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MOLECULAR ELECTROSTATIC POTENTIALS—II

MECHANISTIC ASPECTS OF ELECTROPHILIC INTERACTIONS OF SOME FIVE-MEMBERED HETEROCYCLES

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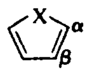
Abstract—The interactions of furan, pyrrole and N-methyl pyrrole with electrophiles have been investigated by means of the calculated molecular electrostatic potentials, obtained from INDO wave functions, which indicate the most attractive sites and pathways of attack for an approaching electrophile. The very distinct preference of these heterocycles for α-substitution can be interpreted quite satisfactorily in the case of furan if it is assumed that the α-hydrogen moves out of the plane of the molecule, forming a quasi-tetrahedral carbon, as an initial step in the reaction. For pyrrole and N-methyl pyrrole it is found to be necessary to invoke out-of-plane "bending" of the N–H, N–CH$_3$ and C$_\alpha$–H$_\alpha$ bonds to explain both the preference for α-substitution, and also the relative selectivities of furan, pyrrole and N-methyl pyrrole. The energies, atomic charges and bond orders of various forms of these heterocycles are also discussed.

Furan **1**, pyrrole **2** and N-methyl pyrrole **3** are heterocyclic molecules having the structure

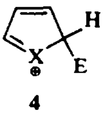


1: X = O
2: X = N—H
3: X = N—CH$_3$

The chemical properties of these molecules, such as their distinct preference for undergoing substitution rather than addition,[1,2] have been taken as indicative of a certain degree of aromatic character.[1-3] This is generally attributed to the delocalization into the ring of the "lone-pair" electrons on the heteroatom.[1-3] This would formally lead to a total of six delocalized pi electrons, the same number as in benzene although these molecules have only five-membered rings. They are consequently sometimes labeled "π-excessive".[2,4]

While it is generally accepted that these molecules possess some aromaticity, there is considerable disagreement as to its degree.[3] Resonance energies estimated from thermochemical data range from 16 to 23 kcal/mole for furan, and 21–31 kcal/mole for pyrrole (compared to 36 kcal/mole for benzene).[5,6] On the other hand, semi-empirical calculations have predicted values of 20·0–22·6 kcal/mole for benzene, but only 5·3–8·5 kcal/mole for pyrrole and 1·6–4·3 kcal/mole for furan.[7] More recently, it has been argued that the calculated resonance energy for pyrrole should be higher, approximately 2/3 of the value for benzene.[8] Ring current measurements suggest a pyrrole aromaticity which is 0·59–0·67 as great as that of benzene, while that of furan is 0·46–0·52 as great.[9] Thus, various methods of estimating the degree of aromaticity have led to a wide range of predictions, the two common factors being that furan is always found to be less aromatic than pyrrole, and both are less aromatic than benzene. Experimental evidence supports both these conclusions, and indicates that the degrees of aromaticity of pyrrole and furan are rather on the low side. Furan has enough diene character to undergo the Diels-Alder reaction with maleic anhydride, as well as other addition reactions;[1,2] the diene character of pyrrole is less marked, but Diels-Alder and other adducts have been postulated as intermediates in some of its reactions.[1,2,10] N-Methyl-pyrrole is known to undergo a Diels-Alder reaction with dimethylacetonedicarboxylate.[2]

It is well-established that electrophilic substitution in these molecules occurs predominantly at the α-position.[1-4] This has been rationalized in terms of the resonance opportunities open to the presumed intermediates;[3] in the case of α-substitution, three contributing structures can be written,



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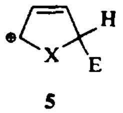

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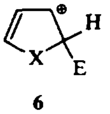

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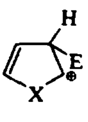
(E$^+$ = electrophile)

whereas only two are possible in the event of β-attack:



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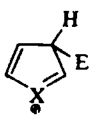

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The α-intermediate should therefore be the more stable, and α-substitution accordingly preferred.

While this is the general pattern that is observed, the degree of selectivity varies significantly from one molecule to another. Electrophilic substitution on furan gives almost entirely the α-product; in the case of pyrrole, however, as much as 20% β-substitution may occur, and N-methyl pyrrole is even less selective.[1,2,11,12] As far as the *rates* of substitution (in the α-position) are concerned, the order is N-methyl pyrrole > pyrrole ≫ furan ≫ benzene;[12–14] in trifluoroacetylation, for example, the rates (relative to a value of 1·0 for thiophene) are 1×10^8 (N-methyl pyrrole), $5{\cdot}3 \times 10^7$ (pyrrole), and $1{\cdot}4 \times 10^2$ (furan).[14]

It might seem reasonable to anticipate that the preference for α-substitution would be reflected in the net charges on the α- and β-carbon atoms in these molecules, as calculated by various semiempirical or *ab initio* methods. However, the correlations sought have not been found; as shall be discussed in more detail later, it is the β-carbons that appear to have the more negative net charges.[3,4,15–19]

