Structure and Reactivity of Aryl-cyanohydrins

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Aryl-cyanohydrins, quantum calculations

The relation between structure and reactivity of some aryl-cyanohydrins is discussed. The CNDO/2 method has been applied and the various energy terms of the fundamental state as well as the charge change of the carbonyl C-atom have been quantitatively analysed. The limitation of the present approach is pointed out.

Introduction

The relation between structure and reactivity of cyanohydrins has been discussed from various points of view\textsuperscript{1-3} and the importance of several factors on the stability of these compounds has been pointed out. Among these factors we can mention the following: Degree of polarization of the $\text{C} = \text{O}$ bond in the corresponding aldehyde; influence of the $\pi$-electrons when the carbonyl C-atom is attached to an aromatic ring; influence of substituents in the aromatic ring; steric hindrance; pH of the medium; resonance interaction of certain groups, such as $p$-dimethylamino, etc.

In the present paper we describe the relative stability of a number of aryl-cyanohydrins (for which the equilibrium constants have been measured\textsuperscript{4}), applying Daudel's formulation of the Quantum Theory of the Chemical Reactivity\textsuperscript{5}. We employ the CNDO/2 method\textsuperscript{6} for the calculations and a quantitative examination is made of the various energy terms for the fundamental state in order to discuss their comparative importance. Naturally this approach involves a certain number of necessary approximations, mainly due to the impossibility of evaluating all the terms related to an equilibrium constant. We shall mention below the meaning of these approximations. We use the net charge as a reactivity index for the discussion of the results.

Equilibrium Constants

Let us consider the following equilibrium equation

$$G + H \rightleftharpoons I + J$$

We have the equality,

$$K = \frac{f_0 f_H}{f_I f_J} \exp \left(-\frac{\Delta E_a}{kT}\right)$$

where:

- $f_0$ is the partition function corresponding to the $P$ molecule,
- $\Delta E_a$ is the difference between ground state energies,
- $Z$ is the Boltzmann's constant,
- $T$ is the absolute temperature.

For a large molecule the ground state energy $\varepsilon_a$ may be divided into several parts:

a. The vibrational energy $\varepsilon_v$ corresponding to the zero point energy,

b. the energy $\varepsilon_l$ associated with the localized bonds and the atomic cores ($\sigma$-energy),

c. the energy $\varepsilon_d$ associated with the interaction of delocalized and localized bonds ($\pi$-energy),

d. the energy $\varepsilon_{nb}$ corresponding to the interaction between nonbonded atoms, including steric effects, and

e. the solvation energy $\varepsilon_s$ must be defined when the reaction takes place in a solvent.

Finally we have

$$K = \frac{f_0 f_H}{f_I f_J} \exp \left(-\frac{\Delta E_v + \Delta E_l + \Delta E_d + \Delta E_{nb} + \Delta E_s}{kT}\right)$$

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Method of Calculation and Approximations

The following equilibrium is described from a quantitatively point of view:

\[
\text{[HO-]} \quad \text{Ar-C(OH)(CN)H} \rightleftharpoons \text{Ar-COH} + \text{HCN} \quad K
\]

We have assumed two usual approximations in order to correlate \( K \) with the various energy terms:

1) \( \Delta \varepsilon_v = 0 \), and
2) \( \int_0^1 \int_1^2 = 1 \) (see for example ref. 5).

These approximations are chosen because of the impossibility to calculate, even roughly, the different terms for molecules like the ones considered here.

The other energy terms were calculated in the following way:

i) \( \Delta \varepsilon_1 + \Delta \varepsilon_d \) from the CNDO/2 method as a difference in total energies,

ii) \( \Delta \varepsilon_s \) was calculated from the formula (see ref. 8)

\[
\Delta \varepsilon_s = - \sum_i \frac{\mathcal{A}Q_i^2}{2\tau_i} \left( 1 - \frac{1}{D} \right)
\]

where the \( Q_i \)'s are the apparent charges of each atom; they were calculated from the density matrix given by the CNDO/2 method; \( \tau_i \) represents a certain empirical effective radius and the necessary values were taken from ref. 9. The dielectric constant \( D \) is the corresponding one to the used solvent.

iii) There are many different possibilities of evaluating \( \Delta \varepsilon_{nb}^{10-12} \), we have chosen a formula in our opinion of wide applicability, given by:

\[
\varepsilon_{nb} = - \frac{3}{2} \frac{\alpha \alpha'}{I + I'}
\]

where \( \alpha \) and \( \alpha' \) are the atomic polarizabilities, \( I \) and \( I' \) are the ionization atomic energies and \( r \) is the interatomic distance. The atomic polarizabilities were calculated from a simple variational procedure suggested by HYLLERAAS 13 and HASSE 14. The ionization energies were taken from ref. 6 and the mean interatomic distances from ref. 15.

