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The Electrostatic Molecular Potential for Imidazole, Pyrazole, Oxazole and Isoxazole

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The electrostatic molecular potentials arising from *ab initio* MO LCAO GTO SCF wavefunctions for some five membered heterocycles are used to make evident differences in reactivity of some sites (tertiary nitrogen, carbon atoms) towards electrophilic reagents. Results are in general accordance with experiment.

Introduction

The electrostatic potential arising from the charge distribution of a molecule calculated in the SCF approximation may be used to obtain an estimate of the chemical reactivity of specific positions of the molecule[1].

The definition of the electrostatic molecular potential $V(\boldsymbol{r})$ and some tentative applications may be found in Refs. [1–7]. In this paper we shall concern ourselves with the following five-membered heterocycles: imidazole, pyrazole, oxazole and isoxazole (see Table 1). The SCF wavefunctions here employed were calculated by one of the authors [8] via a gaussian basis set [9] roughly equivalent to a minimal STO. Some information on the influence of the basis on the $V(\boldsymbol{r})$ value may be found in Ref. [5]; such influence may be considered inessential to a qualitative discussion and the results here presented may be regarded as sufficiently representative of the exact molecular potentials.

Results and Discussion

The physical observable $V(\boldsymbol{r})$ is a function of the point in space and its interpretation depends on the value as well as on the neighbouring shape of the function itself. The most direct presentation is obtained by three-dimensional iso-

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[1] In particular, such an approach can be of some use in characterizing the approach channels of the two partners.

potential graphs or by maps in selected planes[2]. To save space, however, we present here the essential information as numerical indexes pertaining to the relevant atoms, although we are aware of the fact that such a description neglects a considerable portion of the information from the complete $V(\mathbf{r})$ function.

The discussion of the results is here partitioned in two sections, the first concerning the molecular plane and the second the regions above (and below) the ring.

Molecular Plane

In the molecular plane, regions of positive $V(\mathbf{r})$ values (repulsive for positively charged reagents) surround the entire molecule, except the areas near the O and —N= atoms. Each of these regions exhibits a minimum clearly related to each —N= or —O— atoms, even in isoxazole, where a unique negative region encloses both adjacent heteroatoms. The values of such minima are reported in Table 1.

In any case the N heteroatoms result clearly more reactive, with respect to positively charged reagents, than O atoms, in accordance with chemical evidence.

The relative depths of the minima found near the =N— atoms are in qualitative accordance with the general chemical behaviour of the present set of molecules.

Several types of reactions involving the =N— atoms in the neutral molecules can, in principle, be related to this first-order picture of the interaction energy with respect to an approaching positively charged reagent[3]. Among them, the most important are: the quaternization reactions, formation of coordination compounds and hydrogen-bridged associates, and electrophilic substitutions (in imidazole and pyrazole). For the last type of reaction a connection with the electrostatic potential around =N— is of course possible only in the cases where an electrophilic attack at the tertiary nitrogen is followed by a loss of the proton from the imino-group (S_E2' mechanism).

Unfortunately, only very few quantitative data concerning the chemical behaviour of these compounds are available. For the simplest reaction, protonation, quantitative thermodynamics data exist, but they are not supplemented by analogous kinetic information. Moreover, such data are given as acidic ionization constants (pK_a's). In order to compare the free energies of protonation in solution obtained from the pK values with the electrostatic interaction energy values, it is necessary to assume that the entropy variations and changes in solvation energy following the protonation are fairly constant along the series considered. Such assumptions do not seem to be completely unrealistic and consequently we may consider the order of pK_a values as reproducing the ordering of the related proton affinities (gas phase enthalpies). The correlation between the $V(\mathbf{r})$ minima and pK_a values is gratifying (pK_a values: I, 6.95 [10]; II, 2.48 [11]; III, 0.8 [12]; IV, −2.03 [12][4]).

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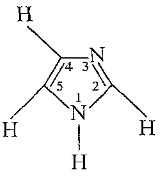
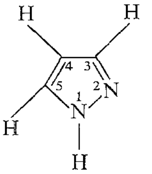
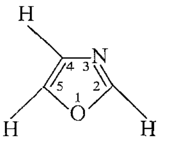
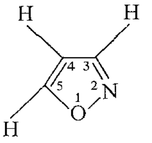
[2] Some of the maps are available upon request to the authors.

[3] Some of these reactions do not necessarily involve charged reagents: *mutatis mutandis* the picture is still valid at least for reagents exhibiting permanent dipole moments. As an example, see Ref. [6].

[4] A discussion about the reliability of these values is beyond the scope of this paper. We note, however, that an older value for isoxazole; +1.3 [13] is commonly quoted. The value given in Ref. [12] is, at least from an operative point of view, more comparable with the oxazole pK_a in the same reference.