Our primary purpose in this investigation has been to learn more about the factors which govern site selection in electrophilic substitutions on these heterocycles, and also to gain some insight into the mechanisms of these reactions. We approached this problem by computing semi-empirical wave functions, using the INDO procedure, for the three molecules under consideration,[20,21] using the geometries cited in Ref. 22. In addition to the usual quantities obtained from such calculations (e.g. atomic populations, bond orders, etc.), we also used the INDO wave functions to compute the molecular electrostatic potentials. This property has been shown in recent years to be an effective means of studying electrophilic processes.[23a]

METHODS OF ANALYSIS

Atomic charges and bond orders

In the INDO procedure, the electronic population q_A on an atom A is defined as

$$q_A = \sum_i \sum_\mu N_i C_{i\mu} C_{i\mu} \qquad (1)$$

where $C_{i\mu}$ is the coefficient of basis orbital μ, centered on atom A, in molecular orbital i. N_i represents the number of electrons in the molecular orbital. The total bond order between two atoms, A and B, is defined here as

$$P_{AB} = \sum_i \sum_\mu \sum_\nu C_{i\mu} C_{i\nu} \qquad (2)$$

In Table 1 are presented the calculated valence electron populations and net charges of the major atoms in furan, pyrrole, and N-methyl pyrrole. These values are in good qualitative agreement with the results of other computational approaches, such as the CNDO/2, extended-Hückel, and *ab initio* SCF methods.[17,19] While it is true that such charges have little significance in an absolute sense,[24] they can sometimes provide an indication of the relative degrees of electronic density concentration around the various atoms and hence can have some physical meaning. That they do in the case under discussion is shown by the correlations which have been shown to exist between the net atomic charges calculated for various heterocyclic molecules, including furan and pyrrole, and the experimentally-determined proton and ^{13}C chemical shifts in these molecules.[15–17]

Molecular electrostatic potentials

A new theoretical tool which has been found in recent years to be very useful in predicting sites and pathways of electrophilic attack is the molecular electrostatic potential.[23a] This is defined as

$$V(\bar{r}) = \sum_A \frac{Z_A}{|\bar{R}_A - \bar{r}|} - \int \frac{\rho(\bar{r}')}{|\bar{r}' - \bar{r}|} d\bar{r}' \qquad (3)$$

where Z_A is the nuclear charge of atom A, located at $\bar{R}_A$, and $\rho(\bar{r}')$ is the electronic density at the point $\bar{r}'$. In terms of molecular orbitals ψ_i,

$$\rho(\bar{r}') = \sum_i N_i \psi_i^*(\bar{r}') \psi_i(\bar{r}') \qquad (4)$$

$V(\bar{r})$ represents the electrostatic potential that is produced at any point $\bar{r}$ by the nuclei and electrons of the molecule in question. It is numerically equal to the energy of interaction of a positive point charge, of magnitude +1·0 electron units, with the unperturbed charge distribution of the molecule; $V(\bar{r}) < 0$ corresponds to an attractive interaction, $V(\bar{r}) > 0$ to a repulsive one. In reality, of course, such a point charge would have some perturbing effect upon the electronic density distribution in the molecule; $V(\bar{r})$ corresponds to the first-order interaction energy in a perturbation treatment of the system.[23] The procedure that we have used in computing $V(\bar{r})$ has been described in Ref. 25.

The electrostatic potential, as given by Eqn (3), is a rigorously-defined physical property of a molecule, whereas atomic charges represent an attempt to condense its charge distribution into an arbitrarily-defined set of point charges. The sign and magnitude of the potential at each point in space are determined by contributions from both the total charge distribution of the unperturbed molecule, and its nuclei. It is reasonable to anticipate, therefore, that the electrostatic potential will be a better indicator of the most attractive sites and pathways of attack for an approaching electrophile. Of course, even though Eqn (3) is an exact expression for $V(\bar{r})$, the accuracy of the calculated potentials depends upon the quality of the approximate wave function that is used to compute $\rho(\bar{r})$.

The electrostatic potential has been used successfully in predicting the protonation sites and relative tendencies toward protonation in a number of organic molecules,[23,26,27] including some of the nucleic acid bases,[28] as well as the hydration sites of large molecules[29] and the reactivity of drugs in interactions with macromolecular receptors.[30] It cannot predict the stabilities of various possible intermediate or final structures; the only types of information sought are sites and pathways of electrophilic attack, and their relative importance. It is certainly not being claimed that electrostatic effects are the sole factors involved in the interaction of a substrate with an electrophile; polarization and charge-transfer, for example, undoubtedly also play a role.[23b] In many cases, however, these other factors seem to partially cancel, and their net effect is not sufficient to outweigh the electrostatic contribution.† The importance of taking into account changes in the geometry of the substrate will be emphasized in this discussion.

