Theoretical Studies on the Gas-Phase Nucleophilic Aromatic Substitution Reaction

Ikchoon Lee*, Hyoung Yeon Park, and Bon-Su Lee

Department of Chemistry, Inha University, Incheon 402-751. Received July 18, 1991

The gas-phase nucleophilic substitution reaction of pentafluorobenzene with $\text{OH}^-$ and $\text{NH}_2^-$ nucleophiles have been studied theoretically using the AM1 method. Three reaction channels, $\text{S}_2$, IPPO and $\text{S}_\text{Ar}$ (scheme 1), are all very exothermic so that all are accessible despite the varying central energy barriers which are much lower than the reactants level. In the IPPO and $\text{S}_\text{Ar}$ channels, the reactants form directly a stable $\sigma$-anion complex which proceeds to form a proton transfer complex via a transition barrier corresponding to a loose $n$-type complex with the $\text{F}^-$ (or $\text{OCH}_2^-$) leaving group. Due to a greater number of probable reaction sites available for $\text{S}_\text{Ar}$ compared to the other two processes, the $\text{S}_\text{Ar}$ channel is favored as experimentally observed.

Introduction

Nucleophilic aromatic substitution reactions\(^2\)–\(^7\) have been studied extensively in solution.\(^8\) The reactions proceed via the addition-elimination pathway (the $\text{S}_\text{Ar}$ mechanism)\(^9\) and are normally rationalized by postulation of anion $\sigma$ complexes...
as intermediates. Recently gas-phase reactions between pentafluorobenzene, I, and a number of nucleophiles have been reported. As in the liquid phase, the reaction of the pentafluor-substituted aromatic compound, I, is shown to proceed mainly by the nucleophilic substitution on ring carbon atoms, either at the ipso carbon atom bearing the methoxy substituent (IPSO) or at the fluorine-substituted carbon atoms (SyAr); the reaction was actually found to proceed via three channels, including Sy2 substitution on the methyl group (Sy2), Scheme 1.

The gas-phase results for the SyAr process have been rationalized on the basis of the general reaction scheme, (Scheme 2), in which two types of loose ion-molecule complexes, RC and PC, and a σ-anion complex-often referred to as Jackson-Meisenheimer complex—are envisaged to involve between reactants and products. The very nature of the σ-anion complex, i.e., whether it is a stable intermediate or transition state (TS), was, however, indecisive.

In this work, we have investigated the mechanisms of the nucleophilic aromatic substitution in scheme 1 MO theoretically using the AM1 method. We are particularly interested in the nature of three complexes in Scheme 2.

**Calculation**

The semiempirical AM1-RHF method was used throughout in this work because of rather complex reacting systems involved. All geometries were fully optimized. Transition states were located by the reaction coordinate method refined by the gradient norm minimization, and characterized by confirming only one negative eigenvalue in the Hessian matrix.

**Results and Discussion**

Heats of formation of reactant, reactant complexes (RC) or intermediates, energy barriers corresponding to transition states (TS) and product complexes (PC) are presented together with barrier height (ΔH* ) in Tables 1 and 2 for the three reaction channels of the reactions with the two nucleophiles OH− and NH2−.

For the SyAr processes three different positions (ortho, meta and para) are considered. The structures of RC or intermediate, TS and PC are shown in Figures 1-3 for each reaction channels of the reaction with OH−. For the reactions with NH2−, the structures of the equilibrium point species are entirely similar to those in Figures 1-3 except that OH− is replaced by NH2−. We were unable to locate any stable species corresponding to the reactant complex for the two aromatic substitution channels, IPSO and SyAr. Instead we found a stable intermediate, i.e., a σ-anion complex, after which an energy barrier (TS) intervenes prior to PC formation as shown in Scheme 3 for the SyAr channel at para position. The energy barrier corresponds to departure of the leaving group, OCH3− and F−, respectively, and the PC is formed in a proton abstraction process by the leaving group, F−.

The energy profile for the reactions with OH− is shown in Figure 4. We note that all three channels proceed exothermically. Although the Sy2 channel has a typical double well type energy profile, the central energy barrier is very small due to the large exothermicity of the subsequent PC (and product) formation step. The barrier height for the SyAr channel is higher by ca. 30-40 kcal/mol than that for the IPSO channel, whereas it differs very little between different reaction site of the ring i.e., for ortho, meta and para position.