Table 1. Values of the electrostatic molecular potential $V(r)$ in some characteristic regions

Molecule	Position	$V(r)$[a]
Imidazole 	C_2–H	−5.0
	C_4–H	−15.1
	C_5–H	−7.5
	N_1–H	0
	N_3	*−82.0*
Pyrazole 	C_3–H	−13.6
	C_4–H	−16.7
	C_5–H	−7.5
	N_1–H	−2.0
	N_2	*−74.0*
Oxazole 	C_2–H	+5.0
	C_4–H	−3.6
	C_5–H	+2.0
	O_1	*−31.2*
	N_3	*−68.4*
Isoxazole 	C_3–H	−1.8
	C_4–H	−2.8
	C_5–H	+2.0
	O_1	*−37.0*
	N_2	*−66.8*

[a] All $V(r)$ values are expressed in kcal/mole. The values in italic refer to ring plane points; the other to points 2 Å above the ring plane.

Quantitative comparisons for other reactions are not possible on account of the lack of pertinent experimental data. From a qualitative perusal on the whole set of experimental results (see, e. g. Refs. [14–18]), the reactivity of tertiary nitrogens in these molecules does not seem to be in conflict with the electrostatic potential indications.

Regions Outside the Ring Plane

It is convenient to point out that the path of the electrophilic reagent approaching the —N= atoms (as well as the O atoms) is not limited to the ring plane because the negative region spreads out above (and below) such a plane giving rise to a relatively large solid angle where the approach is electrostatically favoured. There is clear evidence that in these aromatic compounds only one minimum near the O atom (on the ring plane) occurs: note the difference from paraffinic heterocycles (e. g. oxirane and oxaziridine [2, 3]) where two minima near each O atom, corresponding to the two lone pair regions, have been found. The situation found in the present set of molecules is akin to that already found in Ref. [4] for the DNA bases (incidentally, we point out the strictly similar behaviour of $V(\boldsymbol{r})$ in imidazole and in the imidazole moiety of adenine). More interesting is the behaviour of $V(\boldsymbol{r})$ in the regions above the C—H groups. The electrostatic potential, repulsive in the proximity of the ring, becomes attractive at larger distances. Such a finding is in agreement with the fact that electrophilic reaction channels may reach the hydrocarbon portion of the molecule through its π region[5].

In order to underline differences in such a behaviour related to single C—H positions, we have chosen the value of $V(\boldsymbol{r})$ at about 2 Å above the C atoms (values reported in Table 1).

Such a presentation is not sufficient to give hints on the classical reaction paths available for charged reagents, but it is however sufficient for our comparative purposes.

It is convenient to consider separately, in first instance, the two imidazole – oxazole and pyrazole – isoxazole pairs, differing in the relative positions of the two heteroatoms. In the first couple attacks by electrophilic reagents are favoured in position 4. Positions 2 and 5 are nearly equivalent in oxazole but they show a little asymmetry (with position 5 favoured) in imidazole. The reaction channels in imidazole are deeper than in oxazole and a higher reactivity of the former with respect to the latter could be anticipated. In the second couple, position 4 is again favoured and some differences between positions 3 and 5 are evident (especially in pyrazole)[6]. Differences between homologous positions in pyrazole and isoxazole are manifest, and agree with chemical experience [16].

The comparisons between the two pairs of molecules are more difficult to substantiate with experimental data. The Friedel-Craft acylation however offers a hint: for this series of compounds one finds experimentally that such a reaction is possible only in position 4 of pyrazole in accordance with the greater depth of the minimum found above and beneath the C_4—H_4 bond in that molecule.

In conclusion, for neutral molecules the predictions from electrostatic potentials are in accordance with the experimentally known properties (ordering of pK_a values, higher reactivity of position 4) and they also indicate the two-nitrogen ring molecules (I and II) to be more reactive than the N—O heteroatomatics (III and IV). More general statements about reactivity should be made only after an analysis of the corresponding conjugate acids, BH^+, because many of the characteristic reactions in acidic media with electrophilic reagents seem to involve

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[5] The occurence of the negative regions and the differences among different sites might be considered as mainly due to π electrons; it is to be pointed out, however, that the best agreement with our $V(\boldsymbol{r})$ findings is obtained by using total net charges instead of π charges only. (For the population analysis of the wavefunctions here employed see Ref. [8].)

[6] It may be noted that the experimental reactivity properties, as estimated on the basis of reaction products, may sometimes be misleading in the case of both pyrazole and imidazole, because the rapid exchange of the iminic hydrogen between the two N's makes the molecule more symmetrical in a time-average basis.

the protonated species directly. Moreover it is evident that the molecule polarization induced by the approaching reagent plays an important role in determining reactivity properties. Such a polarization is not accounted for by the electrostatic picture which is a valuable one only in the first phases of the partners approach. We hope however that this type of information, although rather limited, may be of some use for interpreting chamical reactivity.

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