

The Correlation of NMR Chemical Shifts with EHT Calculated Electron Densities for 3-Pyridinols

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Received July 20, 1970

The NMR spectra of a series of five 3-pyridinols in dioxane and dimethyl sulfoxide have been correlated with electron densities calculated by the Extended Hückel MO method. The data were found to fit a straight line of the form $y = ax + b$. The effects of hydrogen-bonding between pyridinol molecules on the correlation have been considered, and they have been estimated quantitatively for 6-methyl-3-pyridinol *via* Extended Hückel Calculations on a hydrogen-bonded model.

Die Kernresonanzspektren von fünf 3-Pyridinolen in Dioxan und Dimethylsulfoxyd wurden mit den Elektronendichten aus dem erweiterten Hückelverfahren korreliert, und zwar ergibt sich eine lineare Beziehung. Der Einfluß von intermolekularen Wasserstoffbrücken ist für einen Fall (die 6-Methyl-Verbindung) durch EHT-Rechnungen festgestellt und in den übrigen Fällen geschätzt worden.

Les spectres NMR d'une série de cinq 3-pyridinols dans le dioxane et le diméthyle-sulfoxyde ont été corrélés avec les densités électroniques calculées par la méthode de Hückel Étendue. Les données se placent correctement sur une droite $y = ax + b$. Les effets de la liaison hydrogène entre les molécules de pyridinol ont été envisagés et estimés quantitativement pour le 6-méthyl-3-pyridinol par des calculs EHT sur un modèle à liaison hydrogène.

In the design of biologically active compounds, it has become extremely important to learn as much about the chemical and physical properties of the structures under study as possible. Such information is valuable in postulating mechanisms to explain biological activity and in designing an efficient synthesis program. One tool which has recently proven quite valuable in obtaining useful information about organic molecules is the Extended Hückel Molecular Orbital Theory (EHT).

EHT calculations have become very useful in determining electronic and conformational properties of many organic molecules. The intensive studies by the Pullmans [1] in the field of nucleic acids is a classical demonstration of the power of the quantum mechanical approach in interpreting the chemical and physical properties of very complex organic systems and relating them to biological properties. L. B. Kier [2] has been quite successful in using molecular orbital theory to predict the stable conformations of many biologically active structures. Our own previous efforts in this area have been in the areas of organophosphates [3], folic acid analogues [4], and imidazolines [5].

The pyridine nucleus has become an integral part of many new biologically active structures ranging from insecticides and antimicrobial agents to compounds which are useful as drugs. Because of our continuing interest in pyridine

chemistry, we found it desirable to characterize pyridine and its derivatives as completely as possible. This paper will describe the results of our molecular orbital calculations on 3-pyridinol, and its methyl substituted derivatives, and how they relate to experimentally observed properties.

Details of the Calculations

In EHT [6] the basis set for the linear combination of atomic orbitals (LCAO), $\psi_i = \sum c_{ir} \phi_r$, is enlarged to include all available valence shell atomic orbitals. Thus in the case of the 3-pyridinols, the 1s Slater orbital for hydrogen and the 2s and three 2p Slater orbitals for carbon, nitrogen, and oxygen are included. Minimization of the total energy gives the secular determinant

$$\det(H_{ij} - ES_{ij}) = 0 \quad (1)$$

in which i and j have the values 1 to n , with n being the total number of atomic orbitals being combined. The overlap integrals S_{ij} are retained and calculated from standard sources [7]. The exchange integrals H_{ij} are computed according to the approximation

$$H_{ij} = 0.5 K (H_{ii} + H_{jj}) S_{ij} \quad (2)$$

in which $K = 1.75$. The Coulomb integrals are taken as the valence-state ionization potentials. The σ - and π -electron densities and overlap populations are obtained *via* a Mulliken population analysis [8]. The computer input consists of the Cartesian co-ordinates, which are calculated *via* a published computer program¹, and valence-state ionization potentials for each atom in the system.

