b



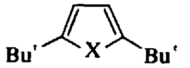
1c

In our preliminary communication[3] we pointed out that comparisons of the basitity of pyrrole and its benzologs with suitable models could provide quantitative estimates of the aromatic delocalisation energy in such compounds. A similar approach was independently adopted by Lloyd and Marshall.[4]

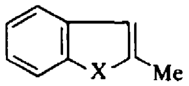
Furans and thiophens form tautomeric cations similar to **1**; in general such cations are unstable and rapidly polymerise. However, certain furans and thiophens with bulky alkyl substituents have been reported[5] to yield stable cation NMR spectra in strongly acid media. We found that 2,5-di-t-butylfuran and -thiophen and also 2-methyl-benzofuran and -benzothiophen undergo reversible protonation in sulphuric acid and we now report on and discuss these basicities and those of pyrrole derivatives with respect to the delocalisation energy of these compounds.

MEASUREMENT OF BASICITIES

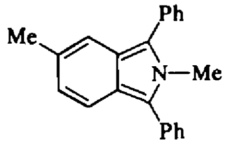
Preparation of compounds. 2,5-Di-t-butyl-furan (**2**), -thiophen (**3**) and -pyrrole (**4**) were each prepared from 2,2,7,7-tetramethylocta-3,6-dione.[6] Physical properties and NMR spectral data agree with those reported elsewhere although we found the 2,5-di-t-butylthiophen was contaminated with a few percent of an impurity, presumed to be the 2,4-isomer, which could not be removed by either chromatography or distillation. 2-Methylbenzo[*b*]furan (**5**) was prepared by cyclisation of *o*-chloroallylphenol[7] and 2-methylbenzo[*b*]thiophen (**6**) from benzo[*b*]thiophen by lithiation followed by methylation.[8] Samples of the isoindoles **7** and **8** were generously donated by Prof. J. D. White.[9] 1,4-Dihydro-1-methylquinoline (**9**) was prepared by sodium amalgam reduction of quinoline methiodide.[10]



2: X = O
3: X = S
4: X = NH



5: X = O
6: X = S



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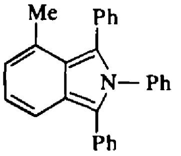

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Basicity studies. The stabilities of **2–6** in concentrated sulphuric acid were investigated by NMR at 38°. Protonation of **2–4** at the 2-position was readily established from the splitting pattern of the NMR signals.[5] The stability of **2** in sulphuric acid was confirmed[5] but **3** and **4** both underwent slow decomposition.[11] The NMR spectra of **5** and **6** in concentrated sulphuric acid indicated that these compounds decompose more readily. Unlike **2–4** the spectra did not correspond to those expected for long lived cationic species. However it seems reasonable to assume that protonation occurs at the 3-position.

The basicities of **2–8** were measured by the UV method. The spectral changes caused by protonation in the acid medium (Table 1) were reversible, although some decomposition was apparent for all but **2**; indeed decomposition of **3** was sufficiently fast to require extrapolation of absorbance data back to zero time. The H_0 values for half protonation of **2–6** and slopes, n, for the log I vs $-H_0$ plots are reported in Table 2. The value of n = 1.6 for **2** shows that it does not behave as a Hammett base, but in a manner similar to those carbon bases, e.g. azulene, aromatic polyethers, which were used by Reagan[12] to establish the H_c scale. A plot of the data for **2** vs H_c gives a value of H_c for half protonation of -10.01 (n = 1.22) which we take as the pK_a. This value contrasts with what appears to be the

Table 1. UV spectral data[a]

Compound	Neutral form		Cation	
	$\lambda_{max.}$ (nm)	ε	$\lambda_{max.}$ (nm)	ε
2,5-Di-t-butylfuran (2)	b		255	8900
2,5-Di-t-butylthiophen (3)	245	4000	249 310	4000 3900
2,5-Di-t-butylpyrrole (4)	217	11900	218.5	7900
2-Methylbenzo[b]furan (5)	208 245	9400 5800	217 257	18000 7300
2-Methylbenzo[b]thiophen (6)	230	27500	213	37400

[a] Data for compounds 7 and 8 are reported in Ref 9.

