

## EFFECTS OF PROTONATION ON ELECTRON DENSITIES IN NITROGEN HETEROCYCLIC MOLECULES\*

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**Abstract**—The Extended Hückel Theory (EHT) has been applied to a series of nitrogen heterocyclic molecules, and their anions and mono- and di-protonated derivatives. In particular, pyrrole and the pyrrole anion, imidazole anion, neutral molecule and cation, pyridine and its protonated cation, and the diazines and their protonated and diprotonated cations are discussed in this paper. A considerable polarization of the sigma-bond framework is observed in all cases. The total electron densities are not changed appreciably by use of a hydrogen Slater exponent of 1.3, rather than 1.0, or by the use of real, rather than ideal, geometries. The general effect of protonation of a nitrogen atom is calculated to be an increase in the total electron density at the adjacent carbon atom(s), but a slight decrease in electron density at the ortho hydrogen atoms. These results are shown to be in accord with experimental data, since good correlations are obtained between the total carbon electron densities and (a) proton chemical shifts and (b) carbon-13 chemical shifts.

A PRINCIPAL difficulty in obtaining a reliable description of the electron density distribution in heterocyclic molecules has been the fact that the great majority of such calculations have been made in the  $\pi$ -electron approximation.<sup>1</sup> While such an approach has yielded excellent results in homocyclic systems, there has been an increasing preoccupation with the neglect of  $\sigma$ -bond polarization in heterocyclic systems.<sup>2</sup> Attempts can be made to take some account of  $\sigma$ -bond polarization by the use of variable parameters in the  $\pi$ -electron approach,<sup>3</sup> but it is still doubtful to what extent the results represent the actual overall electronic distribution, rather than that of the  $\pi$ -framework under the effect of the  $\sigma$ -bond perturbation. The problem becomes compounded when we ask what may be the changes in the electronic distribution when a proton is added to the heteroatom or heteroatoms in the ring system. The reason for this difficulty is that, considering pyridine as an example, the proton is added to what was formally a pure lone pair of electrons on an  $sp^2$  hybridized nitrogen atom, thus forming a nitrogen-hydrogen single bond. This is purely a  $\sigma$ -effect, and there have been no direct changes in the  $\pi$ -framework of the molecule. The only way that an account can be made of this change, in the  $\pi$ -approximation, is to use different parameters for the protonated nitrogen atom, introducing a further problem in parameter choice.

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<sup>1</sup> A. Streitwieser *Molecular Orbital Theory for Organic Chemists* Chap. 5. Wiley, N.Y. (1961).

<sup>2</sup> P. Lykos *Advances in Quantum Chemistry* Vol. 1; p. 181. Academic Press, N.Y. (1964).

<sup>3</sup> R. D. Brown and M. L. Heffernan, *Austr. J. Chem.* **13**, 49 (1960); <sup>4</sup> M. K. Orloff and D. D. Fitts, *J. Am. Chem. Soc.* **85**, 3721 (1963).

An alternative approach has been that if we keep the one-electron Hamiltonian, and use some appropriate approximation for the off-diagonal Hamiltonian elements  $H_{ij}$ , modern computing techniques render it perfectly reasonable to consider *all* valence electrons in reasonably-sized organic molecules and retain all overlap integrals. One such method is the Extended Hückel Theory developed by Hoffmann.<sup>4</sup> This has been used successfully on some heterocyclic systems,<sup>5</sup> and shown to give a reasonable account of the  $\sigma$ - as well as the  $\pi$ -electron distribution in these systems. The heteroatom effect is introduced only through the use of an appropriate Slater orbital exponent and Valence-State Ionization Potential, and the same values are used for one particular heteroatom in *any* molecule, and in *any* state of ionization or protonation. This method therefore seemed the simplest approach capable of giving a reasonable description of the electron density changes resulting from protonation. This problem is a particularly important one to any chemist interested in the effects of hydrogen bonding solvents on, for example, nitrogen heterocyclics. The effect of hydrogen bonding gives a state resembling a configuration between the neutral molecule and the fully protonated cation, resembling the latter more or less depending on the hydrogen donating ability of the solvent. We have therefore applied the EHT method to the five-membered ring systems pyrrole, imidazole and pyrazole, their anions, and their protonated derivatives, and to pyridine, the diazines, and their protonated derivatives.