The geometry of the pyridine nucleus was approximated as an ideal hexagon with all bond lengths taken as 1.40 Å. The carbon-hydrogen bond lengths were all taken as 1.09 Å, and the normal oxygen-hydrogen bond length was taken as 0.96 Å. The oxygen-hydrogen bond angle was taken as 109.47°. The "ring-carbon"-oxygen bond length was taken as 1.46 Å. The methyl groups were regarded as tetrahedral with the "methyl-carbon"--"ring-carbon" bond distance taken as 1.53 Å. The following values of the valence-state ionization potentials were used: H(1s) = -13.6 eV, C(2s) = -21.43 eV, C(2p) = -11.42 eV, N(2s) = -27.50 eV, N(2p) = -14.49 eV, O(2s) = -35.30 eV, and O(2p) = -17.76 eV [9]. The Slater orbital exponents were calculated to be H, 1.30; C, 1.625; N, 1.950; and O, 2.275.

The calculations on pyridinol hydrogen bonding were carried out on 6-methyl-3-pyridinol (III), employing the model configuration shown in Fig. 1. The O...H...N distance was fixed at 2.80 Å², and the position of the hydrogen

¹ Program obtained from P. M. Kuznesof of Northwestern University and modified by M. A. Newman and D. R. Petersen of the Chemical Physics Research Laboratory to work on the B 5500 Computer.

² This is the average O...H...N hydrogen bond distance: Pimentel, G. C., McClellan, A. L.: The hydrogen bond, p. 289. San Francisco: W. H. Freeman and Co. 1960.

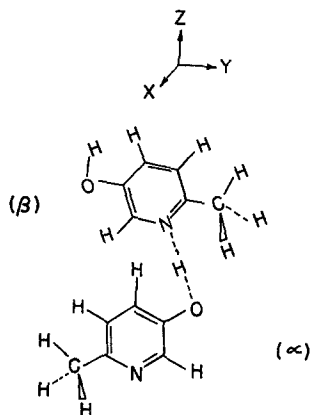


Fig. 1

Fig. 1. Configuration chosen for the 6-methyl-3-pyridinol hydrogen bonding system

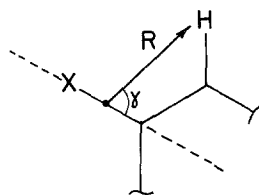


Fig. 2

Fig. 2. The relationship between γ and R in Eq. (3)

was varied from 0.2 Å away from the oxygen atom to 0.2 Å away from the nitrogen atom³.

The magnetic anisotropy calculations were carried out as described by Bothner-By and Pople [10]. The magnetic anisotropy contribution (δ_{ma}) to the observed chemical shifts from an adjacent axially symmetric electron grouping (g) was calculated from Eq. (3) in which

$$\delta_{ma}(\text{ppm}) = (1 - 3 \cos^2 \gamma) \Delta \chi_g / 3 N R^3. \quad (3)$$

N is Avogadro's number, γ is the angle between the symmetry axis of the electron group and the radius vector R between the group and the shielded nucleus (Fig. 2), and $\Delta \chi_g$ is the difference between the susceptibility along the principle axis ($\chi_{||}$) and the value perpendicular to it (χ_{\perp}).

Results and Discussion

A study of the series of 3-pyridinols reported here had been made previously employing the simple Hückel approach to calculate the charge distributions [11]. In this study, the authors attempted to correlate the NMR chemical shifts (δ) in dioxane and dimethyl sulfoxide, of the ring protons of the various neutral pyridinols with the calculated charges, and they stated that "there is only a very rough direct correlation between the δ and the calculated charges." We have verified this statement by linear regression analyses of their data, in both dioxane and dimethyl sulfoxide, which give straight lines of the form $y = ax + b$ for both solvents with coefficients of correlation of 0.65 and 0.72, and coefficients of determination of 0.42 and 0.52, respectively. This poor correlation led us to re-examine this problem using EHT.

³ An identical set of calculations has been carried out for the pyridine-water system. Adam, W., Grimison, A., Hoffmann, R., de Oritz, C. Z.: J. Amer. chem. Soc. **90**, 1509 (1968).

Table 1. *Electron densities calculated by EHT for methyl substituted 3-pyridinols*

Compound ^a	N	C ₂	C ₃	C ₄	C ₅	C ₆	O
I	6.1496	3.6349	3.3877	3.9779	4.1139	3.6126	7.1729
II	6.1840	3.4406	3.4327	3.9919	4.1420	3.6290	7.1704
III	6.1830	3.6518	3.4161	3.9818	4.1624	3.4244	7.1740
IV	6.2123	3.4540	3.4670	3.9931	4.1967	3.4373	7.1718
V	6.2268	3.4664	3.5151	3.7991	4.2429	3.4435	7.1848

^a See Table 2 for compound identification.

