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ELECTRON CHARGE REDISTRIBUTION FOLLOWING ELECTROPHILIC ATTACK ON HETEROCYCLES: NITROGEN AS A CHARGE TRANSDUCER†

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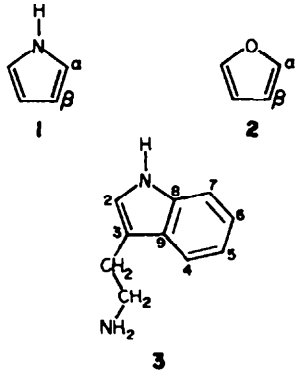
Abstract—It is shown that an electrophilic attack on the ring nitrogen in pyrrole or tryptamine produces an electron charge redistribution that is qualitatively different from the redistribution caused by an attack on the oxygen in furan. The electrophilic attacks are represented theoretically as interactions with a positive point charge and calculated by an *ab-initio* LCAO–SCF method with gaussian basis sets. Results show that an attacked nitrogen responds to the perturbation by moving electronic charge to the adjacent carbons whereas oxygen retains most of the charge polarized by the interaction. The nitrogen also acts as a charge transducer in other systems that are structurally very different. As a consequence of the charge redistribution, the comparative susceptibility of various sites in the heterocyclic molecules to an electrophilic attack may also depend on the response of the molecule to a prior attack on the heteroatom. The results indicate the need for dynamical reactivity considerations which reflect the variability in the molecular response to an incipient attack and the possibility that enhanced reactivity can be induced at certain sites by this response.

While it is well established experimentally that electrophilic substitution in 5-membered heterocycles such as furan, pyrrole and N-methylpyrrole occurs predominantly at the α position,[1-4] theoretical studies have found that the total electronic charge assigned by a Mulliken population analysis of the electronic charge distribution is larger on β than on the α carbons.[3-6] We have shown that the heteroatom is instrumental to the α *vs* β selectivity in these molecules because it generates an electrostatic field that attracts positively charged reagents to the region of the α carbons, thereby increasing the probability of α protonation.[7] In this respect, the effect of the heteroatoms on the reactivities of furan and pyrrole appeared qualitatively similar. Here we report some theoretical observations on significant *differences* in the reactivity characteristics of O and N containing heterocycles, caused by the apparent ability of N atoms to transfer electronic charge to adjacent centers following an interaction with an electrophile. This special characteristic of the N atom becomes evident when the redistribution of electronic charge density in the molecule in which the N atom is attacked, is compared to the charge redistribution following similar attacks on a ring carbon or an O atom. Dynamical aspects of the behavior of the electron density of the N atom are illustrated here by a comparison of the consequences of an electrophilic attack on the C atoms and the heteroatoms in pyrrole 1, furan 2, and tryptamine 3. The pattern of the electron density redistribution in interacting systems is discussed with respect to the definition of criteria for molecular reactivity.



Theoretical simulation of the interaction

(a) *Computational methods.* All the calculations were performed in an *ab-initio* LCAO–SCF scheme, using the POLYATOM programs.[8] The atomic basis for the calculation was that of Whitman and Hornback[9] with 5s3p gaussian orbitals on heavy atoms and two s-type gaussians on hydrogens, contracted to a minimal basis. In the molecular orbital (MO) representation, the electron density of a molecule A at each point ($\vec{r}$) in space is calculated as

$$\rho_A(\vec{r}) = \sum_i n_i \phi_i(\vec{r}) \phi_i(\vec{r}) \qquad (1)$$

where ϕ_i are the set of real occupied MO and n_i is the number of electrons in each orbital. This is a continuous function defined at each point in space, in contrast to the charge distribution represented by the Mulliken population analysis,[10] in which the total electronic density is arbitrarily partitioned into discrete point charges (q_i) centred on each atom a by a scheme

$$q_a = 2 \sum_k C_{ki} \left(C_{ki} + \sum_{i \neq j} C_{kj} S_{ij} \right) \qquad (2)$$

where C_{ki} is the coefficient of the atomic orbital i in the molecular orbital k and S_{ij} is the overlap between atomic orbitals i and j.

The electron density distribution in the molecules, $[\rho_A(\vec{r})]$, is presented in the form of density maps which contain contours connecting all the points at which the electron density is identical (iso-density maps) in a given

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plane. The electronic density is expressed as the number of electrons per cubic atomic unit (e/a.u.^{3}; 1a.u. = 0.529 Å). The redistribution of the molecular electron density caused by a change in the system from state A to B [e.g. unperturbed molecule (A) *vs* molecule under attack (B)], are presented here by density difference maps [$\rho_{A-B}(\bar{r})$] which represent iso-density contours of the *difference* between the density at a given point as generated by the system A, and the density that system B generates at the same point.

The most probable sites and geometries for an electrophilic attack are examined from the maps of electrostatic potential $V(\bar{r})$. The electrostatic potential $V_A(\bar{r})$ generated by a molecule A in its surroundings, is numerically equal to the energy of interaction of a positive point charge of unit magnitude with the unperturbed molecule A. Regions in which $V_A(\bar{r})$ is negative will therefore correspond to sites attractive to positively charged species, whereas regions in which $V_A(\bar{r})$ is positive correspond to sites of repulsive interaction with such reagents (Ref. 7 for additional details). Although any positive reagent will have a perturbing effect on the molecule and would cause the absolute value of the interaction energy to be different from that given by $V_A(\bar{r})$, the electrostatic potential has been shown to provide an excellent index of molecular reactivity.[11] Its special significance as a reactivity criterion is enhanced by the fact that it represents an experimentally measurable quantity, obtainable as the "static potential" by scattering of high energy electrons from molecules.[12]

The electrostatic potential $V(\bar{r})$ is calculated from the molecular density distribution $\rho(\bar{r})$ obtained from the *ab-initio* computations,

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

by a procedure described in Ref. 13; it is represented in maps displaying contours of equal interaction energy of the unperturbed molecule with a positive point charge. The units are Kcal/mole.

