Oxazoles: Perturbations by methyl groups

B Rajeshwar Rao
Water Treatment Plant, C-Station
Kothagudem Thermal Power Station, Paloncha-507 115 (AP)

Received 19 April 1999; accepted (revised) 16 December 1999

The effect of methyl groups in oxazoles has been studied and the perturbations caused on the oxygen and nitrogen atoms have been rationalized. The Huckel Molecular Orbital (HMO) method has been used to evaluate the \( \pi \)-electron densities of all the molecules studied.

Oxazoles are known to possess pronounced medicinal and industrial applications. So, it was thought of interest to study methyl group perturbations of oxazole in the present investigation. The presence of a nitrogen atom in a heterocyclic ring produces marked perturbations of electron density in the \( \pi \)-system. The \( \pi \)-frame work contributes to the reactivity of the heterocyclic rings and suffers the greater change in charge distribution. The methyl group has a +I effect and contributes two electrons to the \( \pi \)-framework. This effect is likely to be manifested in the \( \pi \)-electron densities, and methyl groups do not influence the chemical shifts of adjacent protons to any significant extent, but they are reflected in the \( \pi \)-electron densities.

Computational details
The Huckel Molecular Orbital (HMO) method has been used to evaluate the electron densities at all positions in the molecules (1-8). These calculations were performed by developing a program in ‘C’ with a Intel PC (Pentium II).

Results and Discussion
The \( \pi \)-electron density at oxygen is considerably reduced and nitrogen is enhanced in all systems (Table 1). The charge withdrawn from the oxygen atom is redistributed over the whole ring. The nitrogen at the 3-position takes the greater part of the charge from oxygen. The electron density at all positions are greater than or equal to unity except at the C\( _2 \)-position of molecules (1, 2, 3, 5 and 7) and C\( _3 \)-position of compound 4. This result is consistent with the fact that C\( _2 \)-position possess the lowest electron density and usually the most susceptible to attack by nucleophiles. This conclusion finds support from experimental evidence, wherein it has been shown in the preparation of 2-amino-, 2-alkoxy-, and 2-hydrazino-oxazoles. Gompper and Ruhle experimental data made the relative ease of the attack of bromine on the oxazole ring is C\( _{2} \)-C\( _{5} \)>C\( _{4} \)-C\( _{5} \) and C\( _{4} \)-positions of oxazole (1) are more reactive toward electrophiles than at C\( _{2} \)-position. The \( \pi \)-electron density is enhanced at C\( _{2} \)-position by 0.0523 and 0.1864, when the methyl groups are present at C\( _{3} \)-position and C\( _{4} \)-C\( _{5} \)-positions of the respective molecules 4 and 6.

The electron densities on the atoms of oxazoles follow the electronegativity order O>N>C. But the \( \pi \)-polarization may infact be opposed to the \( \sigma \)-polarization in these systems. The order of increasing \( \pi \)-electron density in C\( _{5} \)-C\( _{4} \)-C\( _{5} \) is reflected in the chemical shifts of the protons at these positions. Brown and Ghosh reported that the proton at C\( _{4} \) is at higher fields (8 7.09 ppm) than the proton at C\( _{3} \) (8 7.69 ppm), which is at higher fields than the proton at C\( _{2} \) (8 7.95 ppm) in the oxazole (1). The chemical shifts of the oxazole ring protons and the ability of its \( \pi \)-system to transmit long-range coupling have been considered as aromatic.

In the compound 2, the electron density at methyl group is reduced from 2.0000 to 1.5397. The surplus charge is redistributed throughout the ring. The density at C\( _{2} \)-position is showing a significant increase from the expected value of unity. This conclusion finds support from the experimental evidence in the electrophilic attack at C\( _{4} \) or C\( _{5} \)-positions of oxazole ring, which is activated by the electron releasing substituents.

The presence of methyl groups at C\( _{2} \)-position as in
Table I—π-Electron densities for compounds 1-8

<table>
<thead>
<tr>
<th>Position</th>
<th>1 (O)</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1.6985</td>
<td>1.7885</td>
<td>1.7196</td>
<td>1.7706</td>
<td>1.8192</td>
<td>1.7733</td>
<td>1.8142</td>
<td>1.8197</td>
</tr>
<tr>
<td>2</td>
<td>0.9006</td>
<td>0.9451</td>
<td>0.9028</td>
<td>1.0523</td>
<td>0.9418</td>
<td>1.1864</td>
<td>0.9879</td>
<td>1.0152</td>
</tr>
<tr>
<td>3 (N)</td>
<td>1.2929</td>
<td>1.5011</td>
<td>1.3741</td>
<td>1.2906</td>
<td>1.5627</td>
<td>1.3996</td>
<td>1.5442</td>
<td>1.5650</td>
</tr>
<tr>
<td>4</td>
<td>1.0833</td>
<td>1.0792</td>
<td>1.0388</td>
<td>1.2966</td>
<td>1.0361</td>
<td>1.1666</td>
<td>1.3706</td>
<td>1.2259</td>
</tr>
<tr>
<td>5</td>
<td>1.0239</td>
<td>1.1464</td>
<td>1.2830</td>
<td>0.9963</td>
<td>1.4291</td>
<td>1.0979</td>
<td>1.0496</td>
<td>1.2365</td>
</tr>
<tr>
<td>6 (CH₃)</td>
<td>—</td>
<td>1.5397</td>
<td>—</td>
<td>—</td>
<td>1.5362</td>
<td>—</td>
<td>1.5852</td>
<td>1.5967</td>
</tr>
<tr>
<td>7 (CH₃)</td>
<td>—</td>
<td>—</td>
<td>1.6811</td>
<td>—</td>
<td>1.6748</td>
<td>1.7473</td>
<td>—</td>
<td>1.7853</td>
</tr>
<tr>
<td>8 (CH₃)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.5936</td>
<td>—</td>
<td>1.6289</td>
<td>1.6519</td>
</tr>
</tbody>
</table>

* Using the HMO Method⁴.

compound 2, and along with other at C₄, C₅-positions as in compounds 5, 7 and 8 result in a significant increase in the density from 0.501 to 0.565 electron at the nitrogen (3-position), and decrease the density at the oxygen (from 2.0000 to 1.7885 electron).

When the methyl group is present at C₄- or C₅-positions as in compounds 3, 4 and 6, there is a drastic reduction in the density at the oxygen atom. This effect is significant and can be ascribed as being due mainly to an inductive effect.

When oxygen atom contributes two electrons to the π-system of the oxazole ring, the perturbations caused on the oxygen atom arise as a result of contributions of structures such as =O⁺, which, while imparting aromacity to the molecules, result in a decrease in the π-electron density at the oxygen atom.

Thus, there is a significant exchange of electrons between the oxazole ring and attached methyl groups. The attached methyl group is independent of the ring and exerts a significant perturbation on the distribution of charge in the ring. The relative reactivity is highly dependent upon the position of electron releasing substituent in the oxazole.

Acknowledgement
I wish to thank Prof. M. Tajuddin, Department of Mathematics, Osmania University, Hyderabad, for an illuminating discussion and also thank Er. B Ravi Shankar, and Er. B Srikanth, Computer Centre, KTPS, Paloncha-507 115, for their help in developing the part of the computer programming.

References