#### *Details of the calculation*

In this LCAOMO method, as described previously,<sup>4,5</sup> the basis set for the linear combination of atomic orbitals,  $\psi_1 = \sum_r C_{1r} \phi_r$ , is extended to include all valence shell atomic orbitals. Thus, in the case of pyrrole the 1s Slater orbitals for hydrogen and the 2s and three 2p Slater orbitals for carbon and nitrogen are used. Minimization of the energy, in the Hückel approximation of the total Hamiltonian as a sum of one-electron effective Hamiltonians, gives the secular determinant,

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

where  $i, j$  go from 1 to  $n$ , i.e. through the total number of valence atomic orbitals. All overlap integrals  $S_{ij}$  are retained, and calculated from standard sources.<sup>6</sup> The exchange integrals  $H_{ij}$  are computed using the approximation:

$$H_{ij} = 0.5K(H_{ii} + H_{jj})S_{ij}, \quad \text{where } K = 1.75.$$

The Coulomb integrals  $H_{ii}$  are taken as the appropriate valence state ionization potentials. A Mulliken Population Analysis<sup>7</sup> finally yields the  $\sigma$ - and  $\pi$ -electron densities, and bond overlap populations. A program for carrying out these calculations on the IBM 7094 computer is available.<sup>8\*</sup>

\* A microfilm copy of the complete computer output, including wave functions, is available on request from the authors. Interpretation of this output is aided by a listing of the program, obtainable from the source indicated in Ref. 8.

<sup>4</sup> R. Hoffmann, *J. Chem. Phys.* **40**, 2745 (1964).

<sup>5</sup> W. Adam and A. Grimison, *Tetrahedron* **21**, 3417 (1965); <sup>6</sup> R. Hoffmann, *Ibid.* **22**, 539 (1966);

<sup>7</sup> W. Adam and A. Grimison, *Ibid.* **22**, 835 (1966).

<sup>8</sup> R. S. Mulliken, C. A. Rieke, P. Orloff and H. Orloff, *J. Chem. Phys.* **17**, 1248 (1949).

<sup>9</sup> R. S. Mulliken, *J. Chem. Phys.* **23**, 1833, 2338, 2343 (1955).

\* *Quantum Chemistry Program Exchange QCPE #30*. Chemistry Department, Indiana University.

The valence state ionization potentials were those used previously,<sup>5</sup> H(1s): -13.6 eV, C(2s): -21.4 eV, C(2p): -11.4 eV, N(2s): -26.0 eV, and N(2p): -13.4 eV. The Slater orbital exponents were H: 1.00 or 1.30 (see below), C: 1.625 and N: 1.950.

The calculations on pyridine and the diazines were carried out in three approximations:

- (1) using a hydrogen exponent of 1.0 and ideal geometries
- (2) using a hydrogen exponent of 1.3 and ideal geometries
- (3) using a hydrogen exponent of 1.3 and real geometries.

The calculations on the remaining molecules were made using the first two approximations only. The ideal geometries used were to approximate the five- and six-membered ring systems as regular pentagons and hexagons respectively. All ring bond lengths were taken as 1.40 Å and all carbon and nitrogen to hydrogen bond lengths as 1.10 Å. The real geometries used for pyridine, pyrimidine, pyrazine, and pyridazine were taken from the best available experimental values.<sup>9</sup>

### Results and discussion

The  $\sigma$ - and  $\pi$ -electron densities obtained for pyridine by the use of the three different approximations are shown in Table 1. It is clear that there is no major

TABLE 1. EFFECT OF CHANGING HYDROGEN SLATER ORBITAL EXPONENT AND MOLECULAR GEOMETRY ON THE EHT ELECTRON DENSITIES OF PYRIDINE

Position	Approximation*					
	(1)		(2)		(3)	
	$\pi$	$\sigma + \pi$	$\pi$	$\sigma + \pi$	$\pi$	$\sigma + \pi$
2	0.840	3.69	0.840	3.63	0.848	3.64
3	1.01	4.12	1.01	4.05	1.02	4.07
4	0.870	3.96	0.871	3.89	0.882	3.91