(b) *Geometries and calculated energies.* The geometries of furan and pyrrole used in the calculations are the same as those we used in Ref. 7. The energy calculated for pyrrole is −207.945223 hartrees, lower than the one obtained by Clementi *et al.* for the same geometry.[14] This improvement is probably due here to the expansion of all the 2s orbitals in 5 rather than 3 gaussian basis functions. The energy obtained for furan using the same basis set is −227.683237 hartrees.

The calculations on tryptamine were performed with the averaged crystallographic geometry proposed by Falkenberg,[15] with the side chain in the fully extended conformation (for details see Ref. 16). The calculated energy is −492.480990 hartrees.

(c) *Geometries of interaction with the electrophile.* An electrophilic species was simulated by a positive point charge kept at a fixed distance of 2 Å from the atom under attack. The incipient electrophilic attack on an atom was calculated by placing the point charge either directly above the center, or at an angle of incidence obtained from the position of the corresponding minimum in the electrostatic potential map (see below).

For planar pyrrole, the electrostatic potential map (Fig. 1) reveals only that the region most susceptible to an attack is perpendicular to the ring. However, when the N–H bond is slightly bent (i.e. θ is between 15–30°), in agreement with experimental evidence,[17] a strongly negative region appears above the N atom (Fig. 2). The angle of incidence of this new minimum (14° off a perpendicular to the plane through the N center) provided one direction for the calculation of an attack by the electrophile. This type of approach, along the axis connecting an atomic center with the potential minimum generated by bending of an X–H bond, will be referred to as the "tetrahedral approach". We also performed calculations in which the incipient electrophilic attack was simulated by placing the point charge directly above the

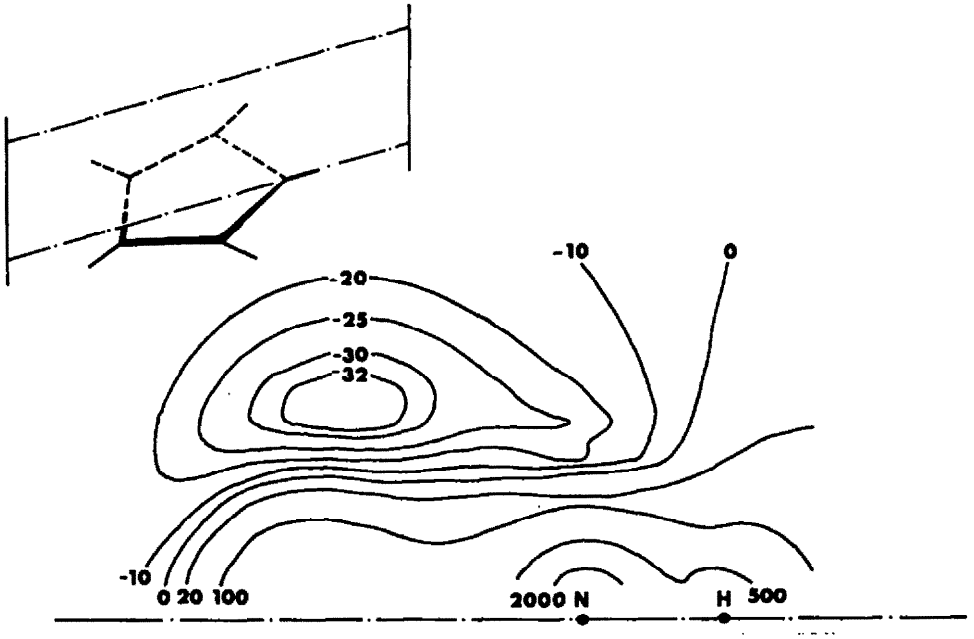


Fig. 1. Molecular electrostatic potential map for the planar pyrrole molecule in the symmetry plane perpendicular to the molecular plane (see insert). See text for details.

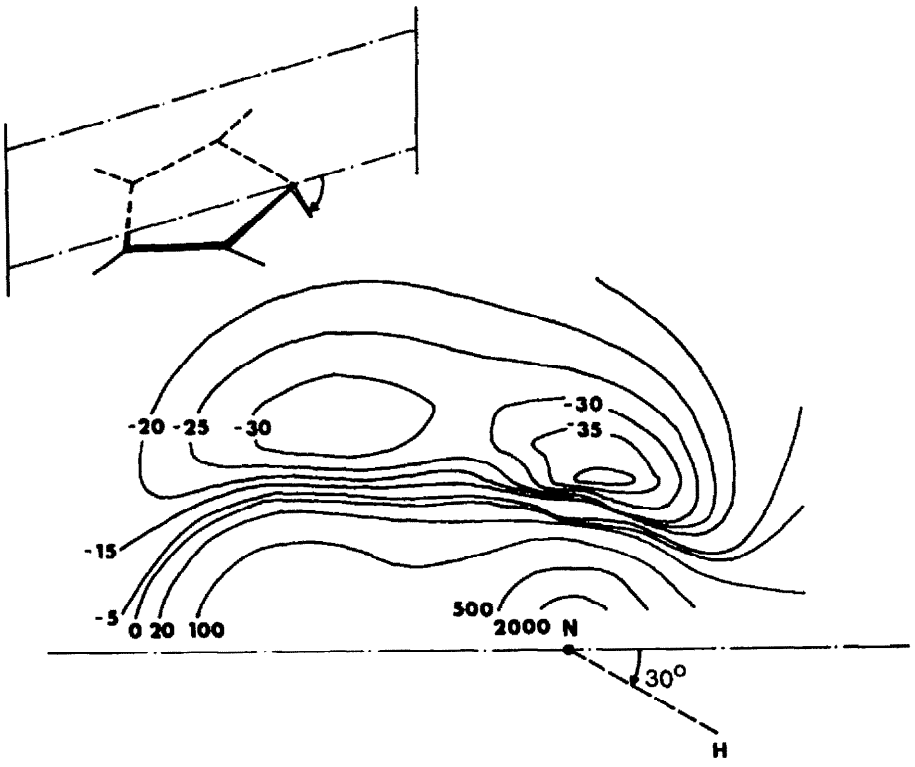


Fig. 2. Molecular electrostatic potential map for pyrrole with bent N–H bond. See insert and Fig. 1 for details.

atom, nitrogen say, at a distance of 2 Å. This direction will be referred to as the "perpendicular approach".