[b] End absorption only.

Table 2. Basicity measurements

Compound no.	H_0 (half protonation)	n[a]	pK_a	Remarks re pK_a value[a]
2	-6.39	1.56 (0.984)	-10.01	H_c function assumed n = 1.22 (0.984)
3	-6.48	1.34 (0.993)	-10.16	H_c function assumed n = 1.01 (0.993)
4	-0.73	1.54 (0.989)	-1.01	H_c function assumed n = 1.07 (0.991)
5	-8.66	1.98 (0.985)	-13.3	H_c function assumed. Extrapolated value (see text)
6	-6.67	1.75 (0.999)	-10.40	H_c function assumed n = 1.34 (0.997)
7			2.05	
8			-0.22	
9			7.9	See experimental

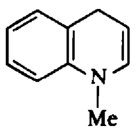
[a] Figures in parentheses refer to correlation coefficients.

only previous estimate of the basicity of a furan derivative viz −0.11 for furan itself,[13] which is improbably high and evidently due to some process other than protonation.

For the thiophen 3 and the pyrrole 4, the H_c values of half protonation −10.16 (slope 1.01) and −1.01 (slope 1.07) are taken as the values for the pK_a. An acidity function for pyrrole protonation was established by Chiang and Whipple[14] which is similar to the H_c scale over much of the acidity range. The pK_a of 4 using the pyrrole acidity function is −1.14.

The slopes of the log I vs H_0 plots for 5 and 6 deviate from unity more than for the monocyclic analogues. The H_c scale does not extend sufficiently to accommodate the data for 5 but using an extrapolation of the H_c curve a value of H_c = *ca.* −13.3 for the half protonation of 5 is obtained. The uncertainty is large and it is by no means clear whether protonation of 5 follows H_c closely. The H_c value of half protonation for 6 is −10.40, slope 1.34. That 6 (and possibly 5) diverge from the H_c scale more so than 2 and 3 may arise from the greater charge expected to reside on the heteroatoms in the former pair, as the H_c scale applies to systems bearing positive charge on carbon.

Data for the isoindoles 7 and 8 demonstrate the expected base weakening effect exerted by an N-phenyl substituent. The pK_a of 9, viz 7.9, measured by a stop flow method, is very similar to that of the cross conjugated dieneamine 10 (7.4).[15]



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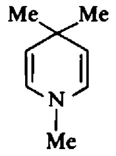


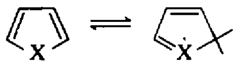
10

AROMATIC RESONANCE ENERGIES

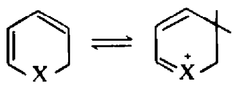
The estimation of the greater stability of cyclic $4n+2\pi$ electron systems compared with non delocalised structures or linear polyenes has played a significant role in discussions of aromaticity. We now estimate aromatic resonance energies by comparing basicities of heteroaromatic compounds with those of nonaromatic analogues which form cations of π electron structure similar to those of the aromatic compounds, relating the weaker basicity of the heteroaromatic compound with the greater loss of resonance energy on protonation. We have discussed the use of linear free energy relationships to convert $\Delta\Delta G^0$ values (i.e. Δ pK_a values) into $\Delta\Delta H^0$ values elsewhere,[16] the $\Delta\Delta H^0$ values being the difference in the resonance energies of the aromatic and model compounds. More recently[1] however we have extended our earlier investigation[17] of ΔH^0:pK_a relationships to other base types and we have found that the slopes of such plots for anilines, 1.14,[1,17] pyridines, 1.11,[1] pyridine

N-oxides, 1.04[1] are remarkably similar. Whilst it is not clear how general this order of slope is, in the absence of other results for C-protonation, we shall hereafter convert the ΔpK_a values referred to above into $\Delta\Delta H^0$ values by multiplying them by a factor of 1.1. The error in $\Delta\Delta H^0$ values so obtained is probably of the order of 20%.