The total electron densities calculated by EHT for neutral 3-pyridinol and the methyl substituted 3-pyridinols are listed in Table 1. It is interesting to compare the results of Table 1 with those obtained earlier by the simple Hückel approach. The simple Hückel approach predicts that C₅ in 3-pyridinol will have a slight positive charge, and that C₅ in the methyl substituted 3-pyridinols will have a slight negative charge. In contrast, our EHT calculations predict that C₅ in 3-pyridinol as well as C₅ in the methyl substituted 3-pyridinols will have a partial negative charge.

The chemical shift (δ) data from the paper of Lezina, Bystrov, Smirnov, and Dyumaev [11] are listed in Table 2 and Table 3⁴. Plotting the data from Table 2 (dioxane solvent) and Table 3 (dimethyl sulfoxide solvent) *versus* the data in Table 1 and carrying out linear regression analyses gives equations of the form $y = ax + b$ (Eqs. (4) and (5)).

$$\delta_{\text{dioxane}} = -2.13q + 12.07, \quad (4)$$

$$\delta_{\text{DMSO}} = -2.00q + 11.67. \quad (5)$$

Eqs. (4) and (5) are presented graphically in Fig. 3 and Fig. 4, respectively. The correlation of the EHT electron densities with the NMR data in dimethyl sulfoxide ($r = 0.96$, $r^2 = 0.92$) is slightly better than that obtained with the NMR data in dioxane ($r = 0.94$, $r^2 = 0.88$). The correlation suffers from one major deficiency,

⁴ We rechecked the NMR data on compound III on a Varian HA-100 instrument. The following

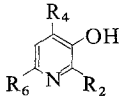
Proton	DMSO- d_6 ^a	Dioxane ^a	DMSO- d_6 + CF ₃ CO ₂ H
2	7.96	7.99	8.25
4	7.01	6.95	7.86
5	7.01	6.95	7.67

^a Chemical shifts in δ units downfield from tetramethylsilane as an internal standard.

Reliable values of the proton spin-spin coupling constants could not be obtained in DMSO- d_6 because of the degenerate chemical shifts. When trifluoroacetic acid was added to the DMSO- d_6 solution, however, the chemical shifts became non-degenerate and the following approximate coupling constants were obtained: $J_{2,4} = 3.7$ Hz, $J_{4,5} = 8.8$ Hz, and $J_{2,5} \leq 0.2$ Hz. Since these results are in good agreement with those obtained by Lezina *et al.* [11], we are reasonably confident in their data.

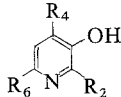
We wish to thank Dr. Thomas E. Evans of the Chemical Physics Research Laboratory for obtaining and interpreting these data.

Table 2. NMR chemical shifts of 3-pyridinol^a

Compound				C ₍₂₎ H	C ₍₄₎ H	C ₍₅₎ H	C ₍₆₎ H
	R ₂	R ₄	R ₆				
I	H	H	H	4.53	3.52	3.52	4.41
II	CH ₃	H	H	—	3.34	3.30	4.30
III	H	H	CH ₃	4.39	3.37	3.37	—
IV	CH ₃	H	CH ₃	—	3.19	3.19	—
V	CH ₃	CH ₃	CH ₃	—	—	3.14	—

^a The data are given in δ units downfield from dioxane (solvent). The values relative to tetramethylsilane are given by $\delta_{\text{TMS}} = 3.56 + \delta_{\text{s}}$. These data are from Lezina, V. P., Bystrov, V. F., Smirnov, L. D., Dyumaev, K. M.: *Teoreticheskaya i Experimental'naya Khimiya* 1, 281 (1965).