We have previously described a mechanism by which out-of-plane distortions, of both the N–H and the C–H bond at an attacked center are essential of the dynamics of protonation for these heterocycles.[7] Thus, local minima are generated above the α or β carbons when the corresponding C–H bond is bent out of the molecular plane, as shown in Fig. 3. In the case of C_α protonation, we showed[7] that the attacking proton moves in a fully attractive (negative) potential field around the heteroatom and the bent C–H bond, toward the minimum generated in a tetrahedral position at the α-carbon. For the *tetrahedral approach* to the carbons, the attacking point charge was therefore positioned 2 Å from the C atom along the axis connecting its center with the minimum generated in the electrostatic potential following out of plane bending. For comparison (see below) we also performed calculations with the *perpendicular approach* on the carbons with the C–H bond either kept planar or bent out of plane.

For furan, the interaction with the oxygen was calculated with the point charge placed in the molecular plane, at 2 Å from the heteroatom. This geometry was indicated by the position of the strong minimum in the electrostatic potential map of furan (Fig. 4). The attack was simulated along the bisector of the C–O–C angle. All attacks on carbon atoms in furan and tryptamine were calculated in the perpendicular approach.

In all cases discussed below, the redistribution of the electronic charge caused by the electrophilic attack was studied from density difference maps (ρ_{A-B}) in parallel planes. At 1 Å above the molecule, a region that is significant for reactivity, the ρ_{A-B} map describes mainly changes induced in the π-electron density. The corresponding changes in the σ-electron frame were examined in parallel planes at 0.25 Å above the molecule.

The redistribution of electronic density following an electrophilic attack

Figure 5 shows the changes that an electrophilic attack on the N atom induced in the electron density of pyrrole in a plane 1 Å above the molecule. A comparison of Fig. 5(a) and (b) indicates that the results are qualitatively identical whether the molecule is kept planar (a) or the N–H bond is bent 30° (b). For each case, the density distribution in the attacked molecule (with N–H planar or bent, respectively) is subtracted from the density of the corresponding isolated molecule. Consequently, the negative contours indicate the regions in which electronic density is accumulated following the electrophilic attack. The main characteristic of the charge redistribution following the attack is that more charge is accumulated on the α carbons than on the N atom itself. This result is fundamentally different from the charge redistribution observed after an attack on either C_α or C_β. Thus, Fig. 6 presents the density difference maps for electrophilic attacks on C_α and C_β (Fig. 6(a) and 6(b), respectively), showing that the charge accumulates on the attacked site rather than on neighboring centers. Figure 7 shows that identical results are obtained from the density difference maps of the bent species (i.e. bent N–H and C_α–H; bent N–H and C_β–H), interacting with the positive charge. This indicates that the characteristics of the electron density redistributions are independent of the geometry distortions that are considered to occur during interaction.[7] Rather, these redistributions are caused by electronic properties inherent to that particular molecular structure.

Results obtained from the simulation of an electrophilic attack on the O containing heterocycle, furan,