(i) *α-Protonation of pyrroles, furans and thiophens.* Equation (1) shows the α-protonation of this series, and eqn (2) the protonation of the nonaromatic model.


(1)

Model


(2)

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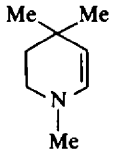
Chiang and Whipple[14] demonstrated that both N and C methylation of pyrroles enhance ring basicity. Although there is no data for the basicities of dieneamines of type **11**, whether substituted or not, Kosower and Sorensen[15] reported pK_a 10.45 for **12**; and we believe the basicity of **11** X = N-Me will be similar to within ± 2 pK_a units. Combining this value with the literature[14] pK_a value for α-protonation of N-methylpyrrole (−2.9), gives $\Delta\Delta H^0 = 15 \pm 5$ kcal mole^{-1}. The *total* resonance stabilization of **10** is probably[15] of the order of 6 kcal mole^{-1} but cross conjugated dieneamines are *ca.* 2.3 kcal mole^{-1} more stable than dieneamines of type **11**, X = N-Me,[18] and we therefore estimate the total resonance energy of N-methylpyrrole, A_{pyrrole} as 19 ± 5 kcal mole^{-1}. Such a value falls into the range 14–31 kcal mole^{-1} obtained from thermochemical data.[19]



12

To estimate the resonance energy of furan the basicities of furan and the model dienol ether, **11**, X = O, are required. 2,5-Di-t-butylpyrrole investigated above is 2.8 pK_a units more basic than pyrrole itself[14] and on the basis of this and the pK_a of −10.01 for 2,5-di-t-butylfuran **2** we estimate that the pK_a of furan at the 2-position is -13 ± 1. No estimates of dienol ether basicity are available presumably because of their facile hydrolysis in acid medium. However the pK_a of an enol can be estimated from the following scheme in which $\log K = pK_1 - pK_2$.

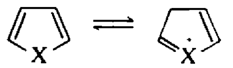
$$\begin{tikzcd} \mathrm{RCH{=}C(OH)R'} \arrow[rr, shift left, "K"] & & \mathrm{RCH_2COR'} \arrow[ll, shift left] \\ & \mathrm{RCH_2COH{\cdot}R'} \arrow[ul, shift left] \arrow[ul, shift right, "K_1"'] \arrow[ur, shift left] \arrow[ur, shift right, "K_2"] & \end{tikzcd}$$

Scheme

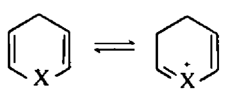
The keto:enol tautomerism equilibrium constant for cyclohexanone has been measured[20] as 2.4×10^5 and can be estimated from kinetic data[21] for ketone enolisation and enol ether hydrolysis as $2.0 \times 10.^5$ Combining this with a value of *ca.* −5.6 for the pK_a for cyclohexanone[22] provides a value of *ca.* −0.2 for the pK_a of an enol. Assuming that the pK_a of **11**, X = O, is also -0.2 ± 2 and that its resonance stabilization is comparable to that of **11**, X = N-Me, leads to a value for A_{furan} of 18 ± 5 kcal mole^{-1}. This value is very similar to that obtained above for A_{pyrrole} and compares with values in the range 15.8–23 kcal mole^{-1} obtained from thermochemical data.[19]

No estimates for A_{thiophen} are possible because of the absence of any basicity data for nonaromatic analogues. However, applying the reverse argument to the one above, we suggest that thioenol ethers are stronger bases than enol ethers on the basis of the similar pK_a values for **2** and **3** and the previously reported greater resonance energy of the thiophen ring system.[19]

