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HETEROAROMATICITY.8. THE INFLUENCE OF N-OXIDE FORMATION ON HETEROCYCLIC AROMATICITY

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Abstract - A recently described aromaticity index has been used to examine the changes in the aromaticity of nitrogen heterocycles that accompany their N-oxidation. Some instances are noted where there is an unforeseen increase in aromatic character. The aromaticity indices of isomeric furoxans can be a useful indication as to their relative stabilities.

N-Oxide derivatives play an important role in the chemistry of nitrogen heterocycles[1,2,3]. A variety of physicochemical measurements show that the N-oxide function displays a duality of behaviour both in increasing the polarisation of ring electrons towards the positively charged nitrogen, and also in donating electrons from oxygen into the ring as illustrated in Figure I for pyridine N-oxide.

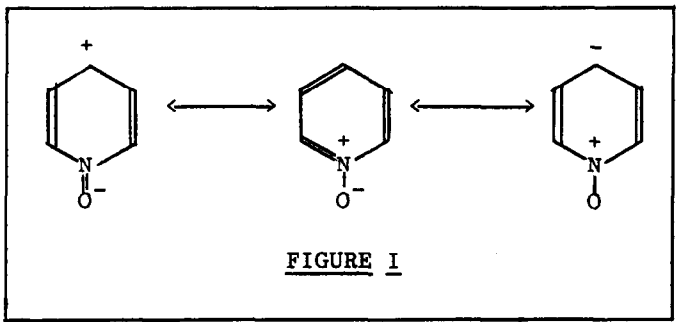


FIGURE I

The availability of molecular dimensions for a substantial number of heterocyclic N-oxides suggested that the application of the previously presented[4] aromaticity index, I_A, to such systems might provide a quantitative rationale for at least some aspects of N-oxide behaviour. The aromaticity index is based upon a statistical evaluation of the extent of variation of ring bond orders as given by the expression $I_A = 100F(1-V/V_K)$ where $V = \frac{100}{\bar{N}}\sqrt{\frac{(N-\bar{N})^2}{n}}$ and $\bar{N}$ is the arithmetic mean of the n various ring bond orders, N. These are readily obtained[5] from the corresponding bond lengths. V_K is the value of V for the corresponding non-delocalised form of the ring and F is a scaling factor with values of 1.235, 1, 2.085 and 1.84 for 5-,6-, 5,6- and 6,6-membered ring systems. On this scale benzene, with a resonance energy of 2β, has an I_A of 100 so that a unitary increment on the I_A scale corresponds to 0.02β, that is 0.36 Kcals/mole if we assume the commonly ascribed value of 18 Kcals/mole for β.

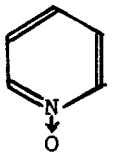
Aromaticity indices for a range of pyridine N-oxides are presented in

TABLE I. Aromaticity Indices, I_A, for Pyridine N-Oxides. (References are to sources of molecular dimensions).

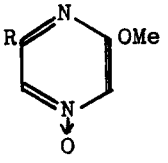
Pyridine N-Oxide	I_A	Ref.
1. Parent	74.4	7
2. 4-Dimethylamino-	73.6	8
3. 4-Cyano-	71.6	9
4. 4-Nitro-	67.4	10
5. 3-Methyl-4-nitro-	70.8	11
6. 3,5-Dimethyl-4-nitro-	70.2	11
7. 2-Hydroxymethyl-	72.2	12
8. 2-Carboxy-6-methyl-	70.0	13
9. 2,6-Dicarboxy-	67.9	14
10. 2-(o-Hydroxyphenyl)-	62.9	15

Table I. As might be anticipated the I_A of 74.4 for pyridine N-oxide lies between the values of 86 for pyridine[6] and 66.7 for pyridinium methiodide[6]. Comparison of the I_A's for the first four entries in Table I indicates that there is only a very modest interaction between electron donating or electron withdrawing substituents and the pyridine N-oxide ring. The introduction of methyl groups adjacent to the nitro group, entries 5 and 6, prevents its coplanarity with the ring and thereby reduces its effect. Intramolecular hydrogen bonding, as in entries 7 to 10, also lowers the I_A's. However, the effect of the carboxyl groups is not as large as that observed for intermolecular complexes such as that formed[16] between pyridine N-oxide and fumaric acid with an I_A of 63.4.