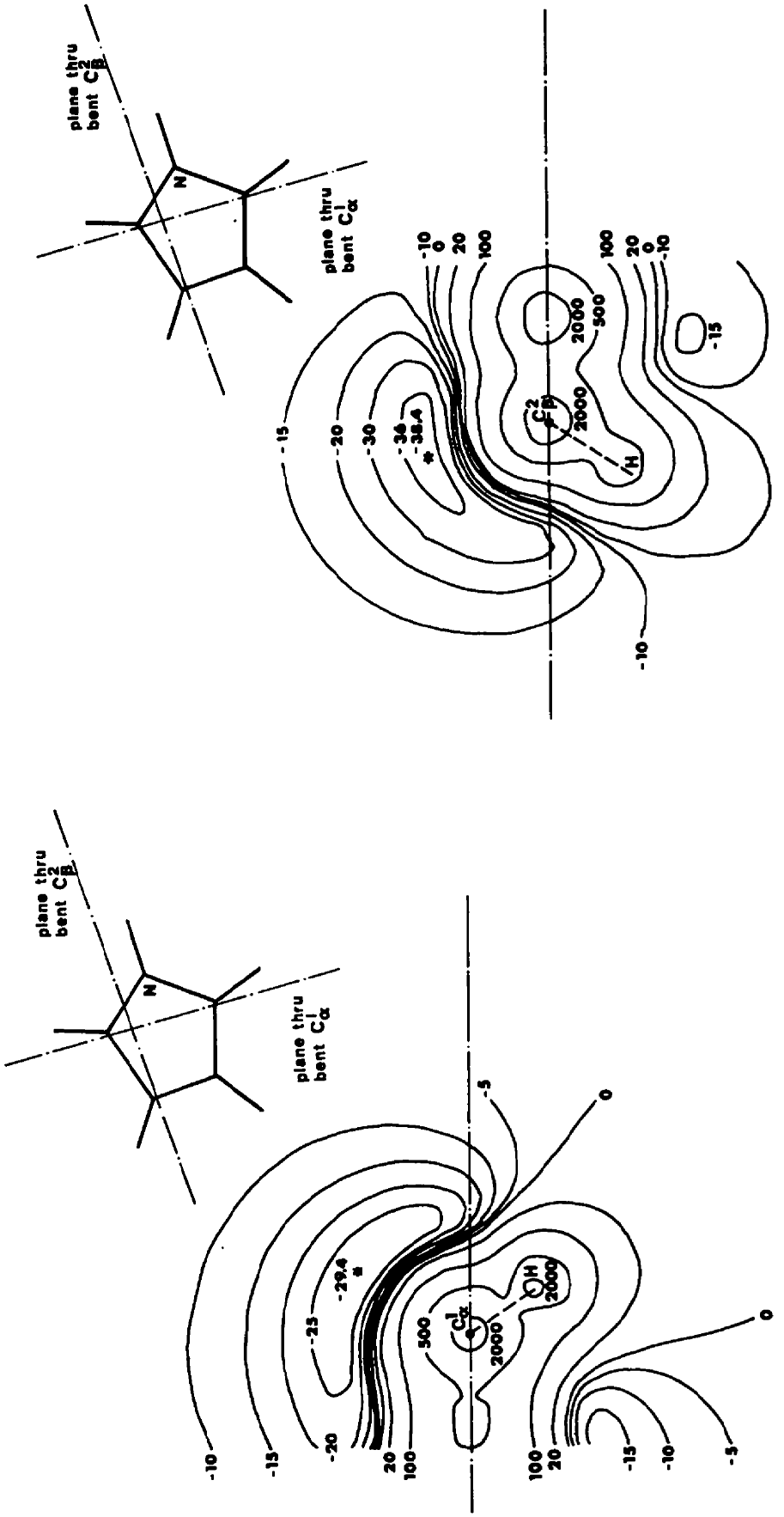


Fig. 3. Molecular electrostatic potentials in the region of the bent C_α–H bond: (a), and of the bent C_β–H bond: (b). Bending is 52° below molecular plane. Inserts indicate the position of the planes perpendicular to the molecular plane of pyrrole.

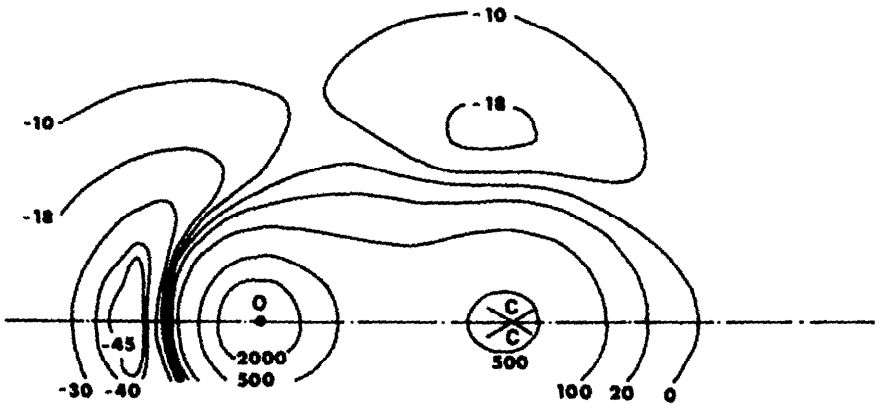


Fig. 4. Electrostatic potential map in the symmetry plane perpendicular to the molecular plane of furan. See Fig. 1 and text for details.

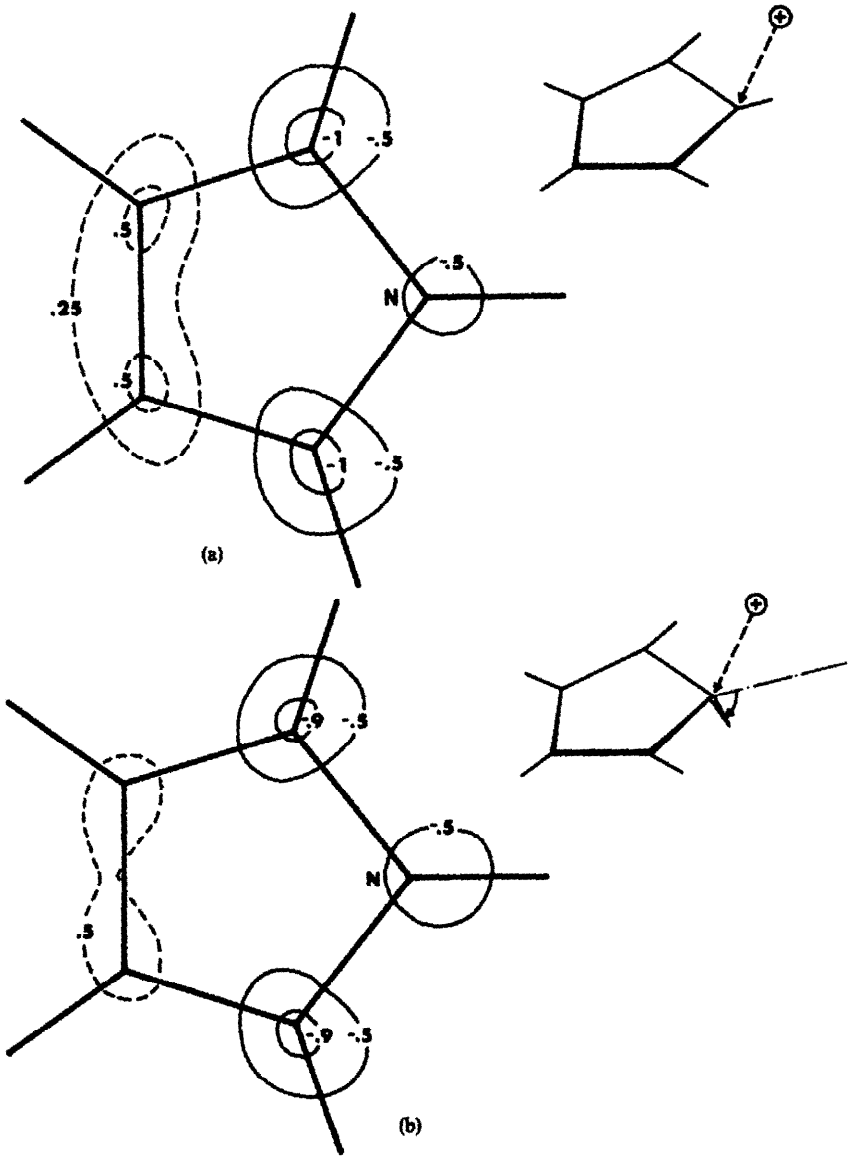
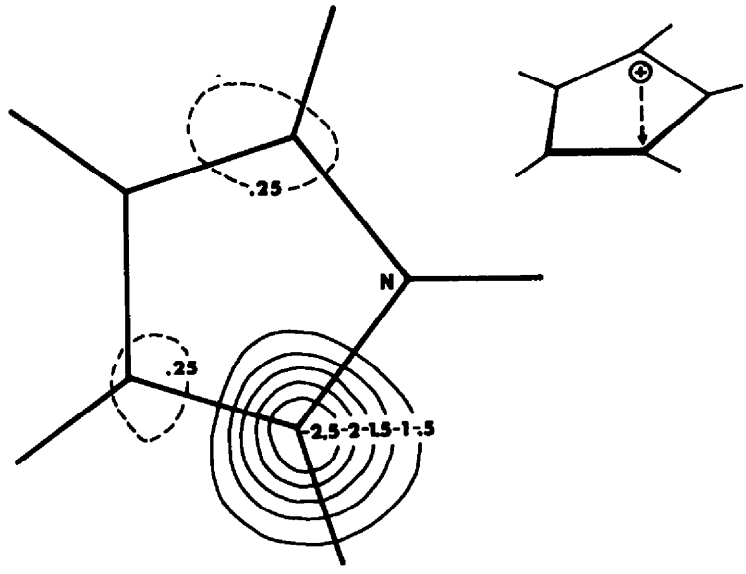
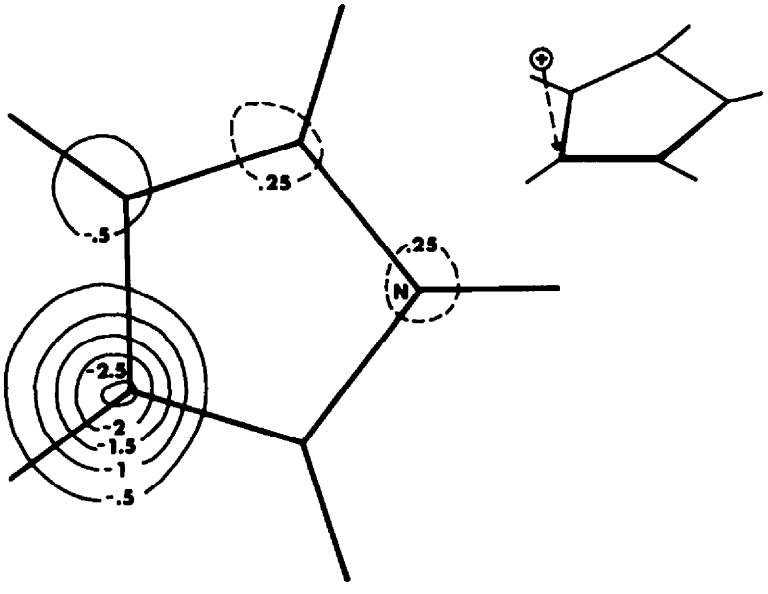