Table 3. NMR chemical shifts of 3-pyridinol^a

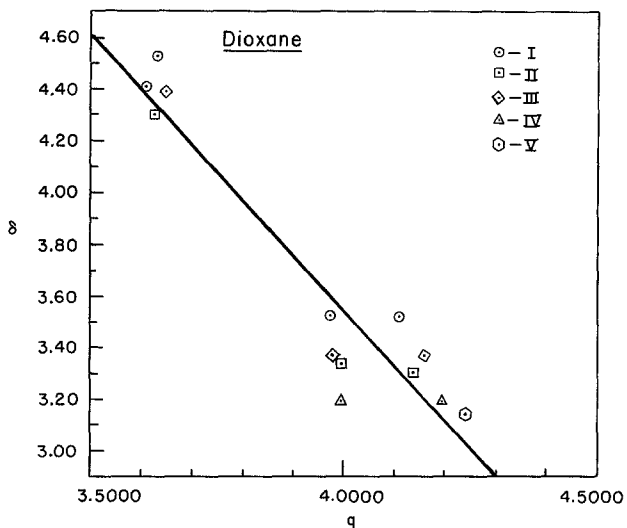
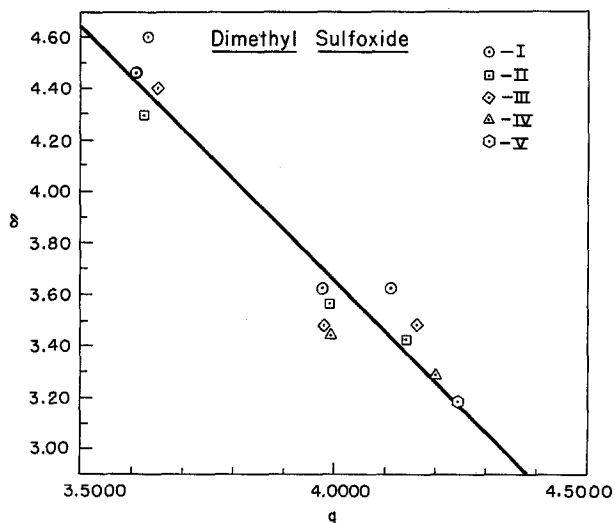
Compound				C ₍₂₎ H	C ₍₄₎ H	C ₍₅₎ H	C ₍₆₎ H
	R ₂	R ₄	R ₆				
I	H	H	H	4.60	3.62	3.62	4.46
II	CH ₃	H	H	—	3.56	3.42	4.30
III	H	H	CH ₃	4.40	3.48	3.48	—
IV	CH ₃	H	CH ₃	—	3.45	3.28	—
V	CH ₃	CH ₃	CH ₃	—	—	3.18	—

^a The data are given in δ units downfield from dioxane (internal standard) in dimethyl sulfoxide as solvent. These data are from Lezina, V. P., Bystrov, V. F., Smirnov, L. D., Dyumaev, K. M.: *Teoreticheskaya i Experimental'naya Khimiya* 1, 281 (1965).

however, in that from the EHT electron densities one is forced to predict that the hydrogens at C₄ and C₅ should have considerably different chemical shifts when, experimentally, the compounds studied, except II and IV in dimethyl sulfoxide, all had hydrogens at C₄ and C₅ with identical, or nearly identical, chemical shifts. Chemical shifts are known to be affected by the dipole moments and diamagnetic anisotropies of adjacent C–N, C–O, and C–CH₃ bonds, and by hydrogen bonding. Since we felt that the previous factors (*vide supra*) were primarily responsible for the deficiency observed in predicting the shifts of the C₄ and C₅ hydrogens, we decided to quantitatively assess the magnitude of their effect.

The observed chemical shift (δ_{obs}) of a proton is made up of an electronic term (δ_{elect}) and a magnetic anisotropy term (δ_{ma}). In an attempt to improve our correlation, we

$$\delta_{\text{obs}} = \delta_{\text{elect}} + \delta_{\text{ma}}$$

Fig. 3. Plot of δ (dioxane) versus EHT electron densitiesFig. 4. Plot of δ (dimethyl sulfoxide) versus EHT electron densities

calculated values of δ_{ma} using Eq. (3) and subtracted these from the values of δ_{obs} listed in Tables 2 and 3 to give corrected values (δ_{elect}). Linear regression analyses on the corrected data give straight line equations of $\delta_{\text{dioxane}} = -2.27q + 12.53$ ($r = -0.94$, $r^2 = 0.89$) and $\delta_{\text{DMSO}} = -2.14q + 12.13$ ($r = -0.96$, $r^2 = 0.92$). If these results are compared to those described by Eqs. (4) and (5), it is easily seen that there is no real improvement in the correlation. This is not surprising, since there is considerable controversy over the values of $\Delta\chi_g$ for C-H, C-C, and C-O bonds [12], thus making the calculated values of δ_{ma} highly unreliable.