Results and Discussion

The studied aryl-cyanohydrins and the obtained results are given in the following Table and Correlation Diagram.

<table>
<thead>
<tr>
<th>Molecule numbering</th>
<th>( K \cdot 10^2 )</th>
<th>( \Delta \varepsilon_v )</th>
<th>( \Delta \varepsilon_s )</th>
<th>( \Delta \varepsilon_{nb} )</th>
<th>( \Delta q_i )</th>
<th>( \Delta \varepsilon_{total} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>o-Nitro benz.</td>
<td>(1) 0.07</td>
<td>0.067</td>
<td>0.068</td>
<td>0.001</td>
<td>-0.2015</td>
<td>0.136</td>
</tr>
<tr>
<td>o-Chloro</td>
<td>(2) 0.10</td>
<td>0.050</td>
<td>0.039</td>
<td>0.002</td>
<td>-0.2045</td>
<td>0.091</td>
</tr>
<tr>
<td>m-Chloro</td>
<td>(3) 0.25</td>
<td>0.017</td>
<td>0.043</td>
<td>0.002</td>
<td>-0.2416</td>
<td>0.062</td>
</tr>
<tr>
<td>o-Methoxy</td>
<td>(4) 0.26</td>
<td>0.039</td>
<td>0.024</td>
<td>0.001</td>
<td>-0.2149</td>
<td>0.064</td>
</tr>
<tr>
<td>m-Nitro</td>
<td>(5) 0.27</td>
<td>0.057</td>
<td>0.044</td>
<td>0.002</td>
<td>-0.1680</td>
<td>0.065</td>
</tr>
<tr>
<td>m-Methoxy</td>
<td>(6) 0.43</td>
<td>0.053</td>
<td>0.064</td>
<td>0.002</td>
<td>-0.2154</td>
<td>0.119</td>
</tr>
<tr>
<td>H</td>
<td>(7) 0.47</td>
<td>0.009</td>
<td>0.077</td>
<td>0.002</td>
<td>-0.2345</td>
<td>0.066</td>
</tr>
<tr>
<td>m-Hydroxy</td>
<td>(8) 0.48</td>
<td>0.038</td>
<td>0.022</td>
<td>0.002</td>
<td>-0.2086</td>
<td>0.062</td>
</tr>
<tr>
<td>p-Chloro</td>
<td>(9) 0.49</td>
<td>0.037</td>
<td>0.047</td>
<td>0.002</td>
<td>-0.2171</td>
<td>0.086</td>
</tr>
<tr>
<td>m-Methyl</td>
<td>(10) 0.60</td>
<td>0.041</td>
<td>0.055</td>
<td>0.002</td>
<td>-0.2071</td>
<td>0.098</td>
</tr>
<tr>
<td>p-Methyl</td>
<td>(11) 1.03</td>
<td>0.046</td>
<td>0.054</td>
<td>0.002</td>
<td>-0.2107</td>
<td>0.106</td>
</tr>
<tr>
<td>o-Hydroxy</td>
<td>(12) 1.67</td>
<td>0.052</td>
<td>0.069</td>
<td>0.001</td>
<td>-0.2336</td>
<td>0.122</td>
</tr>
<tr>
<td>p-Nitro</td>
<td>(13) 1.31</td>
<td>0.045</td>
<td>0.045</td>
<td>0.002</td>
<td>-0.2261</td>
<td>0.092</td>
</tr>
<tr>
<td>2-Me-4 MeO</td>
<td>(14) 2.00</td>
<td>0.044</td>
<td>0.048</td>
<td>0.002</td>
<td>-0.2196</td>
<td>0.085</td>
</tr>
<tr>
<td>p-Methoxy</td>
<td>(15) 3.12</td>
<td>0.046</td>
<td>0.036</td>
<td>0.002</td>
<td>-0.2044</td>
<td>0.084</td>
</tr>
<tr>
<td>3-Me-4 MeO</td>
<td>(16) 3.82</td>
<td>0.044</td>
<td>0.033</td>
<td>0.002</td>
<td>-0.2123</td>
<td>0.099</td>
</tr>
<tr>
<td>p-Hydroxy</td>
<td>(17) 7.66</td>
<td>0.045</td>
<td>0.037</td>
<td>0.002</td>
<td>-0.2246</td>
<td>0.084</td>
</tr>
<tr>
<td>p-Di-Me- amino</td>
<td>(18) 39.00</td>
<td>0.041</td>
<td>0.003</td>
<td>0.002</td>
<td>-0.2186</td>
<td>0.040</td>
</tr>
</tbody>
</table>

