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Theoretical Studies on the Gas-Phase Nucleophilic Aromatic Substitution Reaction[1]

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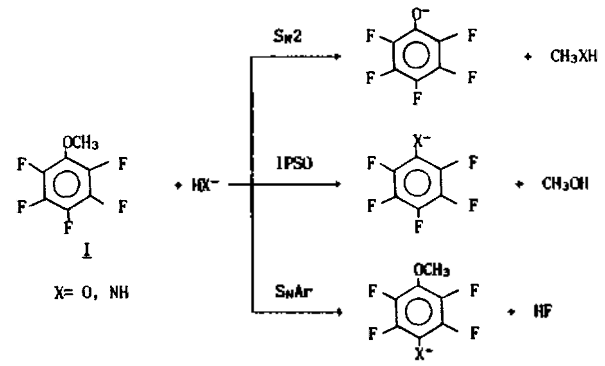
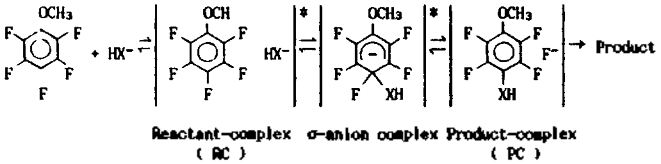
The gas-phase nucleophilic substitution reaction of pentafluoroanisole with OH^- and NH_2^- nucleophiles have been studied theoretically using the AM1 method. Three reaction channels, S_N2, IPSO and S_NAr (scheme 1), are all very exothermic so that all are accessible despite the varying central energy 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 OCH_3^-) 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 reactions[2-7] 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 compond, **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 complexs,[11,12] RC and PC, and a σ-anion complex-often referred to as Jackson-Meisenheimer complex-are envisaged to involove 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 particulary interested in the nature of three complexs in Scheme 2.

Calculation

The semiempirical AM1-RHF method[15] was used throughout in this work because of rather complex reacting systems involved. All grometries 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 together with barrier height ($\Delta H^{\neq}$) in Tables 1 and 2 for the three reaction channels of the reactions with the two nucleophies OH^- and NH_2^-.

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

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 reraction 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

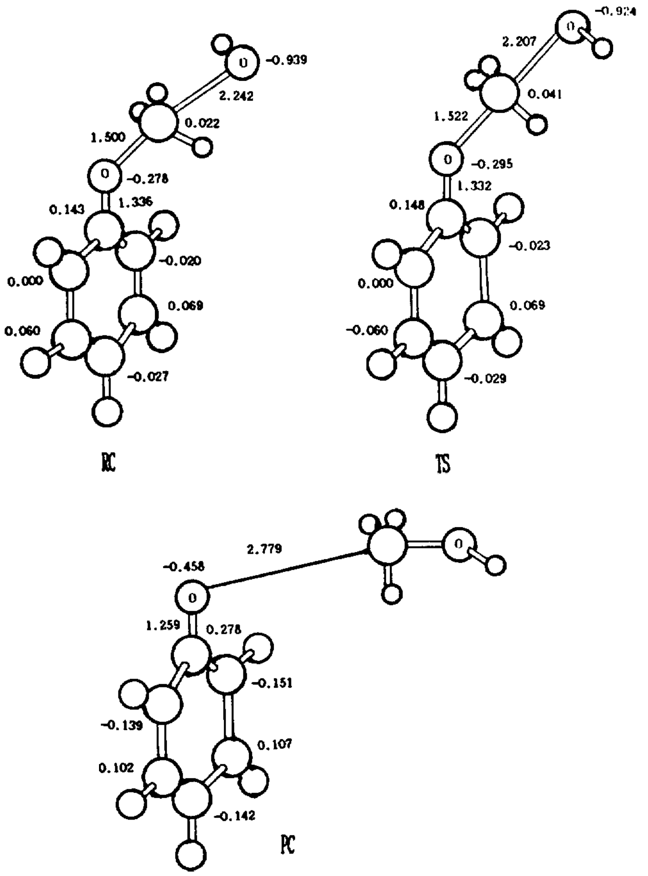


Figure 1. The AM1 structures of the equilibrium point species for the S_N2 channel.

