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# Theoretical Study of Reactivity of Some Pyrimidine Compounds with Hydrogen Atoms

*J. N. Herak*

*Institute »Ruđer Bošković«, Zagreb, Croatia, Yugoslavia*

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Presence of different reactions of various substituted pyrimidines with hydrogen atoms are interpreted in terms of indices of the molecular orbitals in the Hückel approximation. The free valence indices obtained by using $N_{\mathrm{max.}} = 1.732$ are in complete dissagreement with the observed reactions. Much better correlation is found if $N_{\mathrm{max.}}$ calculated according to the suggestion of Herak and Trinajstić is used. The lack of any reaction in 2-amino-4,6-dihydroxy pyrimidine, 4,6-dihydroxy pyrimidine and 5-methyl cytosine is explained by their high localization energies.

## INTRODUCTION

Recently, Herak and Gordy reported the ESR study of hydrogen addition and replacement reactions in some pyrimidine derivatives[1]. They were unable to explain why in some cases only radicals formed by a replacement reaction were observed, whereas in other cases predominantly, or only, radicals formed by hydrogen addition on unsubstituted carbon atoms were observed. This study makes an attempt to understand better the selective reactions observed in various pyrimidine compounds.

## METHODS

Generally, there are two different types of approach to the quantum mechanical interpretation of chemical reactivity: the dynamic (polarized) molecule approximation and the isolated molecule approximation[2,3]. In the dynamic molecule approximation, introduced by Wheland[4], localization energy is the index characterizing the ease of an atom to react. For reaction of atom r of a conjugated system with a radical-like particle, the localization energy is defined as the $\pi$-bonding energy required to isolate one electron at position r from the remainder of the $\pi$-network. Hence, it is a measure of the $\pi$-energy change between the conjugated molecule and the $\sigma$-complex intermediate in substitution or addition reactions. If no change in $\sigma$-bond energy in this transformation is assumed, a correlation between the calculated localization energies and the experimental reactivities is anticipated.

In the isolated molecule approximation, the tendency for reaction at different centers is determined by one of the indices defined in terms of the molecular orbital coefficients of the original molecule. For chemical reactivity with the radical-like particles free valence indices are utilized[2,3,5,6]. Free valence has been defined by Coulson as

$$F_r = N_{max.} - N_r$$

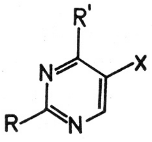
where $N_r$ is the sum of all bond orders for atom $r$, and $N_{max.}$ is its highest possible bonding capacity. Free valence represents a numerical measure of left-over $\pi$-bonding power, hence it is a modern version of Thiele's residual affinity. The higher the $F_r$-value the larger $\pi$-bonding left-over for bonding to an attacking atom. For a carbon atom in a trigonal hybrid, $N_{max.}$ is usually taken as 1.732[8], although different values have been proposed for primary, secondary and tertiary atoms[9]. Recently, Herak and Trinajstić[10] have pointed out that for a carbon atom neighbouring to some heteroatom, different values for $N_{max.}$ should be taken, depending on the heteroatom attached to the carbon in consideration.

It has been shown[2,5,6], that in alternant hydrocarbons both approximations are equally good. In non-alternant hydrocarbons and heterocyclic compounds the isolated molecule approximation should be used with precaution.

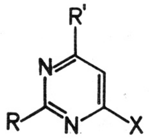
In this study the Hückel MO theory has been used. Parameters for heteroatoms are those from Pullman and Pullman[2]. The methyl group has been treated both in the heteroatom model and in the hyperconjugation model, with parameters recommended by Streitwieser[3].

## RESULTS

Herak and Gordy[1] experimentally observed two different types of reactions of pyrimidine compounds of general forms I or II with hydrogen atoms. All



I



II

examined compounds were uracil derivatives (R = R' = OH). X in I and II represents a substituted group. In some of the compounds only replacement of the substituted groups by hydrogen atoms take place. In another group of these compounds only addition of hydrogen atoms on the unsubstituted carbon atoms $C_{(5)}$ or $C_{(6)}$ is observed. There is also a group of the compounds where both kinds of these reactions take place. Finally, in a number of substituted pyrimidines neither reaction on $C_{(5)}$ and $C_{(6)}$ was observed[12].