RESULTS AND DISCUSSION

Calculated charges and bond orders

A notable feature of the atomic charges in Table 1 is the fact that the β-carbons are invariably more negative than the α-carbons. Thus, if the positions of electrophilic attack were being predicted solely on the basis of ground state atomic charges, the β-carbons would have to be considered the most likely sites for attack. This is of course contrary to the experimental facts mentioned earlier, as has been noted a number of times in the past.[3,4,17,18]

Table 1. Calculated atomic valence electron populations and pi bond orders

Molecule	Atom(s)	Valence electron population	Net charge	Pi bond order
Furan	O	σ: 4·46 π: 1·73	−0·19	
	Cα	σ: 2·79 π: 1·06	+0·15	
	C_β	σ: 2·96 π: 1·07	−0·03	
	O–C_α			0·41
	C_α–C_β			0·85
	C_β–C_β			0·45
Pyrrole	N	σ: 3·43 π: 1·67	−0·10	
	C_α	σ: 2·85 π: 1·08	+0·07	
	C_β	σ: 2·95 π: 1·08	−0·03	
	N–C_α			0·45
	C_α–C_β			0·83
	C_β–C_β			0·47
N-Methyl Pyrrole	CH_3	——	+0·08	
	N	σ: 3·43 π: 1·64	−0·07	
	C_α	σ: 2·85 π: 1·09	+0·06	
	C_β	σ: 2·95 π: 1·08	−0·03	
	N–C_α			0·44
	C_α–C_β			0·83
	C_β–C_β			0·47

Table 1 also includes the calculated pi bond orders [obtained by including only the pi molecular orbitals in the summation over i in Eqn (2)] between the ring atoms in furan, pyrrole, and N-methyl pyrrole. Again, our interest in these is only qualitative; the important point is that in all three molecules, the C_α-C_β pi bond orders (0·83–0·85) are roughly twice as great as the X-C_α and the C_β-C_β (0·41–0·47). In sharp contrast, the pi bond orders in benzene are 0·67, just about halfway between the preceding sets of values. If bond orders are taken to be at least some measure of the degree of pi bonding, then these numbers imply a fairly considerable localization of pi charge in the C_α-C_β bonds and therefore significant diene character. This is consistent with those previous studies which concluded that these heterocycles have a relatively small degree of aromaticity (see above).

Electrostatic potentials

Furan. The tendency of furan to undergo electrophilic attack preferentially in the α-position has already been analyzed in terms of the electrostatic potential, computed from CNDO wave functions.[27] This analysis has now been repeated using INDO functions, with similar conclusions. It is found that ground-state furan has only one region of negative potential (attractive to an electrophile), that being a very extended one near the oxygen atom. There are *no* negative potentials near either the α- or the β-positions (Fig. 1). In order to try to account for the fact that electrophilic substitution does occur very readily,

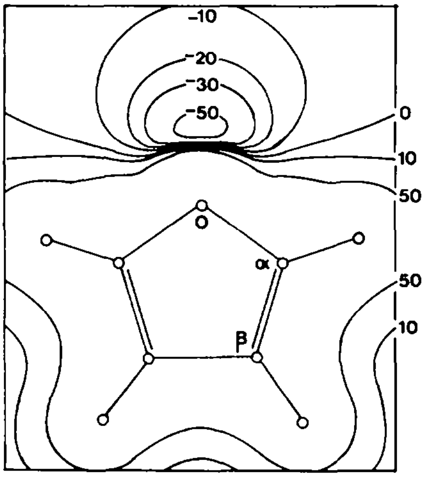

Fig. 1. Electrostatic potential in the molecular plane of furan. This diagram is based on the CNDO/2 calculation of Ref. 27. INDO results show no significant qualitative differences. In this and all subsequent figures, the potential generated by the molecule is represented as contours of equal interaction energy with a positive point charge. Units are kcal/mole.

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†A detailed analysis of the various contributions to the interaction between formamide and an approaching proton has been carried out by Pullman.[31]

with the α-position greatly favored, the possibility was considered that as a first stage in the reaction, the α- or β-hydrogen moves out of the plane of the molecule. This would produce a quasi-tetrahedral carbon with one position unoccupied. When the potential was computed for the two hypothetical structures having a C_α-H or a C_β-H bond bent by 52° out of the molecular plane, it was found that in both cases a very definite attractive region does indeed develop along the fourth tetrahedral direction (Fig. 2).