It became necessary to carry out EHT calculations on a hydrogen bonded model for at least one of the compounds under consideration, since there is good evidence that the 3-pyridinols are strongly intermolecularly hydrogen bonded. It has been shown that the introduction of hydroxyl groups in the pyridine ring decreases the water solubility. Of the mono-hydroxy pyridines, the effect is most pronounced in the case of 3-hydroxypyridine, which is 30 times less soluble in water than either the corresponding 2- or 4-isomer. This "insolubilizing effect" of the hydroxyl group has been attributed to intermolecular hydrogen bonding, from oxygen atoms to the ring nitrogen atoms, in preference to bonding to water. The crystal lattices formed in this way are believed to be very strong due to strengthening of the hydrogen bond by a large dipole. In fact, these molecules have been shown by cryoscopy and osmometry to be associated in aqueous solution [13].

Strong intermolecular hydrogen bonding has also been observed in 3-pyridinols by NMR [14]. In the NMR spectrum of V in carbon tetrachloride the OH resonance was found to occur at 11.42δ (downfield from TMS), whereas in the spectra of 2,6-dialkylphenols the OH resonance was found to occur at approximately 4.4δ [15]. Since in both cases the immediate environment of the hydroxyl group comprises two methyl groups which offer steric hindrance to the formation of OH...O hydrogen bonds, it was concluded that the downfield shift of the OH signal in the pyridinol was due to intermolecular hydrogen bonding of the type leading to partial ionization.



This hypothesis was further substantiated by demonstrating that the association of 2,6-dimethylphenol with triethylamine causes a downfield shift of the OH resonance.

The EHT calculations of hydrogen bonding were carried out on III (as described previously) using the model shown in Fig. 1. The results are shown in Fig. 5, where the total energy of the system is plotted *versus* the hydrogen-

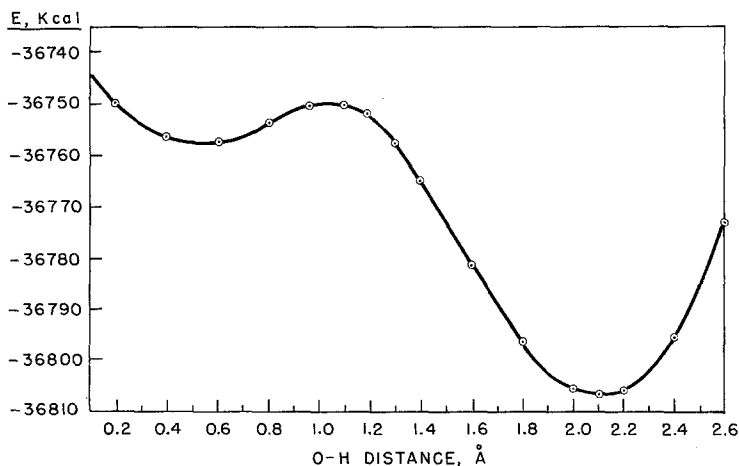


Fig. 5. Plot of total energy versus O-H distance for the hydrogen bonded model of III

oxygen distance. The motion of the proton in the hydrogen bond is described energetically by a double potential minimum in which the proton may assume two stable positions, one near the oxygen atom and one near the nitrogen atom. The calculated energy barrier for proton transfer from oxygen toward nitrogen is approximately 16 Kcal./mole. In contrast, the N-H energy minimum is approximately 50 Kcal. lower in energy than the O-H minimum; i.e., the calculated energy barrier for proton transfer from nitrogen to oxygen is approximately 65 Kcal./mole indicating that, at least for this model, the proton greatly prefers to be close to the nitrogen. The hydrogen bond predicted by these calculations is of the form $O^- \dots H-\overset{+}{N}$ (similar to the hydrogen bond which is believed to be responsible for the solubility effects noted earlier, *vide supra*).