The free valence indices for $C_{(5)}$ and $C_{(6)}$ atoms for all of these compounds are presented in Table I. The values listed in column I were calculated by using $N_{max.} = 1.732$. If the values for $N_{max.}$, calculated according to the suggestion of Herak and Trinajstić [10], are used (see Table II), the free valences listed in column II of Table I are obtained. All the compounds are considered to be in the lactim form except 5-nitro uracil, 5-acetyl uracil, 5-methyl uracil (thymine) and 6-methyl uracil. Actual tautomeric forms are not exactly known and sometimes are not even defined[13]. There are some indications, however, that for 5-nitro uracil, 5-methyl uracil, 5-acetyl uracil and 6-methyl uracil the lactam form might be predominant[13,14].

As judged from Table I, there is no correlation between the free valence indices calculated by using $N_{max.} = 1.732$ and the observed relative reactivities of $C_{(5)}$ and $C_{(6)}$ atoms. The free valences calculated on this basis are always

TABLE I

*Free Valence Indices for Various Pyrimidine Compounds**

| Compound | I | | II | | Observed reaction* |
|---|---|---|---|---|---|
| | On $C_{(5)}$ | On $C_{(6)}$ | On $C_{(5)}$ | On $C_{(6)}$ | |
| 5-Nitro uracil | 0.313 | 0.537 | 0.209 | 0.130 | Replacement |
| 6-Amino uracil | 0.467 | 0.104 | 0.149 | 0.048 | |
| Uracil 5-carboxylic acid | 0.183 | 0.429 | 0.183 | 0.093 | |
| Uracil 6-carboxylic acid | 0.451 | 0.175 | 0.133 | 0.165 | |
| 5-Amino uracil | 0.150 | 0.448 | 0.097 | 0.112 | Addition and Replacement |
| Uracil 5-sulfamic acid | 0.150 | 0.448 | 0.097 | 0.112 | |
| 5-Acetyl uracil | 0.234 | 0.462 | 0.234 | 0.064 | |
| 5-Methyl uracil | 0.326 | 0.445 | 0.192 | 0.058 | Addition |
| 6-Methyl uracil | 0.547 | 0.231 | 0.229 | 0.030 | |
| 4,6-Dihydroxy pyrimidine | 0.442 | 0.165 | 0.124 | 0.055 | None |
| 2-Amino 4,6-dihydroxy pyrimidine | 0.456 | 0.162 | 0.138 | 0.052 | |
| 5-Methyl cytosine | 0.254 | 0.415 | 0.111 | 0.080 | |

I $N_{max.} = 1.732$ is used
II For $N_{max.}$ values from Table II are used

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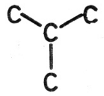
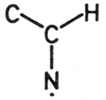
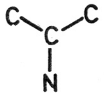
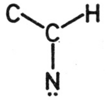
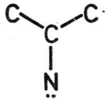
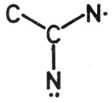
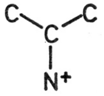
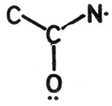
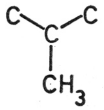
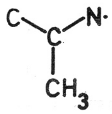
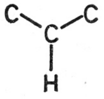
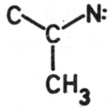
* Only $C_5$ and $C_6$ atoms are considered

larger for the unsubstituted carbon atom than for the substituted one. If the values from Table II are used, a fair correlation between the relative values of free valences and the observed reaction is found. For the compounds where only the replacement reaction is observed, free valences should be larger for the substituted carbon atom than for the unsubstituted one. As seen from column II of Table I, only 6-amino uracil deviates appreciably from that. For the second group of the compounds both values are expected to be about equal. Uracil 5-sulfamic acid and 5-amino uracil are in accord with the observed reactions; 5-acetyl uracil is not. From two methyl substituted compounds, satisfactory results are obtained for one. Of course, the indices for the last three compounds are meaningless for this consideration, since neither addition nor replacement reactions on $C_{(5)}$ or $C_{(6)}$ take place.