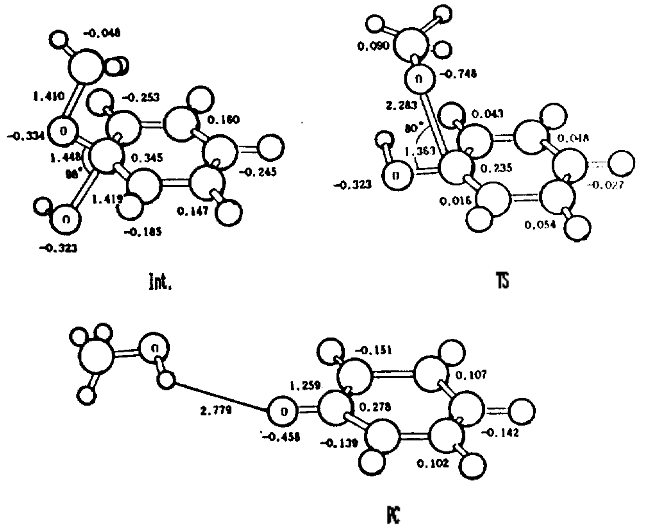


Figure 2. The AM1 structures of the equilibrium point species for the IPSO channel.

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 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.

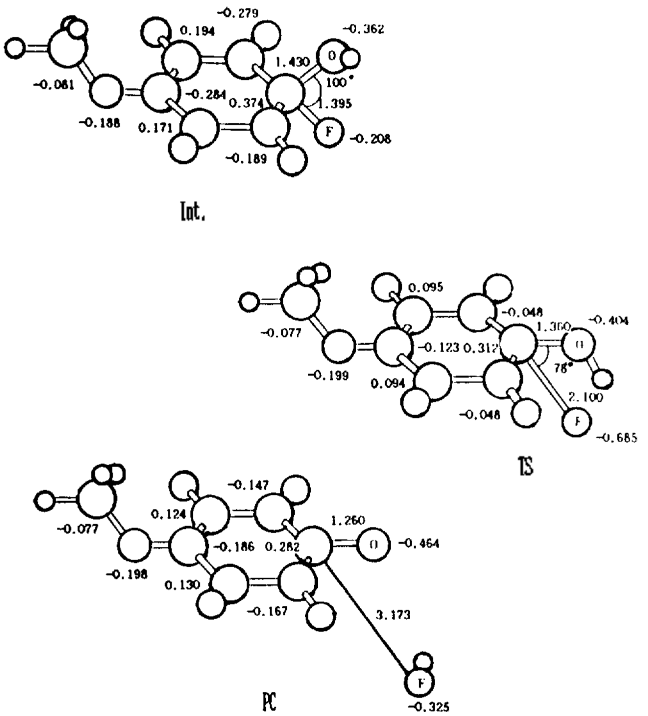
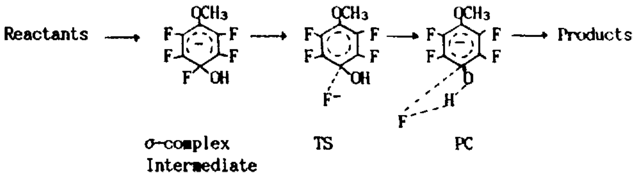


Figure 3. The AM1 structures of the equilibrium point species for the S_NAr channel.



Scheme 3

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

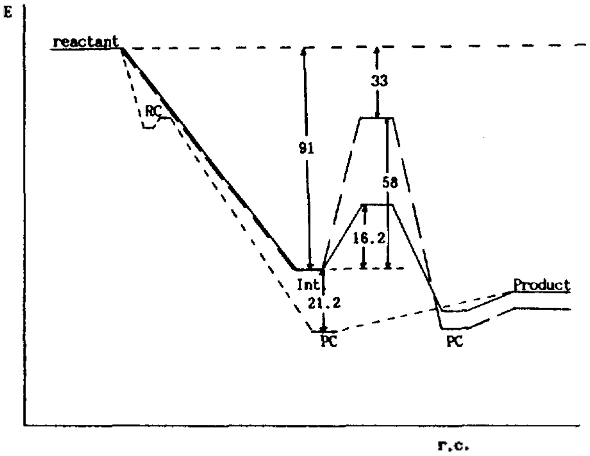


Figure 4. Energy profile for the reactions of pentafluoro-anisole with OH^-. (——: IPSO; – – –:S_NAr; ·········: S_N2 channel).

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_NAr channels of NH_2^-. This is also in agreement with the gas phase experimental results.

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