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MOLECULAR ORBITAL CALCULATIONS ON 8-HYDROXYQUINOLINE AND SOME OF ITS AZA-ANALOGS

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Abstract—Hückel MO calculations have been made on 8-hydroxyquinoline and several of its diazine analogs. The total pi energy difference between neutral and monopositive forms of these molecules and their respective electron densities on the several nitrogen atoms are correlated with pK_{NH} values. The electron density differences between the 8-hydroxy oxygen and the nitrogen at position 1 are similarly related to the OH stretching frequency of these compounds. Of the compounds studied, only one, 5-hydroxyquinoxaline, has a significantly greater basicity on the nitrogen which is not adjacent to the OH group.

THE OH stretching frequency, ν_{OH}, and basicity constant, pK_{NH} in 50% dioxan, of 8-hydroxyquinoline (I) and related aza-analogs have been studied.[1] The aza-analogs included: 2-methyl-8-hydroxyquinoline (II); 8-hydroxycinnoline (III); 4-methyl-8-hydroxycinnoline (IV); 8-hydroxyquinazoline (V); 2,4-dimethyl-8-hydroxyquinazoline (VI); 4-methyl-2-phenyl-8-hydroxyquinazoline (VII); 5-hydroxyquinoxaline (VIII); and 8-hydroxy-1,6-naphthridine (IX). A linear relationship was observed between ν_{OH} and pK_{NH} in this series with the exception of V, VIII and IX. Since N-methylation occurs preferentially at the nitrogen farthest from the OH group in the uncorrelated compounds, it was concluded[1] that relative basicities of the two nitrogens in these diaza compounds were responsible for the higher frequency and subsequent deviation from linearity. The pK_{NH} values of the Rossottis probably do not represent the true values, as indicated by recent studies.[2] However, they do represent the only available self consistent set of data and as such form a valid basis for comparison, as indicated by the $\nu_{OH} - pK_{NH}$ relationship.

Since a number of workers found correlations between values from molecular orbital calculations and pK_{NH} in simple heterocycles[3–6] or ν_{OH} in related systems,[7,8] we used a theoretical approach in an attempt to ascertain the properties of these compounds. In particular, we wished to determine the correspondence between calculated nitrogen basicities in the diazines and the position of predominance in alkylation.[1]

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[1] F. J. C. Rossotti and H. S. Rossotti, *J. Chem. Soc.* 1304 (1958).

[2] A. Albert and W. L. F. Armarego, *Adv. in Hetero. Chem.* **4,** 1 (1965); D. D. Perrin, *Ibid.* **4,** 43 (1965); A. Albert, *J. Chem. Soc.* (B), 427 (1966); J. W. Bunting and D. D. Perrin *Ibid.* 433, 436 (1966).

[3] S. F. Mason, *J. Chem. Soc.* 5010 (1957); 674 (1958); *Prog. in Org. Chem.* **6,** 214 (1964).

[4] R. E. Burton and W. J. Davis, *J. Chem. Soc.* 1766 (1964).

[5] J. Clark and D. D. Perrin, *Quart. Rev.* **18,** 295 (1964).

[6] R. Zahradník and J. Koutecký, *Adv. in Hetero. Chem.* **5,** 69 (1965).

[7] R. Grinter, *J. Molecular Spec.* **17,** 240 (1965).

[8] H. Saito and K. Nukada, *Tetrahedron Letters* No. 2, 111 (1965).