In his classic study of the pyridine-water hydrogen bond, Hoffman⁵ obtained an energy profile and a hydrogen bond picture nearly identical to that which we have found for III, and he concluded that the dipolar form of the hydrogen bond was an artifact of the EHT and therefore not a good description of the system. Although this conclusion is quite valid for the pyridine-water system, we do not feel that this criticism is necessarily valid in the pyridinol case, since there appears to be good evidence (*vide supra*) that the hydrogen bonds in this system are highly polar and of the form $O^- \dots H-\overset{+}{N}$ ⁶. The calculations do, however, suffer from a deficiency which Hoffman also noted, namely, that the energy minima (see Fig. 5) occur too close to the oxygen (0.6 Å) and the nitrogen (0.7 Å) atoms. One would predict that these minima should occur near the "normal" O-H and N-H bond distances of 0.96 Å and 1.00 Å, respectively [16].

In Figs. 6 and 7 are shown the net charges of the oxygen, nitrogen and hydrogen atoms of the hydrogen bond as a function of the oxygen-hydrogen

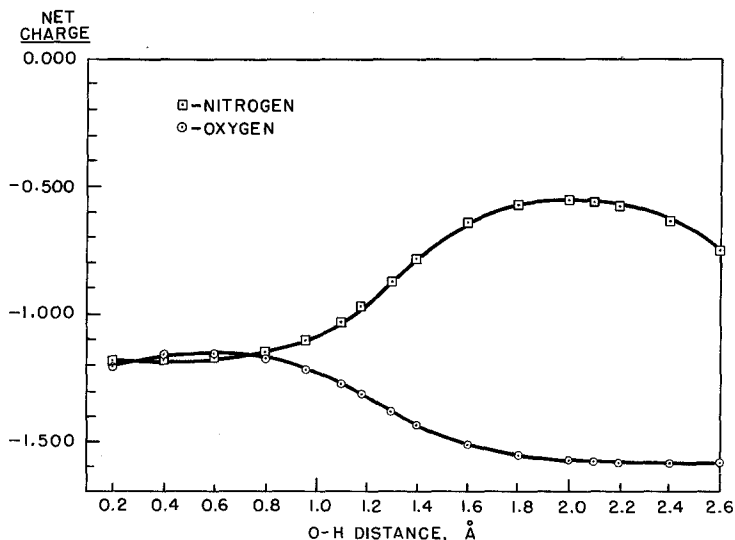


Fig. 6. Net charge on the nitrogen and oxygen atoms versus O-H distance

⁵ See the reference in footnote 3.

⁶ EHT calculated charges are exaggerated. Hence, although the pyridinol hydrogen bond is well represented as being highly polar, the magnitude of the charge separation in the calculated hydrogen bond picture is 15 exaggerated.

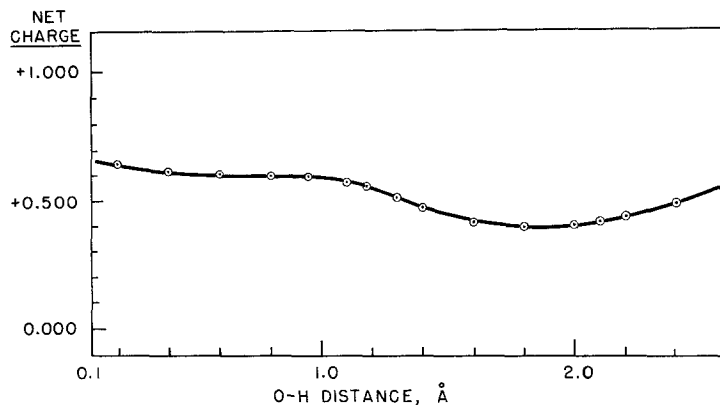


Fig. 7. Net charge on the hydrogen atom of the hydrogen bond versus O-H distance

distance. As the proton approaches the nitrogen, a negative charge begins to form on the oxygen, while a decrease in the negative charge on nitrogen occurs. The positive charge on the hydrogen does not vary a great deal during the transfer, but it does, interestingly, reach a minimum between 1.80 and 1.90 Å.