\* For a description of the approximations see Details of the calculation.

difference between the results of these three approximations. The same similarity was found for the diazines, and their ions, so that only values obtained using approximation (2) will be reported here. Tables 2 and 3 give the  $\sigma$ -,  $\pi$ -, and total electron densities for all of the molecules computed. These results indicate an appreciable polarization of the  $\sigma$ -framework in all cases. Further, opposite directions of polarization may be found for the  $\sigma$ - and the  $\pi$ -framework. A similar effect has been observed for formaldehyde,<sup>10</sup> using an all valence electron self-consistent molecular orbital method.<sup>11</sup>

Since the EHT method makes no attempt to correct for electronic repulsions, the degree of polarization indicated is probably overemphasized. However, the reliability of the relative ordering of electron densities can be demonstrated by a comparison with experimental proton chemical shifts. The chemical shift of a proton should be

<sup>5</sup> B. Bak, L. Hansen-Nygaard, and J. Rastrup-Andersen, *J. Mol. Spectr.* **2**, 361 (1958); <sup>6</sup> W. Cochran, *Physical Methods in Heterocyclic Chemistry* (Edited by A. R. Katritzky) Vol. 1; p. 164. Academic Press, N.Y. (1963); <sup>7</sup> H. Kim and H. F. Hamerka, *J. Am. Chem. Soc.* **85**, 1398 (1963); <sup>8</sup> C. A. Coulson, *J. Chem. Soc.* 5893 (1963).

<sup>10</sup> J. A. Pople and G. A. Segal, *J. Chem. Phys.* **43**, S136 (1965).

<sup>11</sup> J. A. Pople, D. P. Santry, and G. A. Segal, *J. Chem. Phys.* **43**, S129 (1965).

TABLE 2. CALCULATED EHT ELECTRON DENSITIES FOR 5-MEMBERED RING HETEROCYCLICS

Molecule	Position	$\sigma$	$\pi$	$\sigma + \pi$
Pyrrole anion	2	2.79	1.08	3.87
	3	3.03	1.13	4.16
Pyrrole	2	2.82	1.08	3.90
	3	3.03	1.13	4.16
Imidazole anion	2	2.57	0.833	3.40
	4	2.80	1.06	3.86
*Imidazole	2	2.60	0.833	3.43
	4	2.81	1.06	3.87
Imidazole cation	2	2.62	0.833	3.45
	4	2.82	1.06	3.88
Pyrazole anion	3	2.80	0.898	3.70
	4	3.05	1.11	4.16
*Pyrazole	3	2.81	0.898	3.71
	4	3.04	1.11	4.15
Pyrazole cation	3	2.83	0.898	3.73
	4	3.04	1.11	4.15

\* Two nitrogen atoms actually equivalent through facile tautomeric proton shift.

TABLE 3. CALCULATED EHT ELECTRON DENSITIES FOR 6-MEMBERED RING HETEROCYCLICS

Molecule	Position	$\sigma$	$\pi$	$\sigma + \pi$
Pyridine	2	2.79	0.840	3.63
	3	3.04	1.01	4.05
	4	3.02	0.871	3.89
Pyridinium cation	2	2.82	0.840	3.66
	3	3.03	1.01	4.04
	4	3.02	0.871	3.89
Pyrazine	2	2.80	0.840	3.66
*Pyrazinium	2	2.81	0.840	3.65
Pyrazinium dication	2	2.82	0.840	3.66
Pyrimidine	2	2.58	0.651	3.23
	4	2.79	0.734	3.52
	5	3.05	1.02	4.07
*Pyrimidinium cation	2	2.60	0.651	3.25
	4	2.80	0.734	3.53
	5	3.04	1.02	4.06
Pyrimidinium dication	2	2.63	0.651	3.28
	4	2.82	0.734	3.53
	5	3.03	1.02	4.06
Pyridazine	3	2.79	0.796	3.58
	4	3.03	0.874	3.90
*Pyridazinium cation	3	2.81	0.786	3.58
	4	3.03	0.874	3.90
Pyridazinium dication	3	2.82	0.786	3.61
	4	3.03	0.874	3.90

\* Two nitrogen atoms actually equivalent through facile tautomeric proton shift.