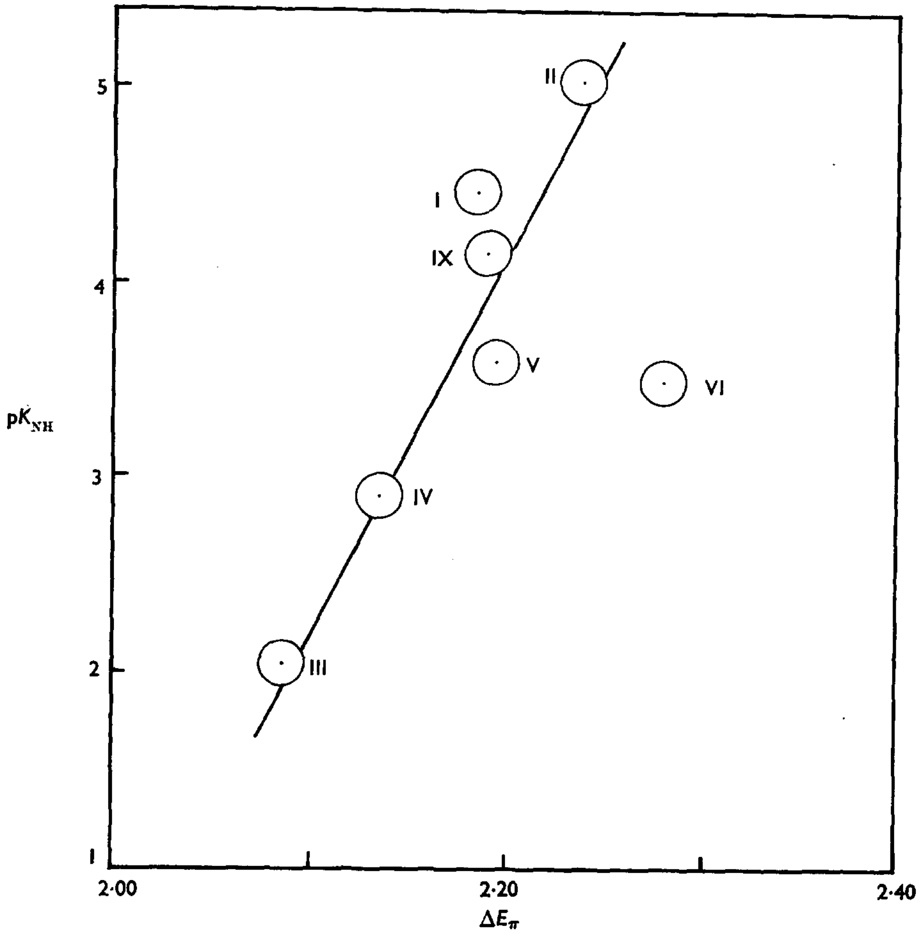

FIG. 1. Correlation of the total pi energy change, ΔE_π, on protonation at N1 with the experimental pK_{NH} (corrected for statistical factor.)

In order to test the Rossottis' hypothesis, LCAO–MO calculations were carried out on compounds I–IX. Although the Hückle MO calculations are not the most exact available quantum mechanical method, this method has been successfully applied to many heterocyclic systems.[6] Since the necessary values were not available for more precise calculations, the Huckel approximations[9] were used to simplify the secular determinant, $|H_{ij} - ES_{ij}| = 0$; and parameters were selected to correct the carbon sp^2 AO coulomb and exchange integrals for heteroatoms:

$$H(X_{p\pi}, X_{p\pi}) = H_{cc} + h_x\beta_{cc}$$
$$H(X_{p\pi}, Y_{p\pi}) = k_{xy}\beta_{cc}$$

Parameter selection was based on established values[3–6,9,10] and systematic variation on the heteroatom novel to this study. The exchange terms, k_{cx}, of 1·0 and 0·8 for

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[9] A. Streitwieser, Jr., *Molecular Orbital Theory* Wiley, New York, N.Y. (1961); B. Pullman and A. Pullman, *Quantum Biochemistry* Interscience, New York, N.Y. (1963).

[10] L. B. Kier, *Tetrahedron Letters* No. 37, 3273 (1965).

the bonds CN and C—O, respectively, were based on the recent evaluations of 8-hydroxyquinoline and its halo-derivatives.[4] The same bond parameter for CN was also recently used[10] in dipole moment calculations on heterocycles. Mason's[3] value of $k_{NN} = 1{\cdot}0$ was employed for the NN bond. The coulomb parameter for O was a literature value[4,6,9], $h_O = 1{\cdot}5$; but a range of values for N, 0·5[4,6,9] and 0·8;[10] and N^+, 1·5[6,9], 1·7[10] and 2·0;[4,9] was tested for compounds I-VI.

Inductive, heteroatom and conjugative models for Me substitutents[9] were applied to compounds II, IV and VI. The heteroatom model with $h_x = 2{\cdot}0$ and $k_{cx} = 0{\cdot}7$ gave the best fit, Fig. 1, for Me, together with h_N and h_{N+} of 0·5 and 2·0, respectively.