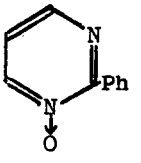
Aromaticity indices for a variety of other heterocyclic N-oxides depicted in Figure II are listed in Table II. For comparative purposes the % reduction in I_A's relative to the parent heterocycle are also listed. It will be noted that, even allowing for substituent effects, there are substantial differences in the magnitude of I_A changes accompanying N-oxide formation with different ring systems. Comparison of the value obtained for the pyrimidine N-oxide (3) with the I_A's of (4), (5) and (6) indicates that a 2-amino substituent enhances the aromaticity. Although N-1 oxidation of 1,2,3-triazine as in (10) causes the expected decrease in I_A only minimal effect is caused by N-2 oxidation, cf. (9) and (10). This may reflect the relief of the concatenation of repulsions between the nitrogen lone-pairs. A similar effect is observed for the conversion of 4,6-diphenyl 1,2,3-triazine to the corresponding 2-methyltriazinium cation[34] with an I_A of 74.2. The same explanation can be ascribed to the enhancement of aromaticity accompanying the formation of (11), (12) and (18). Such an effect may contribute to the relative stability of the 1,3-di-N-oxide[35] (I_A = 112) of the as yet unknown benzo-1,2,3,4-tetrazine. Although various interrelation-



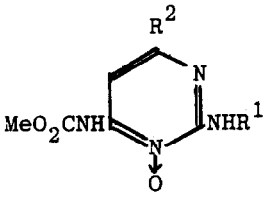
(1)



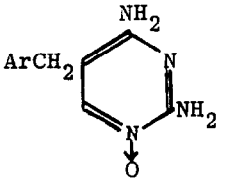
(2a) R=H
(2b) R=Me



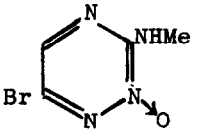
(3)



(4) R^1=H, R^2=OTs
(5) R^1=CO_2Me, R^2=NC_5H_8



(6)



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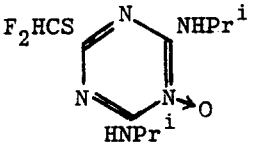

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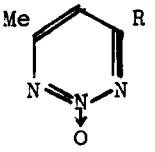
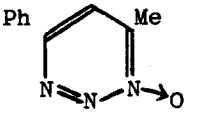
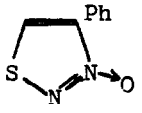


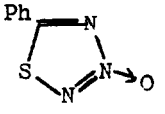
(9a) R=Me
(9b) R=Ph



(10)



(11)



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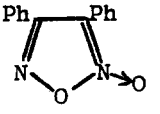

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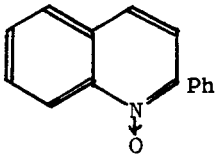

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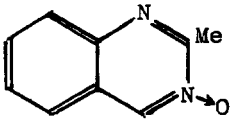
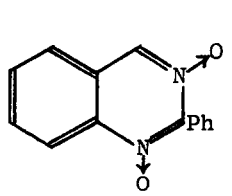


(15)

FIGURE II



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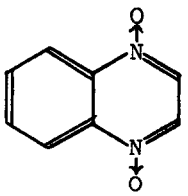

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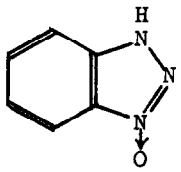

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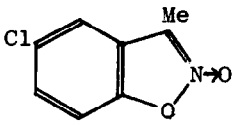

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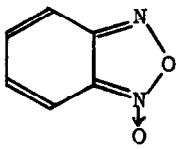


(20)

FIGURE II (cont.)

ships have been established[36] between ^{15}N, ^{13}C nmr chemical shifts and infrared absorption frequencies in heterocyclic N-oxides, all attempts so far to relate these to changes in I_A have been unsuccessful. A possible explanation may be found in the orthogonality observed[37] between classical aromaticity indices such as I_A, and those aromaticity indices based on magnetic properties.

A substantial proportion of the literature concerning X-ray structures of N-oxides is devoted to furoxans (1,2,5-oxadiazole 2-oxides). Unfortunately furoxan itself is as yet unknown but the predicted[38] bond lengths lead to an I_A of 42. In view of their low aromaticity it is not surprising that furoxans are much more sensitive to structural modifications than the foregoing heterocyclic systems. This is well illustrated by the examples presented in Figure III. The role of steric distortion in reducing aromaticity[42] is indicated by comparison of compounds (21), (22) and (23). Strong electron withdrawing groups at C-4 as in (24) or (25) appreciably lower aromaticity whereas they appear to have little effect at C-5 as in (27) versus (22). Conversely electron donating groups at C-4 as in (29) clearly enhance aromaticity.

