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Theoretical Studies on the Gas-Phase Nucleophilic Aromatic Substitution Reaction¹

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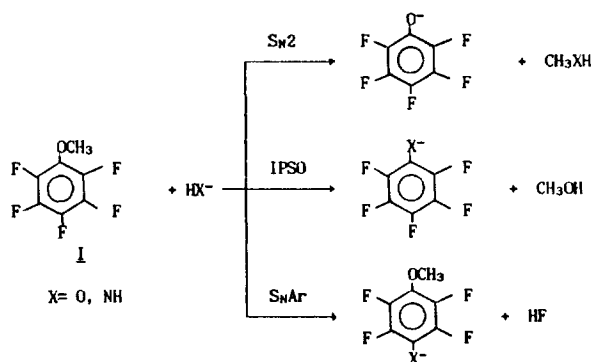
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The gas-phase nucleophilic substitution reaction of pentafluoroanisole with OH⁻ and NH₂⁻ nucleophiles have been studied theoretically using the AM1 method. Three reaction channels, S_N2, IPSO and S_NAr (scheme 1), are all very exothermic so that all are accessible despite the varying central energy barriers which are much lower than the reactants level. In the IPSO and S_NAr channels, the reactants form directly a stable σ-anion complex which proceeds to form a proton transfer complex *via* a transition barrier corresponding to a loose π-type complex with the F⁻ (or OCH₃⁻) leaving group. Due to a greater number of probable reaction sites available for S_NAr compared to the other two processes, the S_NAr channel is favored as experimentally observed.

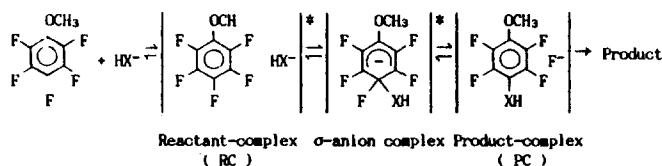
Introduction

Nucleophilic aromatic substitution reactions²⁻⁷ have been

studied extensively in solution.⁸ The reactions proceed via the addition-elimination pathway (the S_NAr mechanism)⁹ and are normally rationalized by postulation of anion σ complexes



Scheme 1



Scheme 2

as intermediates. Recently gas-phase reactions between pentafluoroanisole, I, and a number of nucleophiles have been reported.¹⁰ As in the liquid phase, the reaction of the pentafluoro-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 (S_NAr); the reaction was actually found to proceed *via* three channels, including S_N2 substitution on the methyl group (S_N2), Scheme 1.

The gas-phase results for the S_NAr process have been rationalized on the basis of the general reaction scheme, (Scheme 2), in which two types of loose ion-molecule complexes,^{11,12} RC and PC, and a σ -anion complex—often referred to as Jackson-Meisenheimer complex—are envisaged to involve between reactants and products.⁹ The very nature of the σ -anion complex, *i.e.*, whether it is a stable intermediate^{13, 14} 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.¹⁵ We are particularly interested in the nature of three complexes in Scheme 2.

Calculation

The semiempirical AM1-RHF method¹⁵ 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,^{16,17} refined by the gradient norm minimization, and characterized by confirming only one negative eigenvalue in the Hessian matrix.¹⁸

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 toge-

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

	ΔH_f				
	reactant	RC or Int.	central barrier	PC	barrier height
S_N2	-238.54	-260.12	-259.37	-344.82	0.75
IPSO	-238.54	-232.60	-294.49	-344.82	29.11
S_NAr					
ortho	-238.54	-322.96	-258.09	-354.91	64.87
meta	-238.54	-320.88	-257.70	-353.50	63.18
para	-238.54	-322.87	-258.56	-354.84	64.31

Table 2. Heats of Formation (ΔH_f) of the Reactant, Reactant Complex or Intermediate, Central Barrier and Product Complex (PC), and Barrier Heights in kcal/mol for the NH_2^- Nucleophile

	ΔH_f				
	reactant	RC or Int.	central barrier	PC	barrier height
S_N2	-171.95	-188.58	-186.42	-292.12	2.16
IPSO	-171.95	-266.85	-250.60	-285.64	16.25
S_NAr					
ortho	-171.95	-262.67	-204.87	-295.92	57.80
meta	-171.95	-261.42	-203.65	-294.52	57.77
para	-171.95	-263.45	-204.34	-296.07	59.11

ther with barrier height (ΔH^\ddagger) in Tables 1 and 2 for the three reaction channels of the reactions with the two nucleophiles OH^- and NH_2^- .