**Table 1.** Heats of Formation (ΔHf) of the Reactant, Reactant Complex or Intermediate, Central Barrier and Product Complex (PC), and Barrier Heights in kcal/mol for the OH− Nucleophile

<table>
<thead>
<tr>
<th></th>
<th>reactant RC or Int. central barrier</th>
<th>PC</th>
<th>barrier height</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sy2</td>
<td>-238.54 -260.12 -259.37 -344.82</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>IPSO</td>
<td>-238.54 -232.60 -294.49 -344.82</td>
<td>29.11</td>
<td></td>
</tr>
<tr>
<td>SyAr</td>
<td>ortho -238.54 -322.96 -258.09 -354.91</td>
<td>64.87</td>
<td></td>
</tr>
<tr>
<td></td>
<td>meta -238.54 -320.88 -257.70 -353.50</td>
<td>63.18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>para -238.54 -322.87 -258.56 -354.84</td>
<td>64.31</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2.** Heats of Formation (ΔHf) of the Reactant, Reactant Complex or Intermediate, Central Barrier and Product Complex (PC), and Barrier Heights in kcal/mol for the NH2− Nucleophile

<table>
<thead>
<tr>
<th></th>
<th>reactant RC or Int. central barrier</th>
<th>PC</th>
<th>barrier height</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sy2</td>
<td>-171.95 -188.58 -186.42 -292.12</td>
<td>2.16</td>
<td></td>
</tr>
<tr>
<td>IPSO</td>
<td>-171.95 -266.85 -250.60 -285.64</td>
<td>16.25</td>
<td></td>
</tr>
<tr>
<td>SyAr</td>
<td>ortho -171.95 -262.67 -204.87 -235.92</td>
<td>57.80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>meta -171.95 -261.42 -203.65 -204.52</td>
<td>57.77</td>
<td></td>
</tr>
<tr>
<td></td>
<td>para -171.95 -263.45 -204.34 -296.07</td>
<td>59.11</td>
<td></td>
</tr>
</tbody>
</table>
in $S_{2}Ar$ (Table 1).

The reactivity of the $S_{2}Ar$ channel appears to be lower relative to the IPSO based solely on the higher central energy barrier, which reflects a greater energy needed to break the C-F bond compared to the C-O bond in the elimination of the leaving group. The energy profile in Figure 4 suggests that the RC proposed for $S_{2}Ar$ by Nibbering et al. in Scheme 2 is not sufficiently stable enough to exist due to the large exothermicity of this reaction channel. Owing to a substantial exothermicity of the overall reaction and the fact that the central energy barriers for all channels are lower by more than 30 kcal/mol than the reactants levels, all three channels are accessible thermodynamically in the gas phase. Thus although the $S_{2}Ar$ path is unfavorable due to the higher energy barrier which is lower by ca. 30 kcal/mol than the reactants level, it can still compete with other two channels successfully since probability of the $S_{2}Ar$ attack is ten times greater than that of the other process. We therefore expect that the reaction should proceed mostly via the $S_{2}Ar$ channel as experimentally observed.

Mechanistically the aromatic substitution reaction is similar to the carbonyl addition reaction. The problem of whether the tetrahedral adduct is an energy maximum (TS) or a minimum (intermediate) can be settled by consideration of two factors: the difference in bond energies between a n-bond of the ring and a C-X single bond and the difference in gas-phase basicities for the two anions i.e., $HX^{-}$ and $\sigma$-anion complex. In the present case of the $S_{2}Ar$ and IPSO reaction channels, both of these factors favor formation of the tetrahedral intermediate; the C-F (or C-O) bond is strong enough to remain intact while the ring n-bond is disrupted and the large difference in gas-phase basicities of the two

Figure 1. The AM1 structures of the equilibrium point species for the $S_{2}2$ channel.

Figure 2. The AM1 structures of the equilibrium point species for the IPSO channel.

Figure 3. The AM1 structures of the equilibrium point species for the $S_{2}Ar$ channel.
anionic species also favor formation of the tetrahedral adduct, σ-complex intermediate.

The energetics in Table 1 and 2 for the two different nucleophiles show very little difference between the two, although the central barriers seem little lower for the IPSO and S$_n$Ar channels of NH$_2^-$. This is also in agreement with the gas phase experimental results.

Acknowledgement. We thank the Ministry of Education and Korea Science and Engineering Foundation for support of this work.

References

1. Determination of Reactivity by MO Theory. Part 77.