an approximate measure of the electron density on the atom to which the proton is bonded.<sup>12</sup> Fig. 1 shows the result of plotting EHT total electron densities against literature values of the proton chemical shifts for the various positions in the neutral molecules studied here.<sup>13</sup> To give an indication of the general reliability of the technique, values are included from calculations<sup>14</sup> not specifically discussed here, such as furan, furazan, and 1,3,4-oxadiazole, 1,2,4-triazole, methylslydnone, isoxazole, cyclopentadienyl anion, and benzene. An excellent correlation is obtained, whereas Gawer and Dailey<sup>15</sup> have previously concluded from a study of the proton chemical shifts for the neutral molecules of eleven heteroaromatic compounds that "the proton chemical shifts appear to be a somewhat unreliable measure of  $\pi$ -electron densities, especially in positions adjacent to a nitrogen atom". Reasonable correlations have been obtained,<sup>16</sup> but referred principally to comparisons of different positions in the same molecule.

In Fig. 1 two separate straight lines, with the same slope of  $-2.6$  ppm/electron, are obtained for the 5- and 6-membered ring systems. This shows that the functional relationship between proton chemical shift and electron density is the same for the 5- and 6-membered rings. However, the magnitude of the chemical shift at a given electron density is greater for the 6-membered rings. This displacement is probably due to an increased ring current in the larger ring systems. A naive calculation of the magnitude of this effect using the Pople equation<sup>17</sup> shows the increase to be of the correct order of magnitude when compared to the perimeter distances of the ideal ring systems.

With this indication of the value of the calculated electron densities, we can consider the effect of protonation on the total electron densities of the ring atoms.\* It can be seen that the effect of protonation is to increase the electron density at the carbon atom adjacent to the nitrogen. This trend continues uniformly where a second protonation occurs. The intuitive approach is to consider that "by protonation, electronic charge is withdrawn toward the nitrogen from all positions of the ring",<sup>18</sup> or "essentially the electronegativity of nitrogen has been somewhat increased".<sup>19</sup> Evidence taken for this viewpoint has been the small downfield shift observed in the proton resonance of pyridine on protonation.<sup>20</sup> However, the change of solvent effects from neutral to acidic solution renders this shift rather uncertain.

\* The  $\pi$ -densities in Tables 2 and 3 are necessarily unchanged on protonation, since the EHT assumes  $\sigma$ - $\pi$  orthogonality.

<sup>12</sup> G. K. Fraenkel, R. E. Carter, A. McLachlan, and J. H. Richards, *J. Am. Chem. Soc.* **82**, 5846 (1960).

<sup>13</sup> J. N. Murrell and V. M. S. Gil, *Trans. Farad. Soc.* **61**, 402 (1965); \* A. Veillard, *J. Chim. Phys.* **59**, 1056 (1962); \* K. D. Lawson, W. S. Brey, and L. B. Kier, *J. Am. Chem. Soc.* **86**, 463 (1964);

\* T. Schaeffer and W. G. Schneider, *Canad. J. Chem.* **41**, 966 (1963); \* L. M. Jackman, *Application of Nuclear Magnetic Resonance in Organic Chemistry*. Macmillan, New York (1959). † R. A. Olofson and J. S. Michelman, *J. Org. Chem.* **30**, 1854 (1965); \* K. T. Potts and T. H. Crawford, *J. Org. Chem.* **27**, 2631 (1962); † H. Fener and S. Markorsky, *J. Org. Chem.* **29**, 935 (1964); † C. Ainsworth, *J. Am. Chem. Soc.* **87**, 5800 (1965).

<sup>14</sup> W. Adam and A. Grimison, unpublished data.

<sup>15</sup> A. H. Gawer and B. P. Dailey, *J. Chem. Phys.* **42**, 2658 (1965).

<sup>16</sup> B. M. Lynch, private communication.

<sup>17</sup> J. A. Pople, *J. Chem. Phys.* **24**, 1111 (1956).

<sup>18</sup> S. Castellano, H. Gunther, and S. Ebersole, *J. Phys. Chem.* **69**, 4166 (1965).

<sup>19</sup> R. Daudel, R. LeFebvre, and C. Moser, *Quantum Chemistry* p. 272. Interscience, N.Y. (1959).