For the S_NAr 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 NH_2^- , the structures of the equilibrium point species are entirely similar to those in Figures 1-3 except that OH^- is replaced by NH_2^- . We were unable to locate any stable species corresponding to the reactant complex for the two aromatic substitution channels, IPSO and S_NAr . 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 S_NAr channel at para position. The energy barrier corresponds to departure of the leaving group, OCH_3^- 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 S_N2 channel has a typical double well type energy profile,¹⁹ 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 S_NAr 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

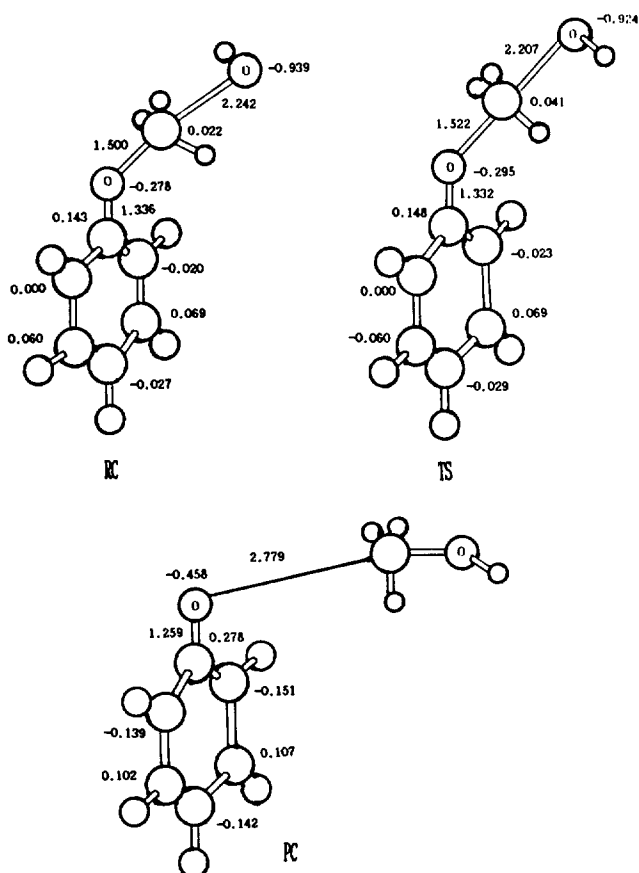


Figure 1. The AM1 structures of the equilibrium point species for the S_N2 channel.

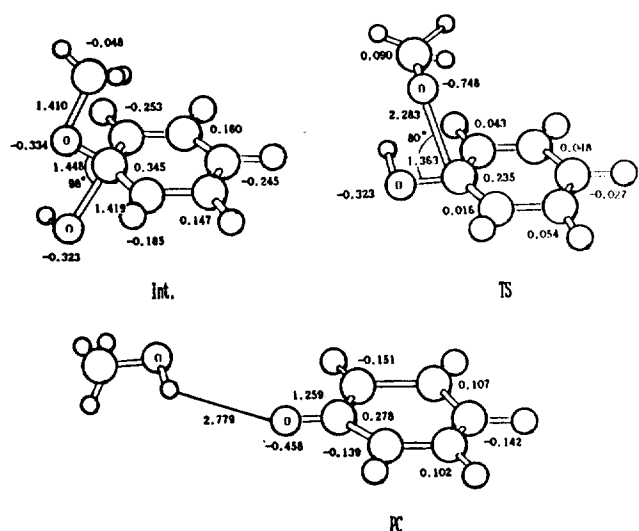


Figure 2. The AM1 structures of the equilibrium point species for the IPSO channel.

in S_NAr (Table 1).