Reported[1] p*K*'s for VII and VIII were <1. Thus it was not possible to include these values in basicity correlations. However, a comparison of ΔE_π for VIII is informative. The energy change on protonation at N1 was 2·118, while N2 protonation gave 2·146. Since the greater energy stabilization is generally favored in a thermodynamic process of this type, protonation should occur at N2 which requires an appreciable deviation from the fit of Fig. 1 (cf. VI), or a pK_{NH} of ~3. Simple electron density values on nitrogen lead to much the same interpretation.

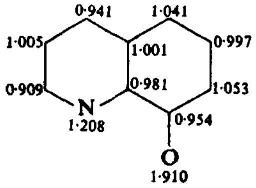
Diagram 1 shows the electron densities calculated for the neutral molecules, $h_N = 0{\cdot}5$. With the exception of VIII and possibly III, the nitrogen atom adjacent to the OH group has the highest electron density. The general effect is a decrease in electron density at N1 when the second nitrogen in the diazines is in the *ortho* or *para* positions (electron withdrawing). This shift is in opposition to the appreciable electron donating effect of Me substituents in these same positions; cf. II–VIII.

Figure 2 shows a plot of pK_{NH} (50% dioxan) vs. electron density at the nitrogen atom adjucant to the OH group ε_{N1}. Although some spread of values is evident, correlation of the electron densities at N1 with the pK_{NH} in 50% dioxan is good except for VI. A significant improvement in this relationship is observed when the pK_{NH} of compounds containing more than one nitrogen is corrected for a statistical factor as has been suggested.[5]

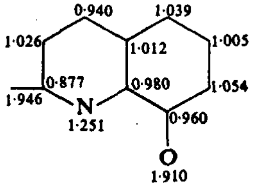
In contrast with the methylation predominance at N2 for V, VIII and IX, both electron densities and total energy changes indicate that N2 is more basic only in VIII. This order of position basicity was maintained over a range of parameters precluding any dependence on the input values selected. Although III showed a change in the order of N2:N1; it is difficult to give any significance to the very small differences in $\varepsilon_N(<0{\cdot}005)$ calculated for this compound. Results of the present work indicate that N1 is the more basic location in V and IX. Thus electron density is evidently not the sole factor in determining the position[1] of V or IX methylation.

In parallel with the aqueous dioxan results on pK_{NH}, the OH stretching frequency in carbon tetrachloride was observed[1] to be base strength dependent and concentration independent. Thus an intramolecular rather than intermolecular hydrogen bonding model should be necessary to relate the ν_{OH} and the relative nitrogen and oxygen affinity for the bridge proton. The electron density difference, $\varepsilon_O - \varepsilon_{N1}$, for the un-ionized compound gives the strength of this interaction if it is assumed that the sigma bond energy between oxygen and hydrogen remains constant. A comparison of ν_{OH} and the $\Delta\varepsilon_{O-N}$ in Fig. 3 shows that the compounds split into two distinct groups. One group contains the monoazines and the *ortho* diazines while the second contains all non-*ortho* diazines. No obvious source of this separation is apparent in molecular structure or parameters for calculation. However, similar separations

Diagram 1. π-Electron densities on the neutral molecules.



I



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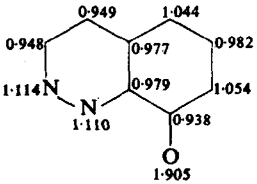

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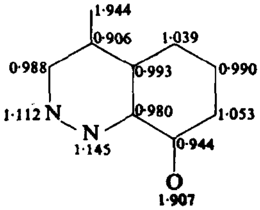

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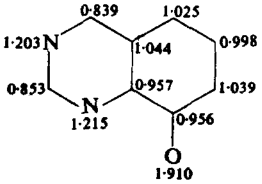

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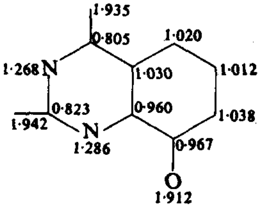
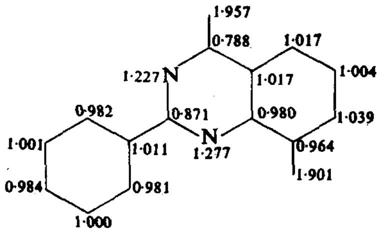
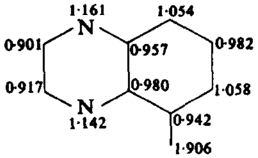