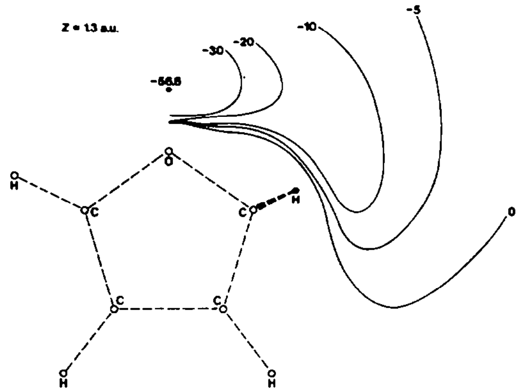

Fig. 2. Electrostatic potential in the plane 1·3 a.u. *above* furan. The α-hydrogen is bent *below* the molecular plane. This figure shows the negative potential that has developed in the fourth tetrahedral direction of the α-carbon.

It was suggested,[27] therefore, that electrophilic attack on furan is preceded by the movement of a hydrogen atom out of the plane of the molecule, which produces a path of negative potential leading to the carbon atom in question. This path turns out to be roughly equally attractive toward an approaching electrophile whether it is the α- or the β-hydrogen that is moved out of the plane, so that this factor alone would not suffice to explain the preference for α substitution. The key difference is that the attractive region which results from bending the α-hydrogen is part of the extensive negative potential near the oxygen atom (Fig. 3), whereas when the β-hydrogen is bent, there remains an intervening positive potential between the two negative regions. Accordingly, an electrophile which approaches the very attractive region near the oxygen can fairly easily migrate to the α-carbon, since there is no positive barrier, while an analogous migration to the β-carbon is hindered.

Thus, α substitution can apparently result from an initial approach to either the α-carbon or the oxygen, whereas β substitution seems to require a direct attack upon the β-carbon. It is to be expected, therefore, that α-substitution will occur with a much greater frequency, as is indeed found to be the case.[1-4] These ideas concerning the mode of electrophilic interaction with furan are consistent with (but do not necessarily imply) the widely-held belief that electrophilic substitutions on the molecules included in this study proceed through a tetrahedral complex, the so-called "Wheland" or "sigma" intermediate.[1,3,32,33]

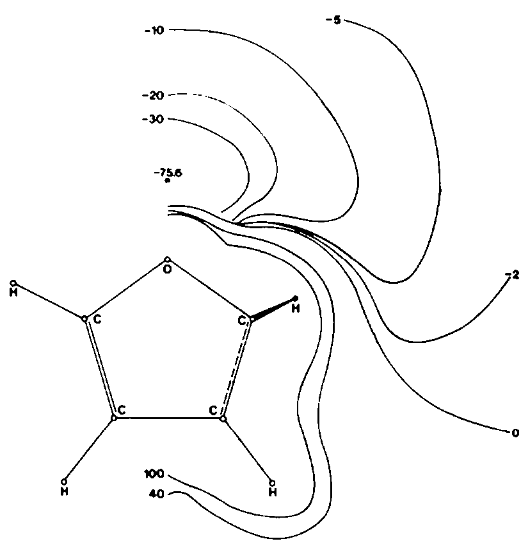

Fig. 3. Electrostatic potential in the molecular plane of furan, with its α-hydrogen bent below the plane.

Pyrrole and N-Methyl pyrrole. As shall be seen, the analysis of the reactive properties of pyrrole and N-methyl pyrrole presents somewhat greater problems than did that for furan. Figs. 4 and 5 show the electrostatic potentials in the planes of these molecules. In contrast to furan, there are no in plane regions of negative potential near the heteroatoms. This is because of the hydrogen or methyl substituent on the nitrogen; hydrogen atoms generally have positive potentials associated with them. The only negative regions in pyrrole and N-methyl pyrrole

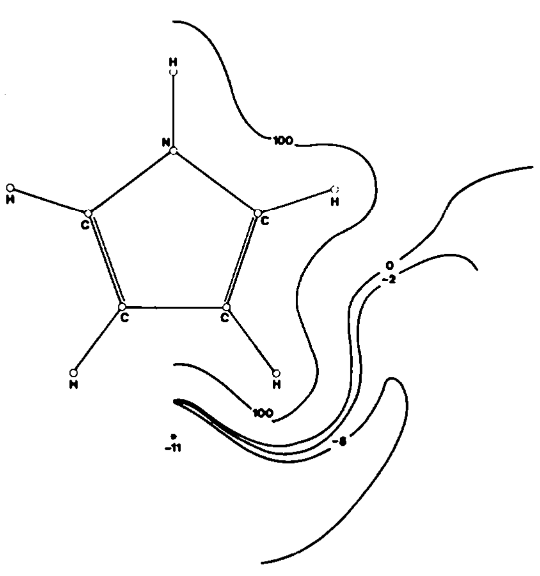

Fig. 4. Electrostatic potential in the molecular plane of pyrrole.