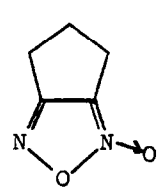
A particularly fascinating feature of furoxan chemistry[49] is the ability of unsymmetrically substituted compounds to undergo thermally promoted interconversion as (30) v. (31). The relative proportions of the two isomers at equilibrium depend upon the substituents A and B. Apart from differ-

TABLE II. Aromaticity Indices, I_A, for Heterocyclic N-Oxides.(References are to sources of molecular dimensions).

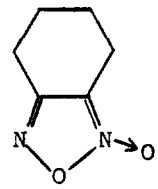
N-Oxide	I_A	P.H.*	% Change	Ref.
(1)	74.4	86	-13.5	7
(2a)	68.4	89	-23.2	17
(2b)	67.2	89	-24.5	17
(3)	66.5	84	-20.8	18
(4)	71.6	84	-14.8	19a
(5)	68.5	84	-18.4	19b
(6)	73.0	84	-13.1	20
(7)	64.1	86.1	-25.6	21
(8)	87.2	100	-12.8	22
(9a)	73.4	77	-4.6	23a
(9b)	76.0	77	-1.3	23a
(10)	68.95	77	-10.5	23b
(11)	68.5	67	+2.3	24
(12)	84.5	80.3	+5.3	25
(13)	48.9	61.9#	-21.0	26
(14)	128.8	134	-3.9	27
(15)	119.8	143	-16.2	28
(16)	115.0	143	-19.6	29
(17)	114.3	132	-13.4	30
(18)	152.1	140	+8.6	31
(19)	91.5	108.4	-15.6	32
(20)	81.0	106.3	-23.8	33

* I_A for parent heterocyclic ring system; # I_A for 4,5-diphenylfuroxan as parent heterocycle is unknown.

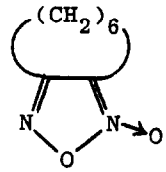
ences in internal rotational or vibrational energies an important factor in determining the position of the equilibrium would be expected to be the relative aromaticities of the two isomers. The aromaticity indices for those pairs of isomers for which structural data are available are listed in Table III along with references to the sources of molecular dimensions. In most cases the differences in I_A's for pairs of isomers is small and this is presumably the reason why both are isolable. With three exceptions the predicted relative stabilities agree with experimental observation. Of the exceptions, that provided by the chloro phenyl furoxans (30c, 31c) is of doubtful significance as the difference in I_A is within experimental error. More puzzling are the situations presented by the methyl dimethyl-carboxamido (30g, 31g) and methyl phenylsulfonyl-furoxans (30i, 31i) where the differences in I_A's predict relative stabilities opposite to those



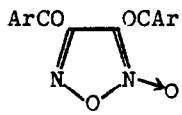
(21) I_A=20.9[39]



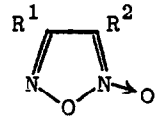
(22) I_A=32.2[40]



(23) I_A=38.7[41]

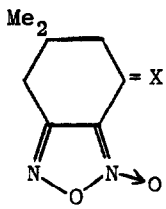


(24) I_A=23.8[43]



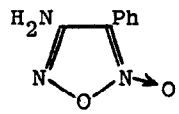
(25) R^1=NO_2; R^2=Me I_A=28.6[44]

(26) R^1=p-BrC_6H_4NH; R^2=Bu I_A=42.7[45]



(27) X=O I_A=32.2[46]

(28) X=NOH I_A=37.1[47]

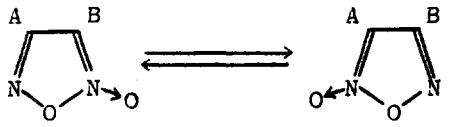


(29) I_A=51.6[48]

FIGURE III (References are to the source of strucural dimensions)

experimentally observed. Apart from the carboxamidofuroxan (30f,31f) and its hydrazide counterpart (30h, 31h), where hydrogen bonding between the N-oxide oxygen and the N-H of the substituent may favour the (30f,h) isomers, there is no universal isomer preference for other carbonyl compounds. Thus, when A is a methyl group, isomer (31) preponderates for B = CO_2Et, COCl, $CONMe_2$[50], COMe[60] while isomer (30) preponderates for B = CHO[61] and (27) is more stable than its isomer[46]. The apparent dichotomy encountered with (30g, 31g) and (30i, 31i) may arise from the fact that the I_A's are derived for molecules constrained to adopt a specific conformation by the crystal lattice, while the relative stabilities are based upon observations in solution where the compounds may assume a different spatial orientation resulting in different substituent-ring interactions.

