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Computational Study of Chemical Reactivity of Vinylpyrrole Derivatives

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The electrostatic potential V(**r**) and the average local ionization energy. $\bar{I}$(**r**) are discussed as a measure for the chemical reactivity of 2- and 3-vinylpyrrole and their 1-methyl-2- or 4-formyl derivatives. A survey of applications of DFT and *ab initio* SCF $\bar{I}$(**r**) computed on molecular surfaces defined by 0.001 au contour of the electronic density ρ(**r**) was presented as a tool of chemistry. The minima of both properties, $V_{S,\min}$ and $\bar{I}_{S,\min}$, were located and determined. Also, the energy gaps ($LUMO_{dienophiles}$-$HOMO_{pyrrol}$) were calculated, for three possible dienophiles and the pyrrole derivatives. AM1//HF/3-21G based wavefunction was generated to map both HOMO and LUMO of the derivatives to compare their relative sizes. The electronic calculations showed that the 2-formyl-1-methyl-4-vinylpyrrole, as a diene, is more reactive toward dienophiles than the 4-formyl-1-methyl-2-vinylpyrrole. The mapped orbitals indicated that a probable electrophilic attack would be HOMO based.

INTRODUCTION

A continuing approach of the computational studies, using both *ab initio* and local density functional theory DFT, is the interpretation and prediction of chemical reactivity[1–6]. Along this trend, both the average local ionization energy, $\bar{I}$(**r**) (known as Politzer I bar)[7] and the electrostatic potential V(**r**) were used effectively in the last few years. Chemical reactivity may depend not only on electronic considerations but also on the size and shape of reactants primarily in terms of the relative difference between the Frontier orbitals and their relative sizes or extensions.[8]

The reactivity of vinylpyrrole derivatives has attracted much of experimental concern.[9, 10] The reactivity of both 4-formyl-1-methyl-2-vinylpyrrole **(1)** and 2-formyl-1-methyl-4-vinylpyrrole **(2)**—as diene system toward dienophiles was studied in view of inductive and mesomeric effects.[11] IR and ^{1}H-NMR spectra indicated that 4-formyl-1-methyl-2-vinylpyrrole is of higher reactivity toward dienophiles than that of 2-formyl-1-methyl-4-vinylpyrrole. However, the analysis of [4π + 2] cycloaddition reaction of each of the two compounds with dimethylacetylene-dicarboxylate (DMAD) showed that the latter (2) is of higher reactivity than the former (1). In our current study we employ computational approaches to judge these contradicted findings and present a theoretical estimate of the subsequent reactivity of both structures.

Despite their obvious overall complexity, molecular orbital descriptions are useful in interpreting chemical reactivity. In this regard, energy gaps and relative sizes or extensions of the highest-occupied molecular orbital (HOMO) and lowest-unoccupied molecular orbital (LUMO) have been employed with some success such as the description of regioselectivity in Diels-Alder cycloadditions.[8] Generally, for the substituted vinylpyrroles, the reactivity increases with increasing π-donor ability of substituents on the diene, and with increasing π-acceptor ability of substituents on the dienophile. This may be rationalized using Frontier Molecular Orbital (FMO) theory where the important interaction is assumed to be between the HOMO on the diene and the LUMO on the dienophile. This stabilizing interaction increases with decreasing energy separation between the interacting orbitals. We should, therefore, be able to increase the overall rate of electrophilic substitution simply by raising the HOMO energy of the diene or by lowering the LUMO energy of the dienophile.

The average local ionization energy $\bar{I}(\mathbf{r})$ is defined within the framework of self-consistent-field molecular orbital (SCF-MO) theory by eqn. (1). It is interpreted as the average energy required to remove an electron from any point **r** in the space of a molecule.[7]

$$\bar{I}(\mathbf{r}) = \sum_i \frac{\rho_i(\mathbf{r})\,|\varepsilon_i|}{\rho(\mathbf{r})} \qquad (1)$$

$\rho_i(\mathbf{r})$ is the electronic density of the i-th molecular orbital at the point r, ε_i is the orbital energy of the i-th molecular orbital, and $\rho(\mathbf{r})$ is the total electronic density function. In the light of Koopmans' theorem[12], $\bar{I}(\mathbf{r})$ can be interpreted as the average energy required to remove an electron from any point **r** in the space of an atom or molecule. The positions at which the surface has its lowest values ($\bar{I}_{S,\min}$) are indicative of the least tightly bound electrons and consequently, the most reactive sites toward electrophiles.[13-15]