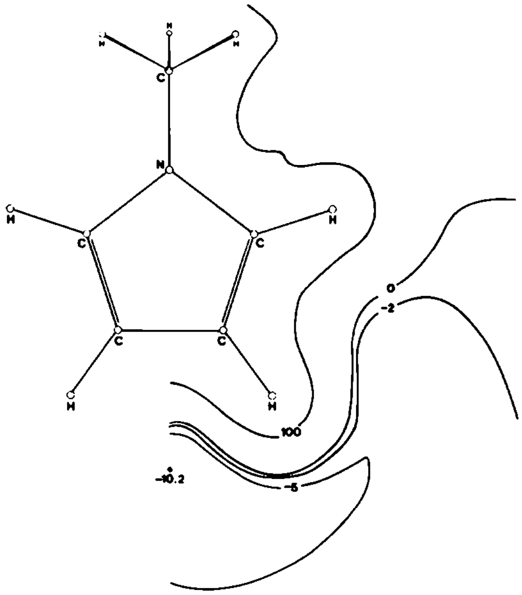

Fig. 5. Electrostatic potential in the molecular plane of N-methyl pyrrole.

are the rather extended ones to the outside of the C_β-C_β bonds. Thus, as in the case of furan, the ground-state potentials provide no basis for predicting a preference for α-substitution; if anything, they suggest that the β-positions might be more vulnerable to electrophiles.

Proceeding as before, we bent first the C_α-H and then the C_β-H bonds out of the molecular plane by angles of 52°. Again this leads to the development of negative potentials in the approximate fourth tetrahedral directions; however the one by the β-carbon is distinctly more attractive for an approaching electrophile (Fig. 6), having a local minimum (in the case of pyrrole) of $-34{\cdot}9$ kcal/mole, while that by the α-carbon has a minimum of only $-21{\cdot}8$ kcal/mole. (The potential diagrams for N-methyl pyrrole are in all instances almost identical with those for pyrrole, except in the neighborhood of the N-H or N-CH_3 groups.) Furthermore, the attractive region by the β-carbon is an integral part of the large negative region near the C_β-C_β bond, while that by the α-carbon is just barely connected to it (Figs. 7 and 8). It appears therefore, that the mechanism of electrophilic attack on pyrrole and N-methyl pyrrole is somewhat more complex than is that for furan.

As was pointed out earlier, an important consequence of the presence of the heteroatom in furan is the large region of negative potential that is associated with it, and that expands to include the space near the α-carbon when the latter's hydrogen is moved out of the plane of the ring. There is no such attractive potential associated with the heteroatoms in pyrrole and N-methyl pyrrole, due in part to the presence of their hydrogen and methyl groups in the molecular plane. Based on previous experience, it seemed reasonable to anticipate that if these groups were moved out of the plane, then negative potentials might develop

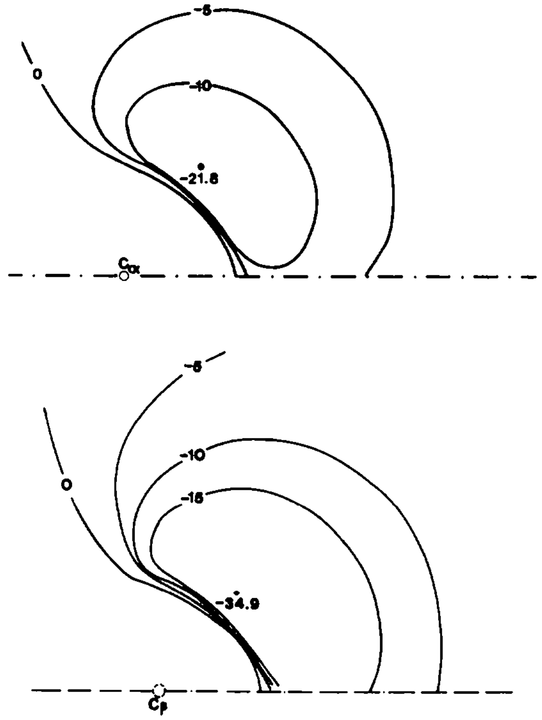

Fig. 6. Electrostatic potentials in perpendicular planes through the (a) α- and (b) β-carbons in the pyrrole structures which have the corresponding hydrogen bent below the molecular plane. These perpendicular planes intersect the molecule along the dotted lines shown in Figs. 7 and 8, respectively.