Although the calculations on the hydrogen bonded model of III suffer from at least one serious deficiency, examination of the calculated electron densities of the carbon, nitrogen and oxygen atoms of the two pyridinol molecules (α and β) involved in the hydrogen bonding still gave some good indications of the effects of hydrogen bonding on the electron densities in the α - and β -rings. The electron density at C_4 of the α -ring was increased such that the net charge went from positive to negative. This is most likely the result of a portion of the negative charge which is being formed on the oxygen being distributed to C_4 via resonance. In addition, the electron density at C_5 of the α -ring decreased slightly. The net result of these two changes is that C_4 and C_5 become similar electronically, leading one to predict that the hydrogens attached to these two carbons should have similar chemical shifts. Thus, we have been led to conclude that the changes in the electron density of the pyridine ring in 3-pyridinols brought on by hydrogen bonding are largely responsible for the observation that the chemical shifts of the hydrogens at C_4 and C_5 are identical. Furthermore, we have concluded that realistic values of the electron densities in systems such as the 3-pyridinols cannot be obtained without considering hydrogen bonded models.

Acknowledgement. We wish to thank Drs. Jerry P. Heeschen, Thomas E. Evans and Robert T. Iwamasa of the Chemical Physics Research Laboratory for many helpful discussions and suggestions during the course of this work.

References

1. Pullman, B., Pullman, A.: Quantum Biochemistry. New York: Wiley, Inc. 1963.
2. Kier, L. B.: Tetrahedron Letters **1967**, 1233.
 - Molecular Pharmacol. **3**, 487 (1967).
 - Molecular Pharmacol. **4**, 70 (1968).
 - J. med. Chem. **12**, 16 (1969).

3. Neely, W. B., Unger, I., Blair, E. H., Nyquist, R. A.: *Biochemistry* **3**, 1477 (1964).
— *Molecular Pharmacol.* **1**, 137 (1965).
4. — *Molecular Pharmacol.* **3**, 108 (1967).
5. — White, H. C., Rudzik, A.: *J. pharmac. Sci.* **57**, 1176 (1968).
6. Hoffmann, R.: *J. chem. Physics* **39**, 1397 (1963).
7. Mulliken, R. S., Rieke, C. A., Orloff, D., Orloff, H.: *J. chem. Physics* **17**, 1248 (1949).
8. — *J. chem. Physics* **23**, 1833 (1955).
— *J. chem. Physics* **23**, 2338 (1955).
— *J. chem. Physics* **23**, 2343 (1955).
9. Skinner, H. A., Pritchard, H. O.: *Trans. Faraday Soc.* **49**, 1254 (1953).
— — *Chem. Reviews* **55**, 745 (1955).
10. Bothner-By, A. A., Pople, J. A.: *Annu. Rev. physic. Chem.* **16**, 43 (1965). See also: McConnell, H.: *J. chem. Physics* **27**, 226 (1957).
11. Lezina, V. P., Bystrov, V. F., Smirnov, L. D., Dyumaev, K. M.: *Theoretical and experimental chemistry* **1**, 180 (1965) (English Translation).
12. Bothner-By, A. A., Pople, J. A.: *Annu. Rev. physic. Chem.* **16**, 43 (1965).
See also: Bothner-By, A. A., Naar-Colin, C.: *Ann. N. Y. acad. Sci.* **70**, 833 (1958).
Musher, J. I.: *J. chem. Physics* **35**, 1159 (1961).
Maritz, A. G., Sheppard, N.: *Molecular Physics* **5**, 361 (1962).
Hall, L. D.: *Tetrahedron Letters* **1964**, 1457.
Musher, J. I.: *Molecular Physics* **6**, 93 (1963).
Narasimhan, P. T., Rogers, M. T.: *J. chem. Physics* **31**, 1302 (1959).
Zürcher, R. F.: *Helv. chim. Acta* **44**, 1755 (1961).
Schaefer, T., Yonemoto, T.: *Canad. J. Chem.* **42**, 2318 (1964).
13. Albert, A.: *Heterocyclic chemistry*, 2nd Ed., pp. 72–73. London: The Athlone Press, University of London 1968.
14. Smirnov, L. D., Lezina, V. P., Bystrov, V. F., Dyumaev, K. M.: *Izv. Akad. Nauk. SSSR, S. K.* 1836 (1965).
15. Bystrov, V. F., Dyumaev, K. M., Lezina, V. P., Nikiforov, G. A.: *Dokl. Akad. Nauk. SSSR* **148**, 1077 (1963).
16. Wheland, G. W.: *Resonance in organic chemistry*. New York: Wiley 1955.

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