The reactivity of the S_NAr channel appears to be lower relative to the IPSO based solely on the higher central energy barrier,²⁰ 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.²¹ The energy profile in Figure 4 suggests that the RC proposed for S_NAr by Nibbering *et*

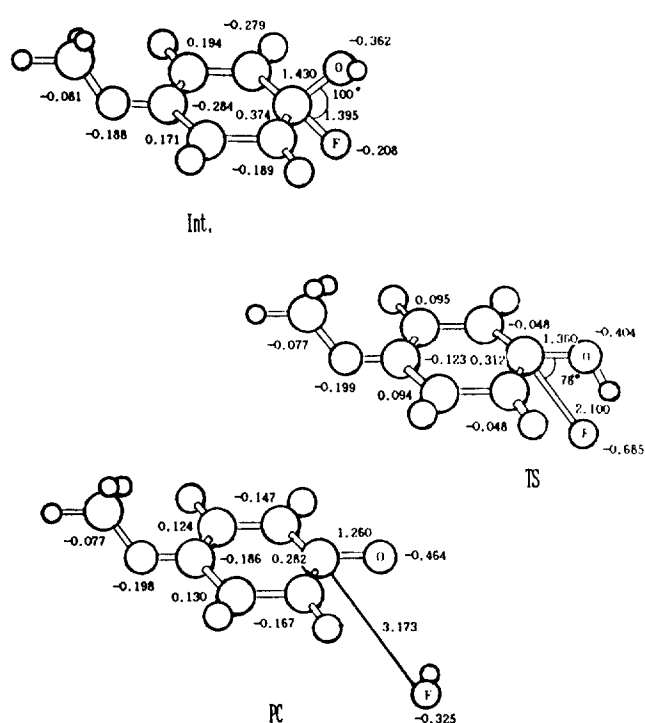
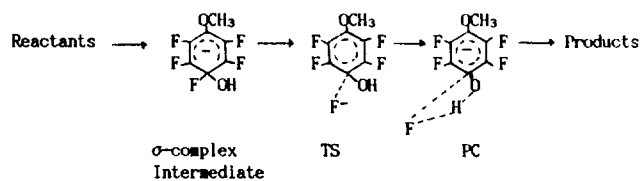


Figure 3. The AM1 structures of the equilibrium point species for the S_NAr channel.



Scheme 3

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_NAr 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_NAr attack is ten times greater than that of the other process. We therefore expect that the reaction should proceed mostly via the S_NAr 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)^{13,14} can be settled by consideration of two factors: the difference in bond energies between a π -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 σ -anion complex. In the present case of the S_NAr 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 π -bond is disrupted and the large difference in gas-phase basicities of the two

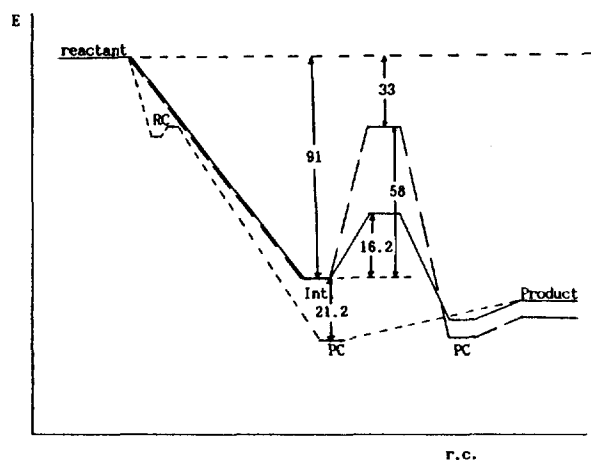


Figure 4. Energy profile for the reactions of pentafluoro-anisole with OH^- . (—: IPSO; ---: $\text{S}_{\text{N}}\text{Ar}$;: $\text{S}_{\text{N}}2$ channel).

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 $\text{S}_{\text{N}}\text{Ar}$ channels of NH_2^- . This is also in agreement with the gas phase experimental results.

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