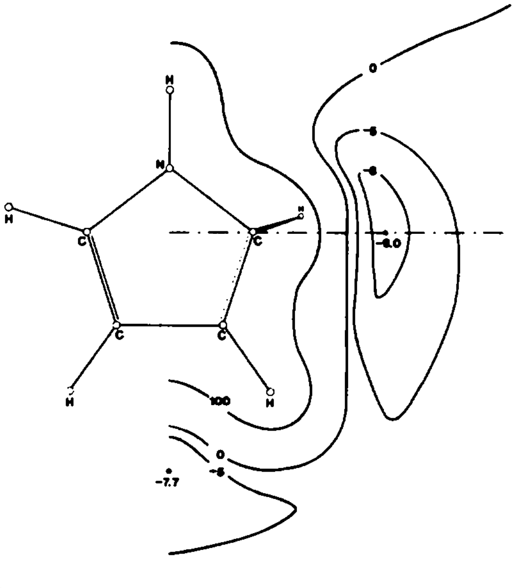

Fig. 7. Electrostatic potential in the molecular plane of pyrrole with its α-hydrogen bent below the plane.

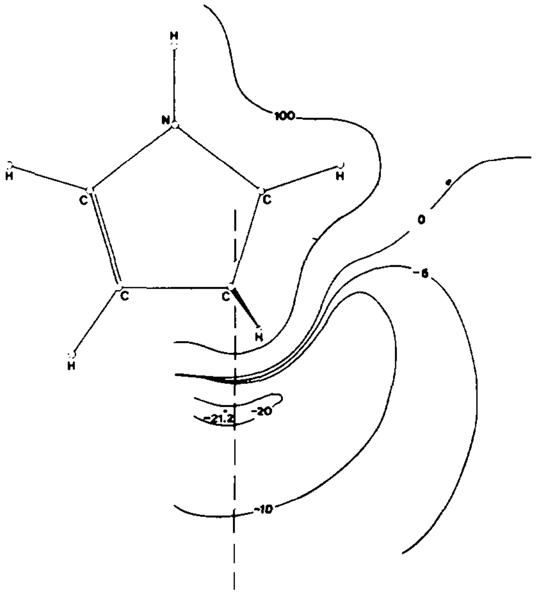

Fig. 8. Electrostatic potential in the molecular plane of pyrrole with its β-hydrogen bent below the plane.

near the nitrogen on the other side of the molecular plane. This might lead to a similar situation as in furan, and permit an analogous interpretation of the preference for α-substitution in pyrrole and N-methyl pyrrole.

These considerations are fully confirmed by the results obtained upon bending the N–H and N–CH_3 bonds out of the ring planes. Fig. 9 shows that when the hydrogen (in pyrrole) is moved out of the plane by an angle of 52°, a fairly extensive and quite deep negative potential, reminiscent of that in planar furan (Fig. 1), develops on the other side of the nitrogen atom. When the α- and β-hydrogens now are bent, negative potentials are again produced in the fourth tetrahedral directions and that by the β-carbon is again the more attractive (Figs. 10 and 11). The important point, however, is that the negative potential by the α-carbon is now joined to the large attractive region of the nitrogen, while that by the β-carbon is separated from it by a positive potential barrier. It is also very significant that the development of the negative potential by the nitrogen is accompanied by a diminishing of that near the β-carbons, thus greatly reducing the role of this region as a possible competitor for an approaching electrophile. It should be noted that Figs. 10 and 11 describe the situation wherein the N–H bond has been bent out of the plane by only 30°, showing that the effects being discussed manifest themselves even for a degree of bending considerably less than the 52° which corresponds to roughly tetrahedral character.

Thus, if an electrophile approaches pyrrole at a time when the N–H bond is bent out of the molecular plane, then α-attack is expected to be greatly favored, by the same reasoning as in the case of furan. At such a moment, bending the α-H leads to the formation of an attractive potential in the fourth tetrahedral direction of the α-carbon which is part of the large, highly attractive region associated with the nitrogen. An electrophile approaching at any point within this region can migrate to the α-carbon without the necessity of passing through a zone of positive potential. Accordingly, even though the β-position does have the more negative minimum, α-substitution should be considerably more likely than β-, for which the electrophile must approach the

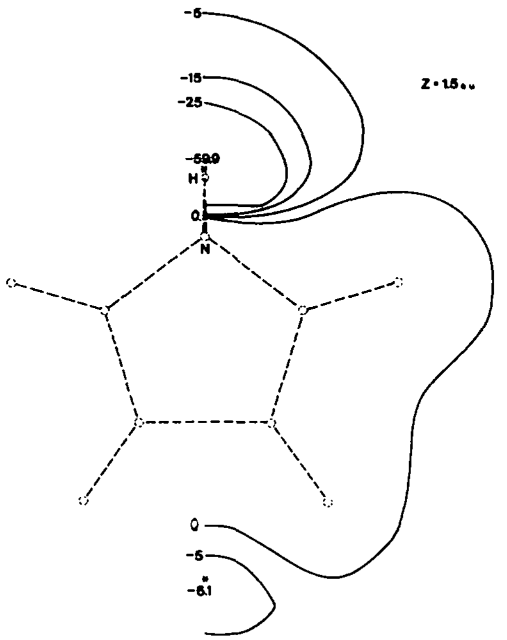

Fig. 9. Electrostatic potential in a plane 1·5 a.u. above the molecular plane of pyrrole, with the hydrogen on the nitrogen atom bent below the molecular plane.