Fig. 5. Density difference map indicating the redistribution of the electron charge density in a parallel plane at 1 Å above the pyrrole molecule attacked by a positive point charge. The attack is at the nitrogen atom (see insert), in the tetrahedral approach (see text). In (a), the N–H bond is kept in the molecular plane; in (b) the N–H bond is bent 30° below the plane (see insert and text). Negative contours (solid lines) indicate regions in which density has accumulated following the attack (i.e., more density is placed there by the perturbed molecule than ty the ground state). Values indicate electron density in units of $n \times 10^{-3}$ electrons/a.u.^{3}.



(a)



(b)

Fig. 6. Electron density redistribution following attack on ring carbons in planar pyrrole. See inserts for position and Fig. 5 for details.

indicate that the behavior of the heteroatom here is qualitatively very different from that of the pyrrole N. Figure 8 shows that unlike the results in pyrrole, the electron density redistribution following an attack on the O in furan is much larger on the attacked center than on the α-carbons. Unlike the N, the O atom does not transfer the polarized charge to its neighbors. The redistribution caused by a similar attack on either C_α or C_β (Fig. 9) is very similar to the results shown in Figs. 6 and 7 for pyrrole, showing an accumulation of density mainly above the site of the interaction. The response of the ring carbons to the attack is identical in both heterocyclic compounds but the heteroatoms respond differently.

The changes in the density corresponding mainly to the redistribution of the σ-electrons following an attack on the heteroatoms is shown in Fig. 10. Here the similarity between the N and O containing molecules is much greater but the α-carbons still capture a greater share of the polarized charge in pyrrole than in furan. The electron charge is reduced on the β carbons in both cases.

Qualitatively identical charge redistributions are observed following electrophilic attacks on the N in a variety of structurally very different systems. For example, the mechanism of charge transduction by N has been observed[14] in the calculation of a reaction between NH_3 and HCl, where the N has been shown to act as a "dispatcher" of electronic charge that is polarized by the interaction and transferred from the amine hydrogens to the Cl atom. Similarly, our studies on indolealkylamines[19] indicated that an electrophilic attack on the indole N in tryptamine and 4-, 5-, 6- and 7-hydroxy-