From the other side, the electrostatic potential V(**r**) is a real physical property that has been demonstrated to be a useful tool for gaining insight into the reactive properties of molecules in both electrophilic and nucleophilic processes.[16-18] The property can be determined experimentally as well as computationally to express the net electrical effect of the nuclei and electrons of a molecule. The value of V(**r**) is expressed rigorously by eqn. (2).

$$V(\mathbf{r}) = \sum_A \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')\,dr'}{|r' - r|} \qquad (2)$$

Z_A is the charge on nucleus A, located at R_A, and $\rho(\mathbf{r})$ is the electronic density function..The two terms on the right side of eqn. (2) represent the contributions of the nuclei and the electrons, respectively. The overall sign of V(**r**) in any particular region depends upon whether the effects of the nuclei or the electrons are dominant there. Thus an approaching electrophile will initially be attracted to the regions in which V(**r**) is negative, and in particular to the points where V(**r**) has its most negative values, V_{min}. However, the situation is not as straightforward for nucleophilic interactions due to the fact that V(**r**) maxima are found only at the positions of the nuclei. Therefore, to identify sites for a possible nucleophilic attack it is necessary to look for the most positive potentials in planes or on surfaces that are some distance away from the nuclei.[17]

Computational Procedures

GAUSSIAN 94[19] was used to compute optimized structures, wavefunctions and frequencies at the restricted Hartree-Fock and density functional B3P86 levels with the 6-31G** basis set for 2- and 3-vinylpyrrole, their derivatives (structures **1** and **2**) and three dienophiles (maleic anhydride, benzoquinone and DMAD). The resulting electronic densities were used to calculate $\bar{I}(\mathbf{r})$ and V(**r**) on the molecular surface *via* eqs. (1) and (2) respectively in accordance with Bader *et al.*[20] $\bar{I}(\mathbf{r})$ were calculated on molecular surfaces defined by 0.001 au contour of the electronic density.

In a parallel work, using PC Spartan[21] the structures were optimized using AM1 method followed by a single point RHF/3-21G calculations. The resulting wavefunctions were used to generate 3D pictures of electrostatic potential, HOMO and LUMO of each of the structures.

RESULTS AND DISCUSSION

Application of average local ionization energy, $\bar{I}(\mathbf{r})$

The calculated values of $\bar{I}_{S,min}$ at both DFT/B3P86 and *ab initio* SCF levels with 6-31G** basis set computed on molecular surfaces of specific atoms for both structures (**1**) and (**2**) is presented in Table-1.

TABLE-1
CALCULATED $\bar{I}_{S,min}$ (eV) FOR SPECIFIC SITES ON MOLECULAR SURFACES

Compound	HF/6-31G**	B3P86/6-31G**
4-formyl-1-methyl-2-vinylpyrrole	C_4: 11.17	C_{12}: 9.03
	C_{12}: 11.38	C_4: 9.19
	C_6: 11.48	C_6: 9.47
2-formyl-1-methyl-4-vinylpyrrole	C_{16}: 11.01	C_{16}: 8.47
	C_4: 11.39	C_2: 9.45
	C_6: 11.48	C_4: 9.48

The locations and magnitudes of the minima $\bar{I}(\mathbf{r})$ are found to be located near different carbons in each of the two structures. For 4-formyl-1-methyl-2-vinylpyrrole **(1)**, C_4 shows the highest affinity for an electrophile with average ionization energy of 11.17 eV followed by C_{12} and C_6. However, for 2-formyl-1-methyl-4-vinylpyrrole **(2)**, C_{16} shows the highest reactivity toward a coming electrophile with average ionization energy of 11.01 eV followed by C_4 and C_6 respectively. It should be obvious that structure **(2)** shows a higher overall reactivity toward the same electrophile since it possesses the least average ionization energy 11.01 eV which is smaller than that of structure **(1)** by around 0.16 eV or 3.69 kcal/mol. These findings support the relative reactivities of both compounds with dimethylacetylene-dicarboxylate.[11]