<sup>20</sup> A. Mathias and V. M. S. Gil, *Tetrahedron Letters* 3163 (1965).

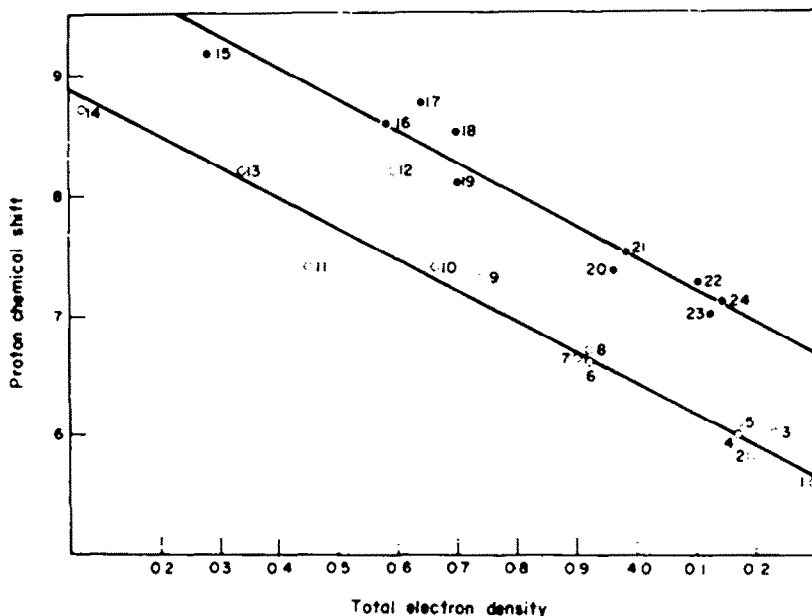


FIG. 1. Proton Chemical Shifts (ppm) of Heterocyclic Molecules versus EHT Total Electron Densities.

Open circles are 5-membered rings, closed circles are 6-membered rings. In the index below, the first number indicates the particular point on the Fig., while the number in parentheses designates a particular position in the ring.

- |   |   |
|---|---|
| 1. Cyclopentadienyl anion. <sup>13a</sup> | 13. 1,2,4-Triazole (3-). <sup>13a</sup>   |
| 2. Isoxazole (4-). <sup>13a</sup>         | 14. 1,3,4-Oxadiazole (2-). <sup>13f</sup> |
| 3. Pyrazole (4-). <sup>13a</sup>          | 15. Pyrimidine (2-). <sup>13a</sup>       |
| 4. Furan (3-). <sup>13a</sup>             | 16. Pyrimidine (4-). <sup>13a</sup>       |
| 5. Pyrrole (3-). <sup>13a</sup>           | 17. Pyridazine (3-). <sup>13a</sup>       |
| 6. Imidazole (4-). <sup>13a</sup>         | 18. Pyridine (2-). <sup>13a</sup>         |
| 7. Pyrrole (2-). <sup>13a</sup>           | 19. Pyrazine (2-). <sup>13a</sup>         |
| 8. Methylsydnone (4-). <sup>13a</sup>     | 20. Pyridine (4-). <sup>13a</sup>         |
| 9. Pyrazole (3-). <sup>13a</sup>          | 21. Pyridazine (4-). <sup>13a</sup>       |
| 10. Furan (2-). <sup>13a</sup>            | 22. Benzene. <sup>13a</sup>               |
| 11. Imidazole (2-). <sup>13a</sup>        | 23. Pyridine (3-). <sup>13a</sup>         |
| 12. Furazan (3-). <sup>13f</sup>          | 24. Pyrimidine (5-). <sup>13a</sup>       |

A much more direct measure of the electron density of a carbon atom is the actual carbon-13 chemical shift of that carbon atom.<sup>21</sup> It has already been reported<sup>20</sup> that the carbon-13 shift of the  $\alpha$ -carbon atom in pyridine and the diazines moves upfield on protonation of the nitrogen atom, suggesting an "unexpected" increase in the carbon electron density. Fortunately, carbon-13 shifts have now been measured by Grant and Pugmire<sup>22</sup> for all of the molecules calculated here, including the protonated and diprotonated species, with the exception of the protonated dication of pyridazine. In Figs. 2 and 3 the total electron densities of different positions in the neutral molecules and protonated species are plotted against the corresponding carbon-13 chemical shift from the data of Grant and Pugmire. A good correlation is obtained, where

<sup>21</sup> J. B. Stothers, *Quart. Revs.* XIX, 144 (1965).