In order to elucidate why in some compounds neither of two reactions was observed, the localization energies for the unsubstituted places $C_{(5)}$ or $C_{(6)}$ were calculated. Localization energy as a measure of the potential barrier for an addition reaction is expected to be high for the compound where no such reaction is observed. It can be seen from Table III that the calculated localization energies correlate with the experimental findings; the highest values are found for the compounds which do not undergo any reaction on $C_{(5)}$ or $C_{(6)}$. According to Table I, these compounds have a larger or approximately equal free valence at the unsubstituted place than at the substituted one, thus the addition reaction, if any, is expected to take place for them. However, as judged from the relative values of the localization energies from Table III, from the compounds studied, 2-amino-2,4-dihydroxy pyrimidine, 4,6-dihydroxy pyrimidine and 5-methyl cytosine have the lowest probability for such reactions.

TABLE II

$N_{max.}$ *Values for the Central Atom of Various Hypothetical Models**

| Hypothetical model | $N_{max.}$ | Hypothetical model | $N_{max.}$ |
|---|---|---|---|
|  | 1.732 |  | 1.396 |
|  | 1.723 |  | 1.335 |
|  | 1.679 |  | 1.676 |
|  | 1.645 |  | 1.622 |
|  | 1.589 |  | 1.584 |
|  | 1.414 |  | 1.534 |

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* Calculated according to ref. 10.

TABLE III

*Localization Energies for the Unsubstituted Place* $C_{(5)}$ *or* $C_{(6)}$

| Compound | Localization Energy in β units |
|---|---|
| 5-Nitro uracil | 2.15 |
| 6-Amino uracil | 2.42 |
| Uracil 5-carboxylic acid | 2.40 |
| Uracil 6-carboxylic acid | 2.37 |
| 5-Methyl uracil | 2.23 |
| 6-Methyl uracil | 2.31 |
| 5-Amino uracil | 2.30 |
| Uracil 5-sulfamic acid | 2.30 |
| 5-Acetyl uracil | 2.30 |
| 2-Amino-4,6-dihydroxy pyrimidine | 2.42 |
| 4,6-Dihydroxy pyrimidine | 2.43 |
| 5-Methyl cytosine | 2.47 |

This is the explanation why no reaction on $C_{(5)}$ or $C_{(6)}$ for these compounds was observed.

## DISCUSSION

The results described above are obtained if the specified tautomeric forms of the compounds are considered. In some cases, the relative values of free valences or localization energies would be different if other forms were used. 5-Nitro uracil, for example, in the lactim form would have larger free valence for $C_{(6)}$ (0.142) than for $C_{(5)}$ (0.117). The localization energy of 2.50 $\beta$ for 5-acetyl uracil in the lactim form is obtained, which is much too high. General conclusions of this study, however, would not be much affected by assuming different forms from the ones that have been used.

Reactivities of the carbon atoms $C_{(5)}$ and $C_{(6)}$ are compared in their free valence indices. The comparison of localization energies between substituted and unsubstituted carbon atoms can not be done, because more than one electron would be isolated by fixation of a hydrogen atom at the substituted carbon. That concept, however, can be applied for the comparison of the unsubstituted places of many similar compounds, as done in Table III.

Despite the fact that agreement between the experimental results and the theoretical predictions is not complete, it is seen that, besides the localization energy concept, the free valence concept can be used for predicting the relative chemical reactivities of carbon atoms in heterocyclic compounds toward radicals. However, free valences ought to be calculated by taking into account neighbouring heteroatoms, as proposed by Herak and Trinajstić[10]. Better agreement between experiments and theoretical predictions than the one obtained is hardly to be expected if the Hückel molecular orbital theory is used.

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## IZVOD

## Teorijsko ispitivanje reaktivnosti nekih pirimidinskih spojeva prema vodikovim atomima

*J. N. Herak*

Zašto neki pirimidini reagiraju s vodikovim atomima na jedan način a neki na drugi, objašnjeno je pomoću elektronskih indeksa izračunatih u Hückelovoj aproksimaciji teorije molekularnih orbitala. Indeksi slobodne valencije dobro su mjerilo reaktivnosti ako se $N_{\mathrm{max.}}$ računa prema Heraku i Trinajstiću. Pokazano je da spojevi koji ne pokazuju nikakve reakcije s vodikovim atomima imaju visoke energije lokalizacije.

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