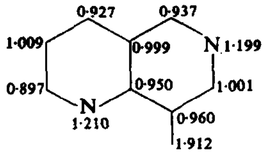
VI



VII



VIII



IX

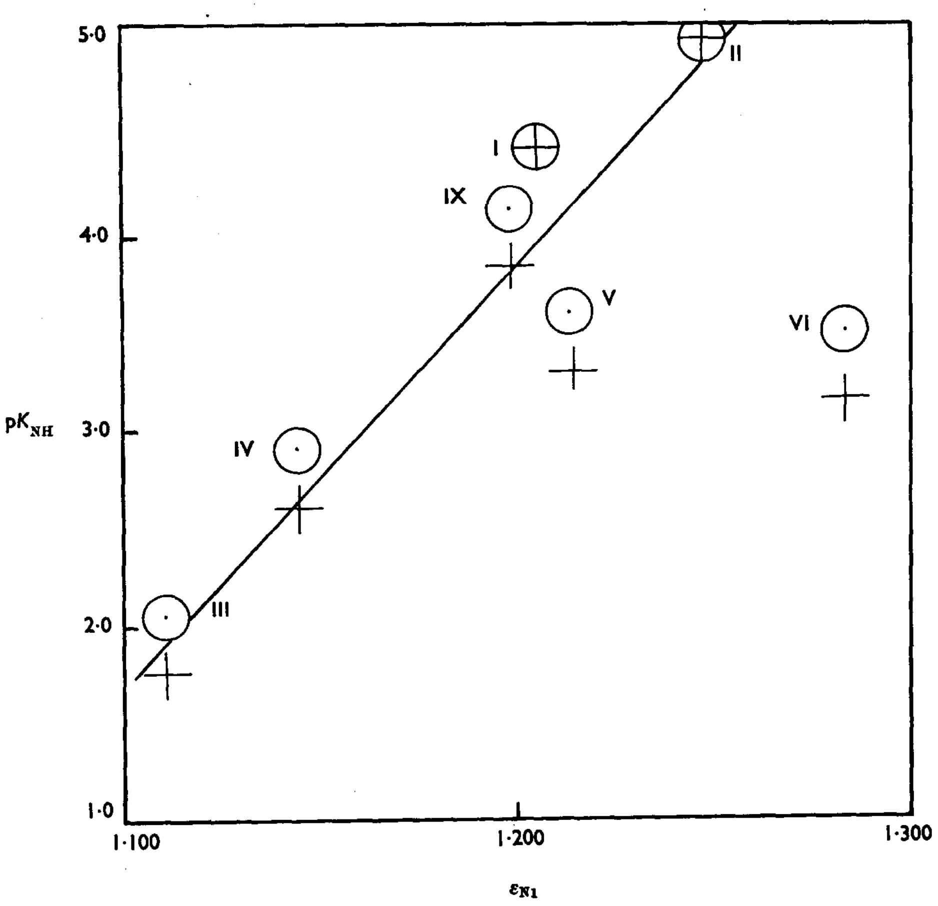


Fig. 2. Correlation of electron density on nitrogen at position 1, ε_{N1}, with the pK_{NH} as measured (+) and as corrected by a statistical factor depending on the number of protonatible nitrogen atoms present (O).

into more than one class have been observed with calculations on hydroxyl ketones even when a term for the hydrogen bond was explicitly included in calculations.[7] The variation of ε_O is quite small and the calculations based on O^- gave similar results. Justification for the inclusion of ε_N then would appear to be empirical or intuitive. However, recently evidence was presented for a 7% ionic contribution from hydrogen bonding in the pyridine-methanol system.[8] Therefore, some contribution from ε_N should be included. In the 8-hydroxyquinoline analogs, hydrogen bonding should be of even greater importance than in the pyridine system because of the molecular stereochemistry. Thus, the dependence of ν_{OH} on the variation of ε_N plays a dominant role[11] even if a constant factor q (where $q < 1$) is applied to the value in Fig. 3, i.e., $\varepsilon_O - q\varepsilon_N$. The electron densities for ε_{N+} directly parallel ε_N, therefore it is not necessary to consider this state unless absolute values are required.

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[11] We are indebted to a referee for calling our attention to this interpretation.