<sup>22</sup> D. M. Grant and R. J. Pugmire, private communication.

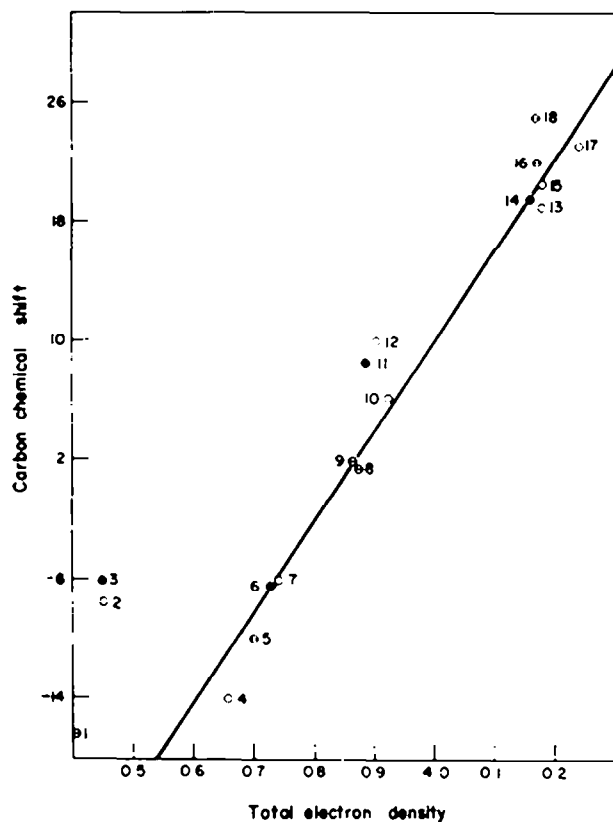


FIG. 2. Carbon-13 Chemical Shifts (ppm) of 5-Membered Ring Heterocyclics versus EHT Total Electron Densities.

Open circles indicate neutral molecules; hatched circles, cations; and halved circles, anions. In the index below, the index number refers to a particular point in the Fig., and the number in the parentheses designates a particular position in the ring.

- |                          |                           |
|--------------------------|---------------------------|
| 1. Imidazole anion (2-)  | 10. Imidazole (4-)        |
| 2. Imidazole (2-)        | 11. Imidazole cation (4-) |
| 3. Imidazole cation (2-) | 12. Pyrrole (2-)          |
| 4. Furan (2-)            | 13. Furan (3-)            |
| 5. Pyrazole anion (3-)   | 14. Pyrazole cation (4-)  |
| 6. Pyrazole cation (3-)  | 15. Pyrrole (3-)          |
| 7. Pyrazole (3-)         | 16. Pyrrole anion (3-)    |
| 8. Pyrrole anion (2-)    | 17. Pyrazole (4-)         |
| 9. Imidazole anion (4-)  | 18. Pyrazole anion (4-)   |

again some additional data is included, that for the nine positions in quinoline and in isoquinoline. The only arrangement where the electron density values consistently lie off the line is that of a carbon atom between two nitrogen atoms, i.e. the 2-position in imidazole and the 2-position in pyrimidine. Even here the same trends are observed on protonation.

Again two distinct lines with similar slopes of 60 and 64 ppm/electron are obtained for the 5- and 6-membered rings, respectively. However, in this instance the 5-membered rings exhibit higher chemical shifts. In the 5-membered rings the average