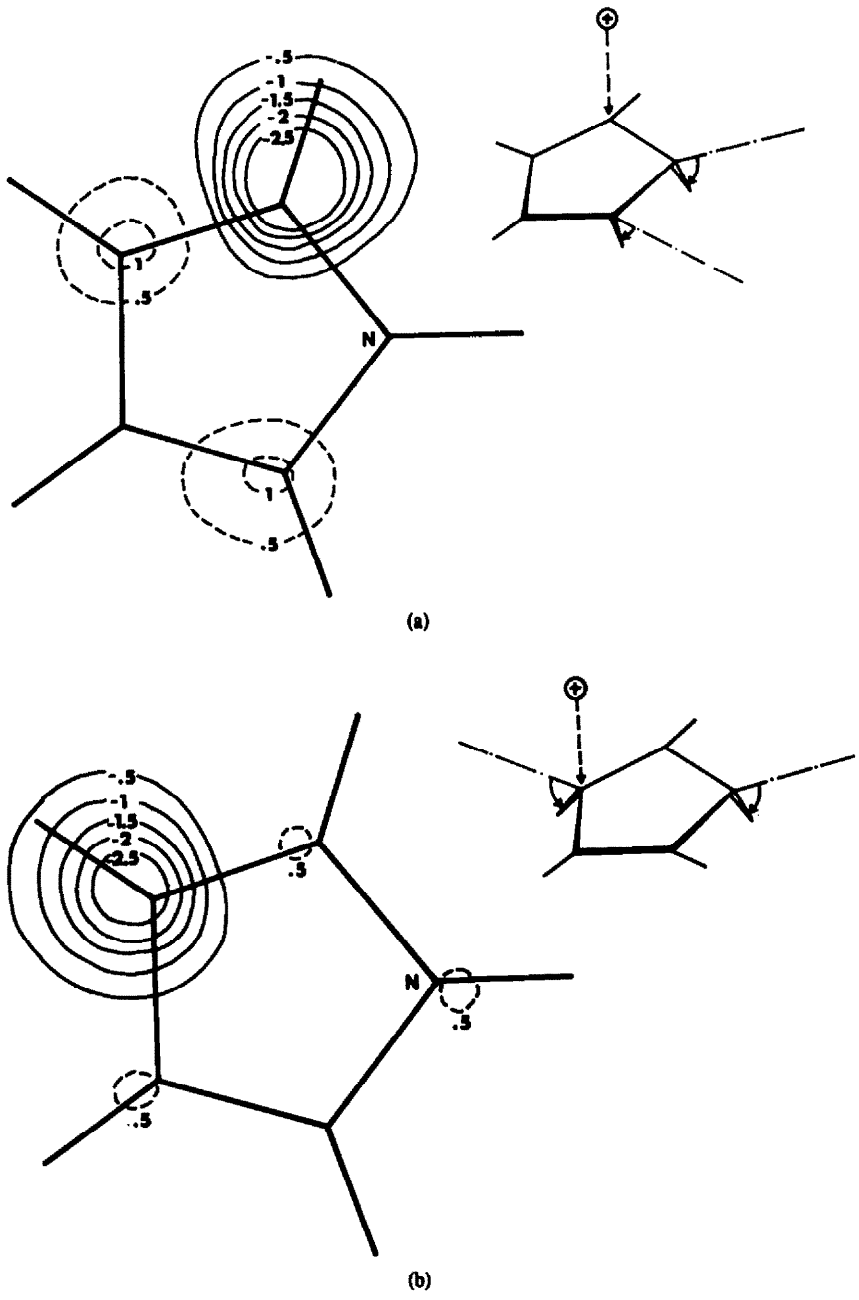


Fig. 7. Electron density redistribution following attack on ring carbons in pyrrole with: (a) bent N–H and C_α–H bonds; (b) bent N–H and C_β–H bonds. See inserts and Fig. 5 for details.

tryptamine will have the same effect of transducing electron density onto the α-carbons, as observed for pyrrole. For example, Fig. 11(a) shows that the characteristic increase in charge density around the α-carbons appears when tryptamine undergoes a perpendicular attack by a positively charged species placed above the indole N. The results of an attack on a ring C are the same as in pyrrole and in furan, showing an accumulation of charge mainly above the attacked center, in this case C2 (Fig. 11b).

Table 1 summarizes the findings for the *total* charge redistribution in terms of a Mulliken population analysis. In both pyrrole and tryptamine, the α-carbons show an increase in negative charge that is almost as large as that of the attacked heteroatom. This does not occur with furan. Attacks on carbons in any of the three molecules cause very little change in the electron charge assigned by the population analysis to the adjacent centers.

Since the attack of an electrophile was simulated here with a positive point charge, it was important to check whether charge transfer and polarization interactions between the attacked molecule and the reagent might change the qualitative picture. This was investigated in several test cases with the electrophile simulated by a positive hydrogen ion (H+) to which electronic charge could be transferred by the heterocyclic molecule during the attack, due to the inclusion of basis functions. An important drawback of such calculations is that the charge redistribution can no longer be analyzed separately for each reactant by the density difference maps

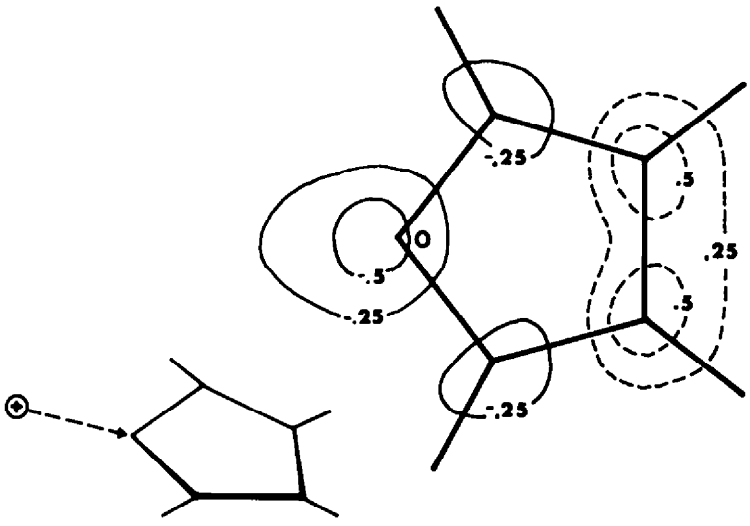


Fig. 8. Electron density redistribution following in-plane (see insert) attack on the oxygen atom in furan. See text for choice of position and Fig. 5 for details on contours.

described above. Such maps would now contain contributions from the electron density of both reactants. However, the Mulliken population analysis[10] provides an indication of the partitioning of the electronic charge. For pyrrole as a test case, such an analysis indicates that the charge transduction by the N remains operative: following an attack by H^+ on the N, the charge on each α-carbon is increased by 0.027e, while that on a β-carbon decreases by 0.044e, and the N loses 0.025e. The attacking proton gains 0.425e. Unlike the attack on the N, an attack on the α-carbon causes an increase in the charge on that atom (by 0.026e) and a decrease in the

Table 1. Mulliken population analysis of the charge redistribution[a]