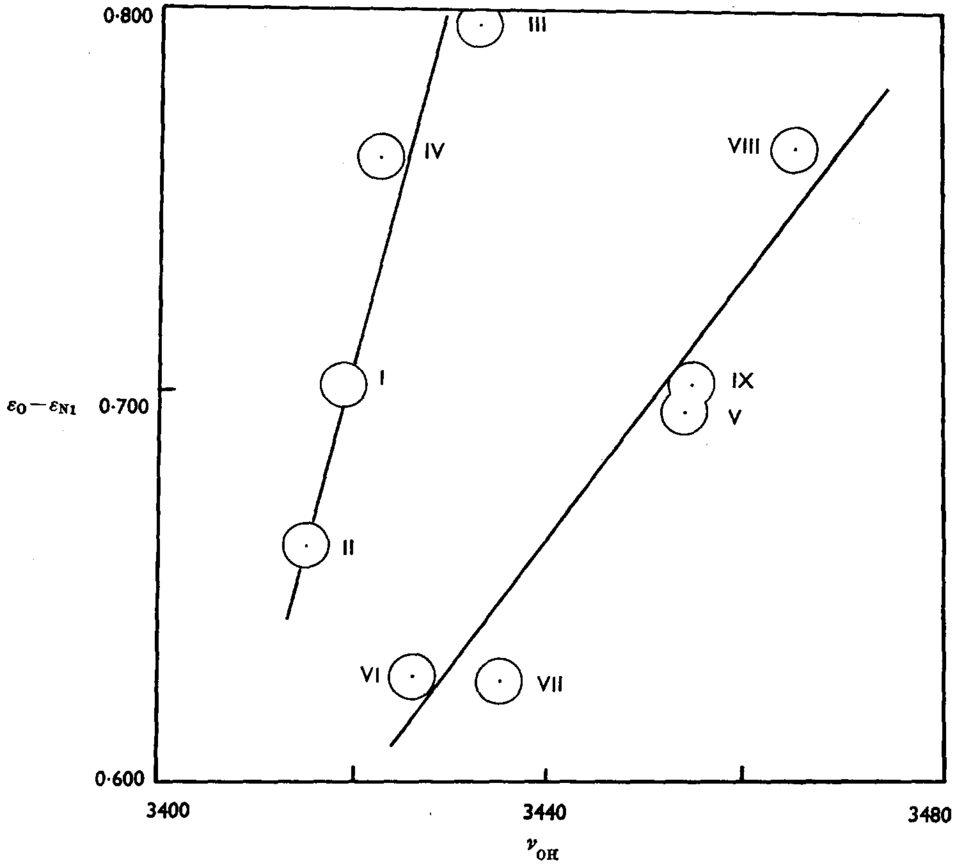

FIG. 3. Relationship of OH stretching frequency, ν_{OH}, in CCl_4 with the electron density difference between adjacent oxygen and nitrogen, $\varepsilon_O - \varepsilon_{N1}$.

CONCLUSIONS

Although there is perhaps some need to reinvestigate the experimental pK_{NH}'s,[2] these values[1] in general give a significant correlation both with the calculated electron densities and the total molecular energy change on protonation for compounds I–IX. More than one group of compounds is evident in the correlations. This multiplicity is less than satisfying and may be due to the approximations inherent in the calculations. However, the existence of two distinct groups, one which contains the monoazines and *ortho* diazines, might have been anticipated from the results of more extensive studies on heterocyclic systems.[6] The relative basicity of the two nitrogen atoms in the diazines is clarified and position 1 is shown to be more basic in all compounds except VIII and possibly III.

EXPERIMENTAL

The Hückel MO calculations were made using a FORTRAN II program written by one of us, Arl. In this program, we have corrected and modified the SHARE library subroutine EIGEN for the calculation of eigenvalues and eigenvectors. This subroutine, along with subroutines for matrix generation, polarizability calculations and matrix operations, is used to obtain energy level values, total molecular energy, electron densities and bond orders. On the 40K IBM 1620 computer with 3 disk drives at Marshall University Computer Center, a version of this program for 20 × 20 matrices occupies, with a 7·5K monitor, the entire core memory. Using disk drives and linkage programs, the major size limitations are the monitor, two N × N matrices and 10·4K for EIGEN. We have successfully used a linked program on the 40K IBM 1620 in a 30 × 30 form with the addition of omega technique calculations[9] and superdelocalizabilities.[5]

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