* Difference between cyanohydrin and aldehyde plus HCN.
** Difference in negative net charge on the carbonilic C-atom between substituted benzaldehyde and benzaldehyde.
We have added a column with the carbonyl C-atom charge in the aldehydes and a column with differences in that charge with regard to the benzaldehyde one, because the reaction was studied in the presence of a basic catalytic medium. It is very important to compare the charge differences under these conditions, so we shall bear in mind this factor as well as the various energy terms in the following discussion about relative stabilities. We take the benzaldehyde and the corresponding cyanohydrin as a reference in our study. From the given values we see that, except the m-chloro benzaldehyde, the negative charge on the carbonilic C-atom of the substituted benzaldehydes is lower than the corresponding to the benzaldehyde (i.e. the positive relative charge is comparatively higher; see the sixth column) so this factor contributes positively for the cyanohydrin formation. The quantity \( K \) is the dissociation constant of the cyanohydrin into carbonyl compound and hydrocyanic acid; therefore the higher the value of \( K \), the less the extent of the synthetic reaction. We can see from the Table that the \( \Delta \varepsilon_{nb} \) term does not affect the results to a great extent and its contribution is practically constant.

A consideration of the data on the derivates of benzaldehyde indicates that the substitution of a nitro, chloro or methoxy group in the ortho position to the aldehyde group, increases the stability of the cyanohydrin as compared with benzaldehyde, while the substitution of a hydroxy group in the same position decreases that stability. It is in agreement with the consideration of the resonant structures (see ref.2–3). But for the same reasons it would be expected a greater positive charge difference on the carbonyl C-atom for acceptor substituents respect to the hydroxy one. This happens with the ortho-chloro and ortho-methoxy derivates but not with the ortho-nitro one, which has a low positive charge difference, anyway this is counterbalanced by the high \( \Delta \varepsilon_{\sigma} + \Delta \varepsilon_{\pi} + \Delta \varepsilon_{\sigma} \) corresponding to the ortho-nitro derivate. The para-dimethyl-amine benzaldehyde does not practically give cyanohydrin \((K = 39.0)\), although it has a marked positive charge difference on the carbonyl C-atom. Here there is not steric hindrance so this high \( K \) value may be originated from the resonant interaction between the amino group and the carbonyl group. The meta-chloro and meta-nitro groups increase the stability of the cyanohydrin in agreement with the greater positive charge difference on the carbonyl C-atom. The meta-methyl, meta-methoxy and meta-hydroxy groups have practically no influence on the \( K \) values respectively to the benzaldehyde one. The meta-methyl has a great positive charge difference and a slight energy \( \Delta \varepsilon_{\sigma} \); the meta-methoxy has a greater \( \Delta \varepsilon_{\pi} \) and an equal positive charge difference. The different influences are then compensated.

All the para substituents have a marked negative influence on the stability of the cyanohydrin, with the exception of the chloro substituent, and they all have a greater positive charge difference on the carbonyl C-atom. The influence of the para-chloro substituent may be explained by its low \( \Delta \varepsilon_{\sigma} + \Delta \varepsilon_{\pi} \) energy and its moderate \( \Delta \varepsilon_{\sigma} \) energy.

We can say, on the basis of the foregoing discussion, that all the above mentioned factors are important. The separate consideration of these factors does not lead to any valid conclusion, so we must take into account all the energy terms and the charge on the carbonyl C-atom to reach a good agreement between experimental and calculated results. We must bear in mind the fact that the calculation of \( \Delta \varepsilon_{\sigma} + \Delta \varepsilon_{\pi} \) is not accurate because it is a small quantity which follows from a difference between two large ones. In addition the molecular geometries we have taken are only approximated, because the experimental values are not very good ones for the
studied molecules. Finally, in order to point out
the limitation of the present type of correlations
we must take into account the fact that the applied
theory implicitly admits each chemical species is
represented by only one conformation, while the
real situation is a totally different one.

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