Applications of electrostatic potential $V(\mathbf{r})$

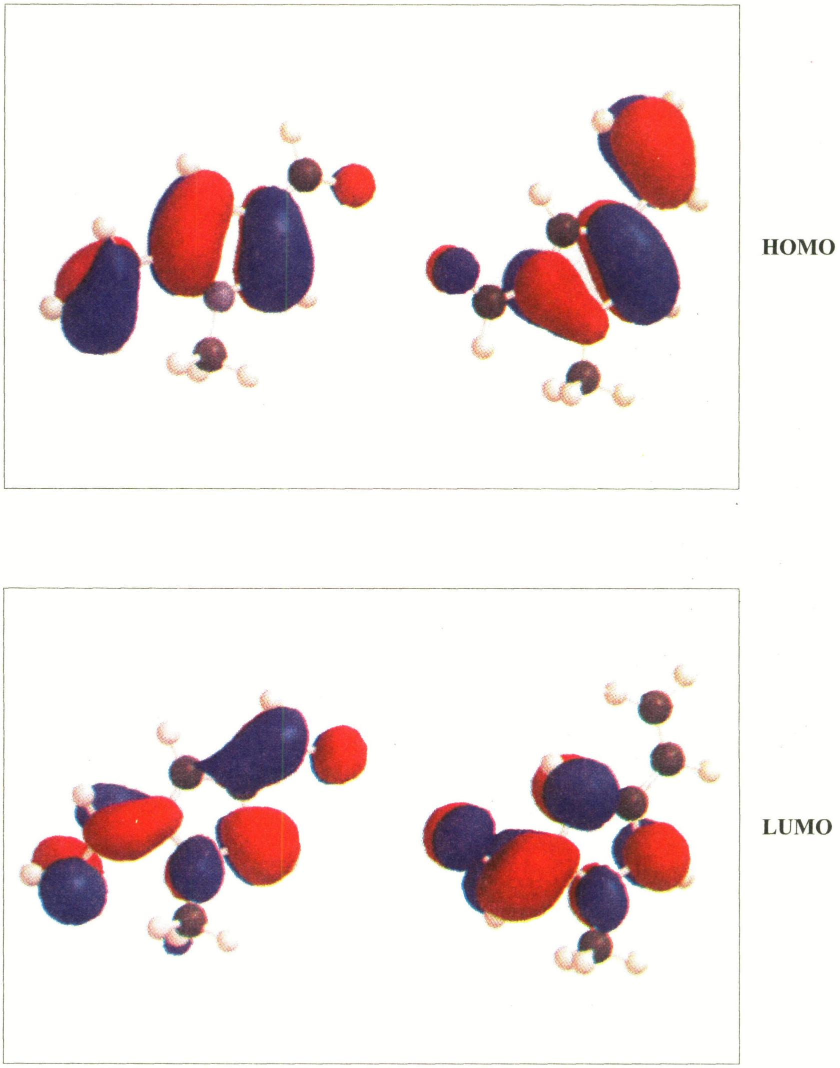
The surface electrostatic potentials of the 2- and 3-vinylpyrrole derivatives have negative regions associated with specific carbons as well as with the oxygens. Positive areas are associated with the hydrogens and other carbons. The distribution of carbons between the two groups is our main concern to investigate and relate to site-specific reactivity. Table-2 is a tabulation of the $V_{S,\,min}$ for both the two compounds. For, 4-formyl-1-methyl-2-vinylpyrrole, $V_{S,\,min}$ is located at the C_4 and C_8 with –18.41 and –14.45 kcal/mol respectively. Different characteristic negative potentials of varying magnitudes are found in the $V(\mathbf{r})$ of 2-formyl-1-methyl-4-vinylpyrrole with most negative potentials ($V_{S,\,min}$) of –19.48 and –19.47 kcal/mol for carbons 9 and 16 respectively followed by C_3 with –16.96 kcal/mol. The 0.01 kcal/mol difference between C_9 and C_{16} makes no dominance of either one. All these moderately negative regions associated with π regions are indicative of the decreasing order of site's attraction of an electrophile.

TABLE-2
CALCULATED $V_{S,\,min}$ (kcal/mol) FOR SPECIFIC SITES ON MOLECULAR SURFACES

Compound	HF/6-31G**	B3P86/6-31G**
4-formyl-1-methyl-2-vinylpyrrole	C_4: 18.41	C_8: – 13.88
	C_8: 14.45	
2-formyl-1-methyl-4-vinylpyrrole	C_9: 19.48	C_{16}: – 17.93
	C_{16}: 19.47	
	C_3: 16.96	