Acknowledgement. I am greatly indebted to Dr. A. W. Parkins for his help in locating the X-ray crystallographic data on which this paper is based.



(30) (31)

TABLE III. Aromaticity Indices for Furoxan Isomers

	Substituents A	B	I_A for (30)	I_A for (31)	Ref.
a)	H	Ph	42.5	40.8	51
b)	Me	p-BrC_6H_4	48.5	43.9	52
c)	Ph	Cl	40.0	39.3	53
d)	Me	NH_2	43.7	41.4	38
e)	$NHCO_2Pr^i$	Me	37.9	35.3	54
f)	Me	$CONH_2$	45.2	42.2	55
g)	Me	$CONMe_2$	40.0	38.6	56,57
h)	Me	$CONHNH_2$	45.1	42.2	58
i)	Me	$PhSO_2$	41.8	35.3	59

REFERENCES

1. Ochiai, E.,"Aromatic Amine Oxides", Elsevier, Amsterdam, 1967.
2. Katritzky, A.R., and Lagowski, J.M., "Chemistry of the Heterocyclic N-Oxides", Academic Press, London, 1971.
3. Katritzky, A.R., and Lam, J.N., Heterocycles, 1992, 33, 1011.
4. Bird, C.W., Tetrahedron, 1992, 48, 335.
5. Bird, C.W., Tetrahedron, 1985, 41, 1409
6. Bird, C.W., Tetrahedron, 1986, 42, 89.
7. Snerling, O., Nielsen, C.J., Nygaard, L., Pedersen, E.J., and Sørensen, G.O., J. Mol. Struct., 1975, 27, 205.
8. Nakai, H., Saito, T., and Yamakawa, M., Acta Crystallogr., 1988, C44, 533.
9. Hardcastle, K.I., Laing, M.J., McGauley,T.J., and Lehner, C.F., J. Cryst. Mol. Struct., 1974, 4, 305.
10. Wang, Y., Blessing, R.H., Ross, F.K., and Coppens, P., Acta Crystallogr. 1976, B32, 572.
11. Shiro, M., Yamakawa M., and Kubota, T., Acta Crystallogr., 1977, B33, 1549.
12. Desiderato, R., and Terry, J.C., J. Heterocyclic Chem., 1971, 8, 617.
13. Dideberg, O., and Dupont, L., Acta Crystallogr, 1975, B31, 2719.
14. Rychlewska, U., and Gdaniec, M., Acta Crystallogr., 1977, B33, 3555.
15. Kubicki, M., Borowiak, T., Antkowiak, R., and Antkowiak, W.Z., J. Cryst. Spectrosc., 1990, 20, 381.
16. Gorres, B.T., McAfee, E.R., and Jacobsen, R.A., Acta Crystallogr., 1975, B31, 158.
17. Peters, D.A., Beddoes, R.L., and Joule, J.A., Acta Crystallogr., 1992, C48, 307.
18. Leban, I., and Polanc, S., Acta Crystallogr., 1992, C48, 2227.
19. a) Muller, J.C., Ramuz, H., and Wagner, H.-P., Helv. Chim. Acta, 1983, 66, 809.
    b) Muller, J.C., Ramuz, H., Daly, J., andSchonholzer, P., Helv. Chim. Acta, 1982, 65, 1454.
20. Oberhansli, W.E., Helv. Chim. Acta, 1970, 53, 1787.
21. Radel, R.J., Atwood, J.L., and Paudler, W.W., J. Org. Chem., 1978, 43, 2514.