(ii) *β-Protonation of pyrroles.* The protonation of five ring heteroaromatics at the β-position and the protonation of the nonaromatic analogues are given by eqns (3) and (4). No data are available in the oxygen and sulphur series but the pK_a for β-protonation of N-methylpyrrole has been reasoned to be −5.1.[14] Comparison of this value with that of 7.4 for **10** which we take as a good estimate for that of **13**, X = N-Me, gives $\Delta\Delta H^0 = 14 \pm 3$ kcal mole^{-1}. Addition of 6 ± 1 kcal mole^{-1} for the resonance energy of **13** (as above) gives a value for $A_{\text{pyrrole}} = 20 \pm 4$ kcal mole^{-1} in good agreement with that obtained using data for α-protonation.

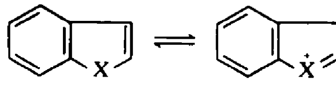

(3)

Model

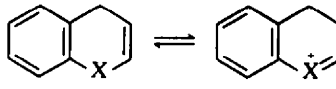

(4)

13

(iii) *β-Protonation of benzo*[b]*fused analogues* (eqns 5 and 6). The H_0 for half protonation of 1-methylindole[23] is −1.8 but the compound is not a Hammett base. Hinman and Lang[24] constructed an acidity function for protonation of indoles and obtained a value of pK_a −2.32 for this compound. Comparison of this value with the basicity of **9**, pK_a 7.9 and assuming the resonance energy of **9** is *ca.* 42 ± 1 kcal mole^{-1} (from benzene,[19] 36, and **10** *ca.* 6 ± 1) gives a value for $A_{\text{indole}} = 53 \pm 3$ kcal mole^{-1} which compares with the range 41.8 − 57.6 kcal mole^{-1} obtained from thermochemical data.[19]


(5)

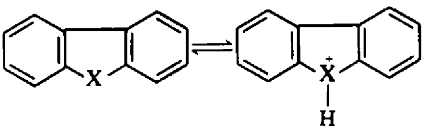
Model


(6)

9: X = NMe

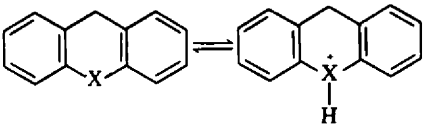
Estimates of benzofuran and benzothiophen resonance energies are precluded by both uncertainties in the pK_a of **5** and **6** and the lack of basicity data for nonaromatic models.

(iv) *Protonation of dibenzofused derivatives* (eqns 7 and 8). In the dibenzofused series data are only available for carbazole[25] which has H_0 for half protonation of −4.94 and an extrapolated $pK_a = -6$. Perhaps the most appropriate model system is provided by the protonation of dibenzoquinuclidine[26] pK_a 4.46 whence $\Delta\Delta H^0 = 12 \pm 2$ kcal mole^{-1}. The aromaticity of dibenzoquinuclidine is expected to be merely twice that of benzene, hence $A_{\text{carbazole}} = 84 \pm 2$ kcal mole^{-1}. An alternative model to dibenzoquinuclidine is diphenylamine[27] pK_a 0.77, the resonance energy for which has been reported [28] as 77–78 kcal mole^{-1}. Using this model $A_{\text{carbazole}} = 85 \pm 2$ kcal mole^{-1} and both values fall within the range obtained using thermochemical data (74–100.7 kcal mole^{-1}).[19]



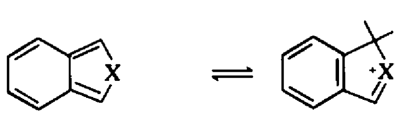
(7)

Model



(8)