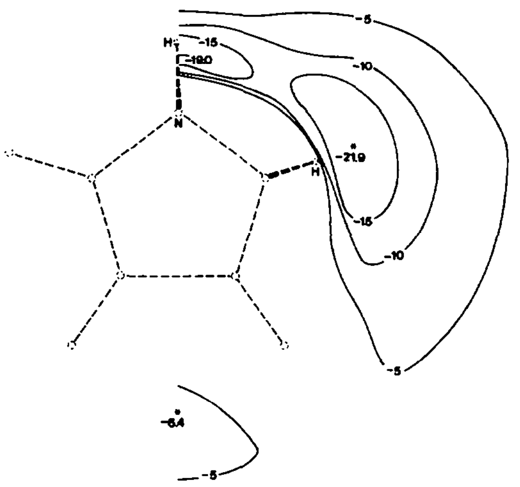

Fig. 10. Electrostatic potential in a plane 1·5 a.u. above the molecular plane of pyrrole, with the hydrogens on the nitrogen atom and on the α-carbon both bent below the molecular plane.

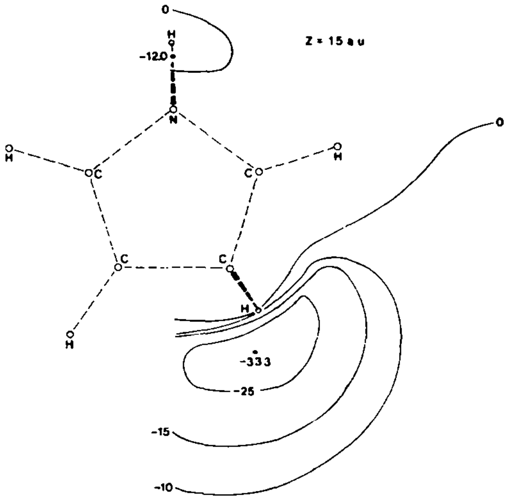

Fig. 11. Electrostatic potential in a plane 1·5 a.u. above the molecular plane of pyrrole, with the hydrogens on the nitrogen atom and on the β-carbon both bent below the molecular plane.

pseudo-tetrahedral β-carbon directly along its fourth bonding direction. However if the approach of the electrophile happens to coincide with the N-H bond being *in* the molecular plane, meaning that there is no attractive potential by the heteroatom which could help the α-position, then electrostatic considerations alone actually favor β-attack, since a more attractive potential results from bending the β-H than the α-H. (Analogous arguments are believed to be applicable to N-methyl pyrrole, in view of the previously-noted similarity of its electrostatic potential to that of pyrrole.)

The experimentally-determined N-H and N-CH_3 bending force constants in pyrrole and N-methyl pyrrole are relatively small, compared for example to those of the C-H bonds (see Table 2).[34] The N-H and N-CH_3 bonds should accordingly be bent out of the plane of the ring, to some degree, most of the time.† Furthermore, it may be anticipated that as an electrophile approaches the resulting region of negative potential near the nitrogen, there will develop a repulsive interaction between it and the H or CH_3 of the nitrogen which will tend to push these even farther away. In view of the analysis presented above, these combined circumstances should make the α-carbon the most likely site for electrophilic attack. This conclusion will be discussed in detail in the Summary and Conclusions section.

Table 2. Bending force constants.[a]

Molecule	Out-of-plane bending force constant		
Furan	C_α-H_α:	0·348	mdyn A/rad^2
	C_β-H_β:	0·381	
	N-H:	0·121	
Pyrrole	C_α-H_α:	0·331	
	C_β-H_β:	0·377	
N-Methyl pyrrole	N-CH_3:	0·238	

[a] Ref. 34.

Calculated energies

In Table 3 are presented our calculated INDO energies for various pyrrole and N-methyl pyrrole structures relevant to this discussion. As with the atomic charges and bond orders, only the relative values have any significance, and even then, comparisons should be limited to the results pertaining to a given one of the two molecules.

Table 3. Calculated energies relative to planar ground states

Structure	Energy (kcal/mole) Pyrrole	Energy (kcal/mole) N-Methyl pyrrole
Planar	0·0	0·0
C_α-H_α bent[a]	+37·2	+37·0
C_β-H_β bent	+40·3	+40·6
N-H or N-CH_3 bent	+11·1	+10·9
N-H and C_α-H_α bent (both 52°)	+49·5	
N-H bent 30° and C_α-H_α bent 52°	+42·3	
N-H bent 30° and C_β-H_β bent 52°	+50·3	
C_α protonated[b]	−323·2	−326·2
C_β protonated	−319·9	−324·9
N protonated	−315·7	
N protonated, C_α-H_α bent	−282·4	

[a] The angle of bending is in all cases 52° (relative to the molecular plane) except as indicated.