22. Shiro, M., Morita, K., and Hayase, Y., Anal. Sci., 1989, 5, 627.
23. a) Yamaguchi, K., Ohsawa, A., and Itoh, T., Acta Crystallogr., 1990, C46, 2177.
b) Yamaguchi, K., Itoh, T., Kaihoh, T., and Ohsawa, A., Acta Crystallogr., 1991, C47, 2193.
24. Winter, W., Plucken, U., and Meier, H., Z. Naturforsch., 1975, 33b,316.
25. Ottersen, T., Acta Chem. Scand., 1976, A30, 351.
26. Sillitoe, A.K., and M.M. Harding, Acta Crystallogr., 1978, B34, 2021.
27. Bocelli, G., Cantoni, A., Giorgini, E., and Tosi, G.,J. Cryst. Spectros., 1990, 20, 419.
29. Brown, K.L., and Gainsford, G.J., Acta Crystallogr., 1979, B35, 2276.
30. Qiuzi, C., Shukun, L., and Hanqing, Jiegou Huaxue, 1989, 8, 31.
31. R. Bosch, Jung, G., and Winter, W., Acta Crystallogr., 1983, C39, 1089.
32. Chiari, G., and Viterbo, D., Acta Crystallogr., 1982, B38, 323.
33. Britton, D., and Olson, J.M., Acta Crystallogr., 1979, B35, 3076.
34. Yamaguchi, K., Itoh, T., Okada, M., and Ohsawa, A., Acta Crystallogr., 1992, C48, 964.
35. Yamaguchi, K., Takahashi, H., Kaihoh, T., Itoh, T., Okada, M., Nagata, K., Matsumura, G., and Ohsawa, A., Acta Crystallogr., 1992, C48, 1237.
36. Paudler, W.W., and Jovanovic, M.V., Heterocycles, 1982, 19, 93; Jovanovic, M.V., Spectrochimica Acta, 1985, 41A, 1135.
37. Katritzky, A.R., Barczynski, P., Musumarra, G., Pisano, D., and Szafran, M., J. Amer. Chem. Soc., 1989, 111, 7.
38. Ugliengo, P., Viterbo, D., and Calleri, M., J. Chem. Soc., Perkin II, 1988, 61.
39. Barnes, J.F., Barrow, M.J., Harding, M.M., Paton, R.M., Ashcroft, P.L., Crosby, J., and Joyce, C.J., J. Chem. Res. (S), 1979, 314.
40. Barrow, M.J., Acta Crystallogr., 1982, B38, 308.
41. Harding, M.M., and Paton, R.M., Acta Crystallogr., 1982, B38, 1395.
42. Bird, C.W., Tetrahedron, 1992, 48, 1675.
43. Viterbo, D., and Ferraris, G., J. Chem. Soc.(B), 1970, 223.
44. Forbes Cameron, A., and Freer, A.A., Acta Crystallogr., 1974, B30,354.
45. Glidewell, C., Holden, H.D., and Liles, D.C., J. Chem. Res.(S),1978,357.
46. Calleri, M., and Viterbo, D., Acta Crystallogr., 1976, B32, 2236.
47. Calleri, M., Bonaccorti, L., and Viterbo, D., Acta Crystallogr., 1977, B33, 3546.
48. Chertanova, L.F., Gazikasheva, A.A., Rakitin, O.A., and Khmelnitzkii, L.I., Zhur. Strukt. Khim., 1991, 32, 148.
49. Gasco, A., and Boulton, A.J., Adv. Heterocyclic Chem., 1981, 29, 252.
50. Gasco, A., and Boulton, A.J., J. Chem. Soc., Perkin II, 1973, 1613.
51. Calleri, M., Ranghino, G., Ugliengo, P., and Viterbo, D., Acta Crystallogr., 1986, B42, 84.
52. Calleri, M., Ferraris, G., and Viterbo, D., Acta Crystallogr., 1969, B25, 1126, 1133.
53. Viterbo, D., Chiari, G., and Calvino, R., Acta Crystallogr., 1982, B38, 3045.
54. Calleri, M., Chiari, G., Chiesi Villa, A., Gaetani Manfredotti, A., Guastini, C., and Viterbo, D., Acta Crystallogr., 1977, B33, 479.
55. Calleri, M., Chiari, G., Chiesi Villa, A., Gaetani Manfredotti, A., Guastini, C., and Viterbo, D., Acta Crystallogr., 1975, B31, 2384.
56. Chiesi Villa, A., Guastini, C., Calleri, M., and Chiari, G., Cryst. Struct. Commun., 1974, 3, 265.
57. Calleri, M., Viterbo, D., Gaetani Manfredotti, A., and Guastini, C., Cryst. Struct. Commun., 1974, 3, 269.
58. Calleri, M., Chiari, G., Germain, G., and Viterbo, D., Acta Crystallogr., 1973, B29, 1618.
59. Calleri, M., Chiari, G., Chiesi Villa, A., Gaetani Manfredotti, A., Guastini, C., and Viterbo, D., Acta Crystallogr., 1976, B32, 1032.
60. Calvino, R., Ferrarotti, B., Serafino, A., and Gasco, A., Heterocycles, 1985, 23, 1955.
61. Fruttero, R., Ferrarotti, B., Serafino, A., Di Stilo, A., and Gasco,A., J. Heterocyclic Chem., 1989, 26, 1435.