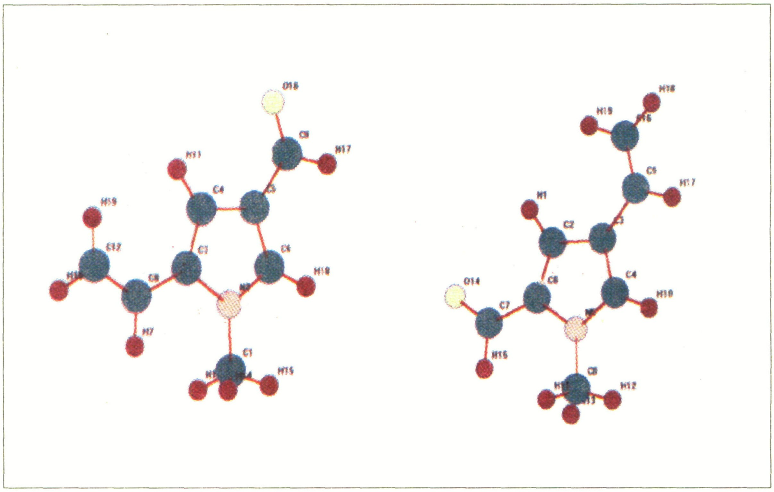
Applications of FMO energies and their relative extensions

A simultaneous display (Fig. 2) of the HOMO and LUMO for both structures **(1)** and **(2)** indicates not only where an electrophile might best attack, *i.e.*, where

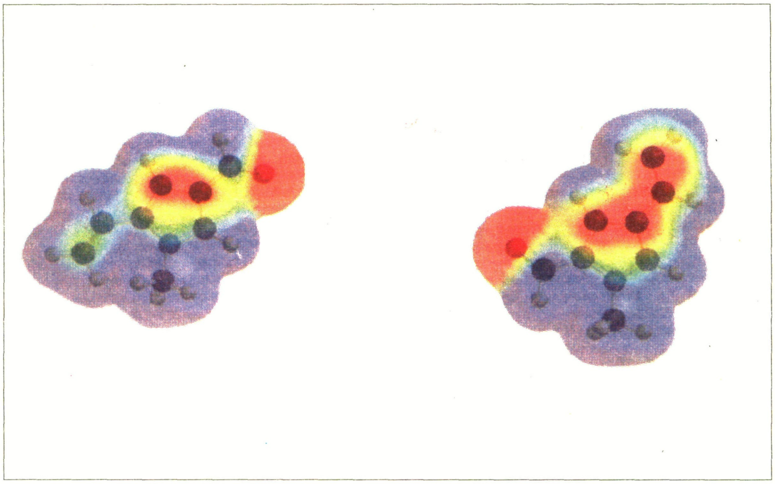


(1) (2)

Fig. 2. Relative sizes and extensions of FMO of 4-formyl-1-methyl-2-vinylpyrrole (1), and 2-formyl-1-methyl-4-vinylpyrrole (2).



(1) 4-formyl-1-methyl-2-vinylpyrrole. (2) 2-formyl-1-methyl-4-vinylpyrrole.



(1) (2)

Fig. 1. A map of calculated electrostatic potential on the molecular surfaces of 4-formyl-1-methyl-2-vinylpyrrole (1) and 2-formyl-1-methyl-4-vinylpyrrole (2). Red colour is associated with sites of most negative electrostatic potential (< −14.0 kcal).

the HOMO is more defused, but also where it would likely avoid, *i.e.*, areas of low electron density. Also, the calculated FMO energies for both the structures and three other dienophiles are listed in Table-3. The point of concern here, as we introduced, is the energy gap between the calculated orbital energies ($LUMO_{dienophile}$–$HOMO_{diene}$). It is obvious that the methyl and acetyl substituents increase the HOMO energy of diene by about 0.3 kcal/mol which would enhance the tendency of the diene for a coming electrophile. This tendency is expected to be supported by the bigger energy gap of about 0.12 kcal/mol that exists in case of 2-formyl-1-methyl-4-vinylpyrrole (**2**).

TABLE-3
ENERGY GAP (kcal) BETWEEN THE CALCULATED ORBITAL ENERGIES
$LUMO_{dienophile}$–$HOMO_{diene}$

Compounds	DMAD*	Maleic anhydride	Benzoquinone
2-Vinylpyrrole	8.86	7.18	9.48
4-Formyl-1-methyl-2-vinylpyrrole	9.17	7.49	9.79
3-Vinylpyrrole	8.98	7.30	9.60
2-Formyl-1-methyl-4-vinylpyrrole	9.29	7.60	9.91

*Dimethylacetylene-dicarboxylate

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