[b] In the protonated structures, both hydrogens are 52° out of the plane. Their C-H bond lengths were taken to be 1·14A.

The computed energies are in good qualitative agreement with the preceding discussion and with the experimental facts. Less energy is required to move the H and CH_3 of the nitrogen out of the molecular plane than is needed for any ring hydrogen, in accord with the force constants given in Table 2. Also in agreement with these force constants, and consistent with preferential α-substitution, the α-hydrogens require less energy to shift out of the ring plane than do the β-hydrogens. This is true for both pyrrole and N-methyl pyrrole, and holds whether or not the N-H bond is also bent.

Included in Table 3 are some computed energies of protonation of pyrrole and N-methyl pyrrole. These protonated species correspond to the tetrahedral complexes that have frequently been proposed as intermediates in electrophilic substitutions on heterocyclic rings.[1,3,32,33]

They could be formed by means of the bending mechanism that has been discussed in this paper, with the proton approaching the site via the fourth tetrahedral direction. For both pyrrole and N-methyl pyrrole, the α-protonated complex is calculated to be the more stable,

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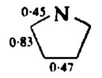
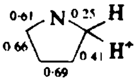
†The mean amplitude out of the plane of the H(N) atom in pyrrole has been calculated to be about 25% greater than those of the other hydrogens in pyrrole.[34]

in agreement with their well-established preference for electrophilic substitution in the α-position. The computed pi bond orders in these complexes, as shown below, indicate that a considerable degree of conjugation develops in forming the α-protonated structure, which may help to explain its greater stability. This explanation is of course the same in principle as that which has been advanced in the past[3] to interpret the greater stability of the α-complex, and it is interesting to note how consistent the computed bond orders are with the resonance structures **4–8** mentioned earlier.





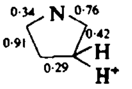


Table 3 also shows that the nitrogen atom in pyrrole is a considerably less likely site for protonation than are any of the carbons. This may seem surprising, in view of the negative charge of the nitrogen (Table 1), but it is in full accord with experimental observations.[4,35]

Summary and conclusions

Our previous study of furan led to the hypothesis that electrophilic substitution involves the shifting of a hydrogen atom out of the molecular plane, with the consequent development of a negative (attractive) electrostatic potential on the other side of the carbon in question, in what is roughly termed the "fourth tetrahedral direction".[27] The preference for the α-position was ascribed to the fact that when this negative potential develops by the α-carbon, it becomes part of the extended and highly-attractive region associated with the oxygen; an electrophile approaching anywhere in this region can therefore easily approach the α-carbon, whereas to approach the β-carbon would require passing through a zone of positive potential.

The situation in pyrrole and N-methyl pyrrole is somewhat more complicated. The presence of the hydrogen or methyl group on the nitrogen precludes the possibility of any negative potential in the immediate vicinity of the latter as long as the N–H and N–CH_3 bonds are in the molecular plane. The movement of an α-H or β-H out of the plane will still produce an attractive region by the representative carbon, of course, but under these circumstances the β-position is actually a more favorable site for attack, from an electrostatic point of view (compare Figs. 7 and 8). However the low force constant and small energy involved in bending the N–H or N–CH_3 bonds indicate that the H and CH_3 will be out of the molecular plane most of the time, and then the situation in pyrrole and N-methyl pyrrole begins to parallel that in furan, depending of course upon the degree of bending. As pointed out earlier, the approach of an electrophile is likely to increase the degree of bending, due to its repulsive interaction with the hydrogen or methyl group.

Usually, therefore, an approaching electrophile can be expected to find and be attracted to the very extended region of negative potential near the nitrogen and the α-carbon, from which it can readily move to its eventual bonding site at the latter. Thus, α-substitution should greatly predominate over β-, which would require that the electrophile should happen to approach the β-carbon itself, along its fourth tetrahedral direction. There is a slight probability, however, that the electrophile will approach when the H or CH_3 is *in* the ring plane, or shifted only very slightly out of it. Electrostatically the β-position will then be the more favored one, although it is necessary to also consider that bending the C–H_β bond requires somewhat more energy than does the C–H_α. Thus, it must be expected that a certain small amount of β-substitution will occur and that pyrrole will not be as selective as furan, in which there is no hydrogen on the heteroatom, so that the situation just described cannot arise. N-Methyl pyrrole should be yet less selective than pyrrole, since the methyl group is more difficult to move out of the ring plane than the hydrogen (see Tables 2 and 3), so that an approaching electrophile is more likely to find the N–CH_3 bond in, or very nearly in, the plane. All of these conclusions are in full agreement with experimental observations.

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