(v) *Protonation of benzo*[c]*fused derivatives* (eqns 9 and 10). Once again, basicity data are available only for the nitrogen series, **14**, X = NR. The nonaromatic model for isoindole, i.e. **15**, X = NR, is unavailable and it is difficult to estimate its basicity. However the cation formed from N-phenylindole, (**16**) possesses structural similarities to the cation of **7**, i.e. **17**. We believe that the greater basicity of **7** pK_a 2.05 over N-phenylindole pK_a *ca.* −5, estimated on the basis of the pK_a of N-methylindole,[24] −2.32, and the base weakening effect of the N-phenyl group (N-methylpyrrole pK_a −3.4, N-phenylpyrrole, pK_a −5.8)[14], points to a greater resonance stabilization of the indole system over the isoindole system. A quantitative estimate of this difference hardly seems meaningful, however, bearing in mind the assumptions inherent in this comparison.



(9)

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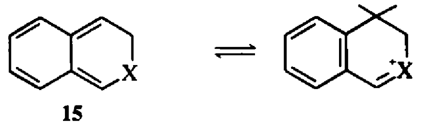
Model



(10)

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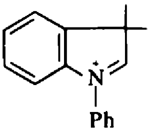

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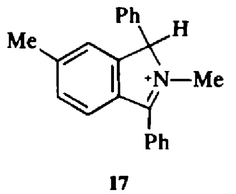

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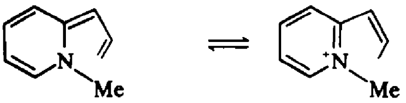
(iv) *Protonation of indolizine* (eqns 11 and 12). The pK_a for protonation of indolizine at the 3-position is 3.94,[29] and we believe the basicity of **18** will be similar to within ±3 pK_a units, to that of 1-methyl-2-pyridone methide pK_a 19.25, which we measured previously.[16] The values provide a value of 17 ± 6 kcal mole^{-1} for the greater resonance energy of indolizine over 1-methyl-2-pyridone methide: in an earlier paper we reported[30] that the resonance energy of the latter is some 18 kcal mole^{-1} less than that of pyridine.

(11)

Model



(12)

18

EXPERIMENTAL

Materials. The following were prepared by literature methods: 2,5-di-t-butylfuran[6] b.p. 65–72°/19 mm (lit[6c] 58.5–59.5°/11–12 mm); 2,5-di-t-butylthiophen[6c] b.p. 110–115°/16 mm (lit[6c] 93–95°/10 mm); 2,5-di-t-butylpyrrole[6c] m.p. 30.5–31.5° (lit[6c] 31.5–32.5°); 2-methylbenzo[*b*]furan[7] b.p. 75–80°/12 mm (lit[31] 88–90°/19 mm); 2-methylbenzo[*b*]thiophen[8] m.p. 50–50.5° (lit[8] 51–52°); 1,4-dihydro 1-methylquinoline[10] (NMR and UV spectral data in agreement with that reported elsewhere[10]). We thank Prof. J. D. White for supplying samples of 2,5-dimethyl-1,3-diphenylisoindole m.p. 171.5–172.5° and 4-methyl-1,2,3-triphenylisoindole m.p. 179–180°.

Spectral measurements. NMR measurements were obtained using a Varian Associates HA 100 spectrometer operating at 38°. UV spectra (Table 1) were normally measured using a Unicam SP500 series 2 spectrophotometer.

*p*K$_a$ *measurements* (Table 2). Most basicity measurements utilized the spectroscopic method (UV absorbance).[32] The pK_a of 1,4-dihydro-1-methylquinoline was measured by placing a stock solution (0.2 ml) in a 4 cm UV cell in a Beckmann DB spectrophotometer connected to a recorder. Buffer solution (10 ml) was rapidly syringed in (in darkness) and the absorbance at 303 nm recorded against time (reproducible curves were obtained from 7 sec after mixing). Extrapolated values of absorbance at zero time from several runs when plotted vs buffer pH gave a sinusoidal plot. Values of log I were then calculated and plotted vs pH to give a plot of gradient −1.0 from which the pK_a value was read.

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