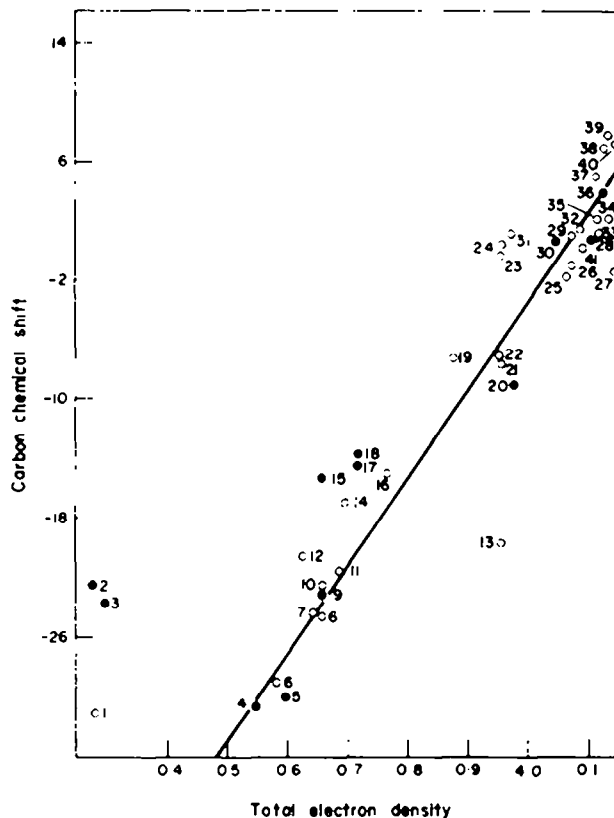


FIG. 3. Carbon-13 Chemical Shifts (ppm) of 6-Membered Ring Heterocyclics versus EHT Total Electron Densities.

Open circles refer to neutral molecules, hatched circles to cations. In the index below, the index number refers to a particular point in the Fig., and the number in parentheses designates a particular position in the ring.

- |                               |                                |
|-------------------------------|--------------------------------|
| 1. Pyrimidine (2-)            | 22. Pyridine (4-)              |
| 2. Pyrimidinium dication (2-) | 23. Isoquinoline (10-)         |
| 3. Pyrimidinium cation (2-)   | 24. Quinoline (5-)             |
| 4. Pyrimidinium dication (4-) | 25. Isoquinoline (7-)          |
| 5. Pyrimidinium cation (4-)   | 26. Quinoline (8-)             |
| 6. Pyrimidine (4-)            | 27. Quinoline (9-)             |
| 7. Pyridazine (3-)            | 28. Pyridinium cation (3-)     |
| 8. Isoquinoline (1-)          | 29. Isoquinoline (9-)          |
| 9. Pyridazinium cation (3-)   | 30. Pyrimidinium dication (5-) |
| 10. Quinoline (2-)            | 31. Pyridazine (4-)            |
| 11. Pyridine (2-)             | 32. Quinoline (6-)             |
| 12. Quinoline (10-)           | 33. Isoquinoline (8-)          |
| 13. Pyridinium cation (4-)    | 34. Isoquinoline (6-)          |
| 14. Pyrazine (2-)             | 35. Quinoline (7-)             |
| 15. Pyrazinium dication (2-)  | 36. Pyrimidinium cation (5-)   |
| 16. Isoquinoline (3-)         | 37. Pyridine (3-)              |
| 17. Pyrazinium cation (2-)    | 38. Pyrimidine (5-)            |
| 18. Pyridinium cation (2-)    | 39. Quinoline (3-)             |
| 19. Isoquinoline (5-)         | 40. Isoquinoline (4-)          |
| 20. Pyridazinium cation (4-)  | 41. Benzene.                   |
| 21. Quinoline (4-)            |                                |



electron density is higher than in the corresponding 6-membered rings since each ring system has 6  $\pi$ -electrons. We suggest that the higher chemical shift in the 5-membered rings are due to an increased screening of the carbon atom being considered, brought about by the higher average electron densities of the other ring atoms.

In conclusion, the theoretical suggestion, that an increase in the electron density of a carbon atom adjacent to a nitrogen occurs if the nitrogen atom is protonated, is consistent with the observed experimental data.

The approximate nature of these calculations needs to be emphasized, but the results indicate no firm basis for the suggestion of an electron withdrawal from the  $\alpha$ -position, although a slight decrease in the proton electron density does occur, for example in pyridine the change is from 0.975 electrons in the neutral molecule to 0.968 electrons in the pyridinium cation. The proposal<sup>15</sup> that improved results might be obtained from the use of actual geometries is not borne out, and we believe that the difficulty in their work lay in the omission of  $\sigma$ -bond polarization.

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