Attack at[b]	Furan	Pyrrole	Tryptamine
hetero atom	8.407 (−0.121) O	N 7.475 (−0.090)	N 7.485 (−0.085)
	C_α^2 6.056 (−0.017)	C_α^2 6.173 (−0.063)	C2 6.165 (−0.082)
	C_α^1 6.056 (−0.017)	C_α^1 6.173 (−0.063)	C8 5.990 (−0.078)
$C_{\alpha,1}$ (or C2)	8.284 (0.002) O	7.403 (−0.018) N	7.421 (−0.021) N
	C_α^1 6.213 (−0.174)	C_α^1 6.283 (−0.173)	C2 6.266 (−0.183)
	C_β^1 6281 (−0.007)	C_β^1 6.274 (−0.012)	C3 6.073 (−0.007)
$C_{\beta,2}$ (or C8)	6.026 (0.013) C_α^2	6.101 (0.009) C_α^2	7.424 (−0.025) N
	C_β^2 6.432 (−0.158)	C_β^2 6.422 (−0.160)	C8 6.081 (−0.165)
	C_β^1 6.314 (−0.041)	C_β^1 6.303 (−0.041)	C7 6.267 (−0.045)

[a] Gross atomic charges are given for the attacked molecules. Values in parentheses are the net changes in the electronic charge on each center, with respect to the unperturbed ground state. Negative numbers indicate a net gain in electronic charge.

[b] All attacks are on the planar molecules.

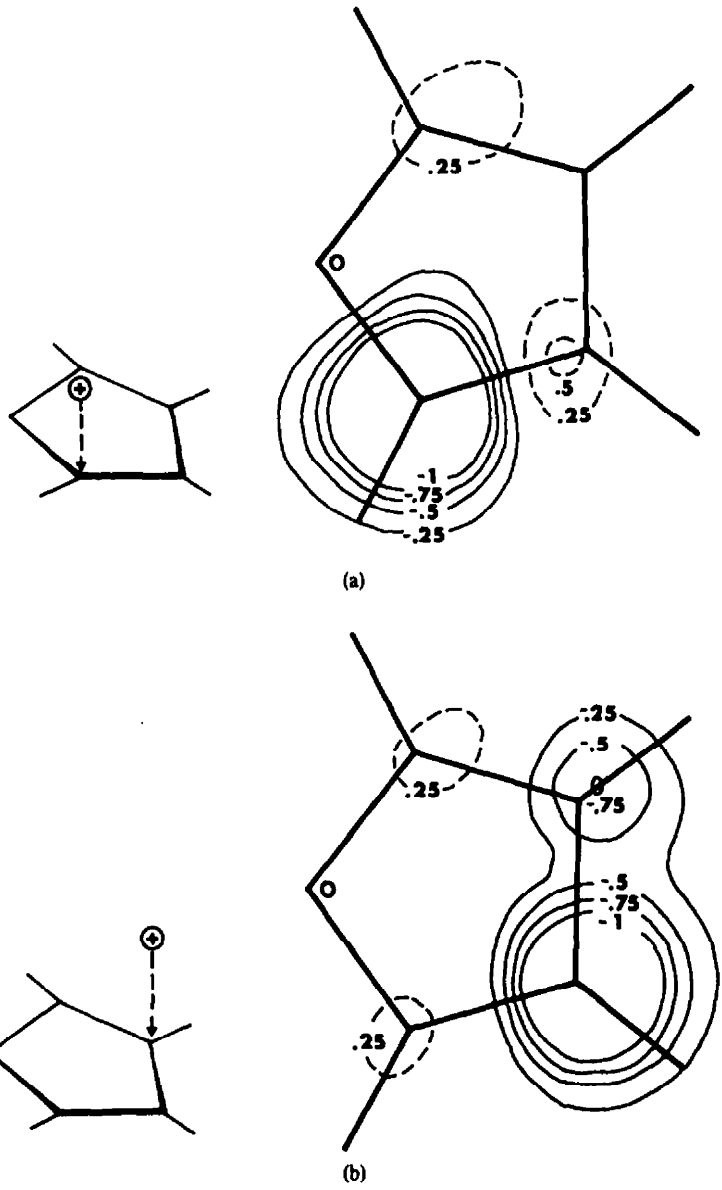


Fig. 9. Electron density redistribution following attacks in the perpendicular approach (see insert) on: (a) the C_α carbon, and (b) the C_β carbon in furan. See Fig. 5 for details on contours.

charge of the neighboring N and β-carbon (by 0.005e, and 0.071e, respectively). These results are in full agreement with the conclusions from Table 1, namely that an attack on the N causes charge to be transferred to the neighboring atom, while the attack on a C atom causes an accumulation of charge at the site of attack.

The charge redistribution observed here as a result of the incipient attack on the heteroatom (indicated by the electrostatic potential to be the most probable sites for an initial approach of a positive species) causes a change in the reactivity of the adjacent centers. In N containing heterocycles, this redistribution would cause the α-carbons to become much more nucleophilic than would be expected from their charge in the ground state; the β-carbons would become less proton attractive. Combined with the attractive electrostatic potential around the heteroatom (which also make α substitutions more probable in furan) the charge redistribution generates a new reactivity pattern for the molecules; it is induced by the interaction itself. Traditionally, however, mainly static indices were used to account for experimental findings and attempts to try to predict reactivity: such considerations include net atomic charges and frontier electron densities for the molecular ground state. Other types of reactivity considerations, such as the stabilization of the end product by polarization and charge transfer are also important for the determination of site selectivity (e.g. due to polarizability, the predominant product of an electrophilic attack on indole in the C3 rather than the C2 adduct[18]). Closer to a dynamical picture of reactivity are the energetical considerations related to charge separation in possible resonance structures of the product but these descriptions lack a satisfactory formalistic basis and a scheme for quantification which can serve for accurate comparisons of reactivity. Our results emphasize the need for a consideration of the dynamical components of the reactivity which reflect the changes occurring in the electronic structure of the reac-

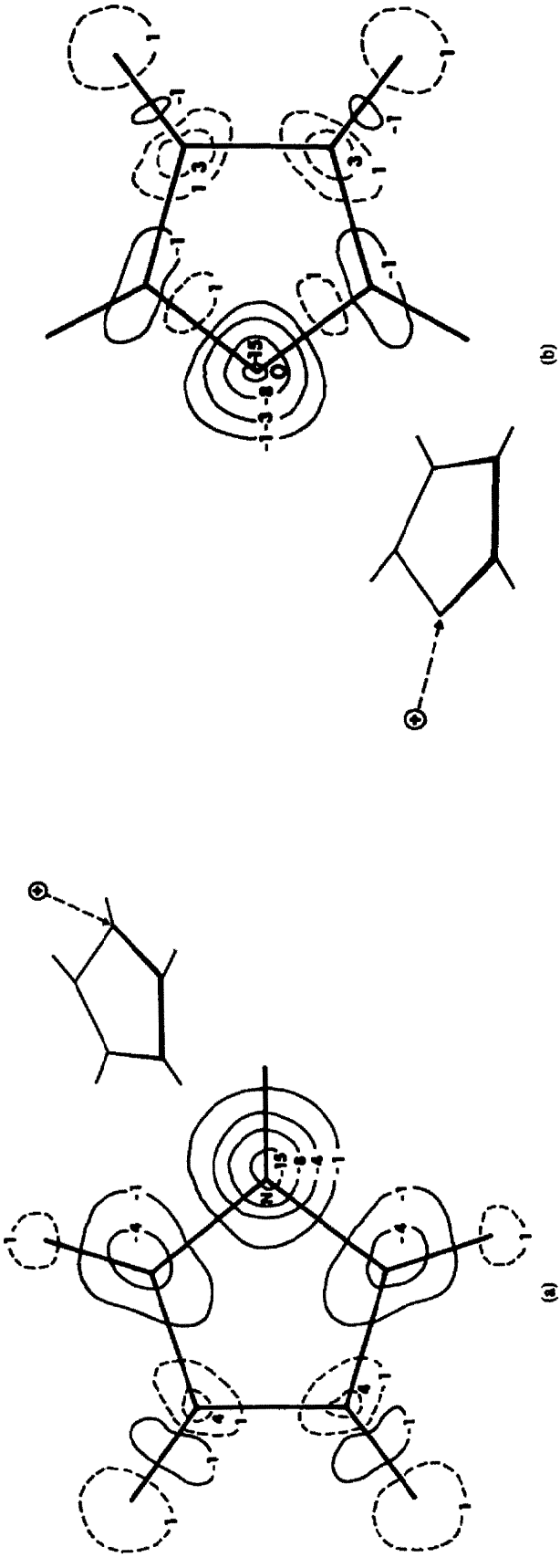
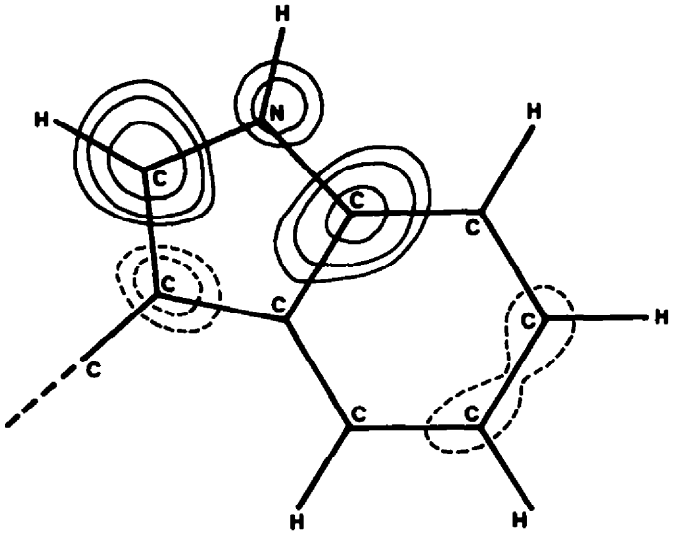
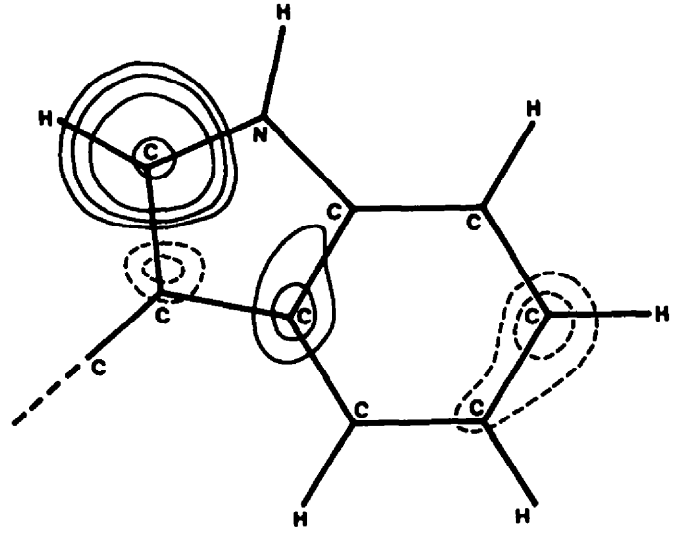


Fig. 10. Electron density redistribution in a parallel plane at 0.25 A above: (a) pyrrole, and (b) furan, following electrophilic attacks on the heteroatoms. Approaches are tetrahedral and in-plane, respectively.



(a)



(b)

Fig. 11. Electron density redistribution in a parallel plane at 1A above the indole portion of tryptamine following an electrophilic attack on: (a) the indole nitrogen, and (b) the C2 carbon. Approaches are perpendicular. See Fig. 5 for details on contour lines. Contour values are 1×10^{-3}, 0.5×10^{-3}, 0.3×10^{-3} electrons/a.u.^{3} respectively, starting with the innermost contour.

tants at each stage of an interaction. Clearly, static reactivity criteria should be applied to different atoms in different molecular structures only if the variation in their *response* to interaction is also considered.

Even more than in addition and substitution reactions in which the mode of stabilization of the final product is very important, the localized dynamical response of the molecule to interaction should strongly affect long range ring-ring interactions such as in molecular complexes involving large heterocyclic compounds. We are currently applying these dynamical reactivity criteria to the study of such interactions between heterocycles of biological importance.[16,19]

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