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Frontier Hybrid Orbitals. III. Study on S_N2 Reactions*

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On the principle of molecular fragments and orbitals interactions, frontier hybrid orbitals are used to discuss the transition states and the related process S_N2 reaction. The influence of the nucleophile, the leaving group, and the reaction center on reactivity are mainly studied. And the effects of alpha-substituents are also analyzed.

INTRODUCTION

The biomolecular substitution reaction S_N2 is a single step reaction:

$$X^- + R_1R_2R_3ZY \rightarrow XZR_1R_2R_3 + Y^- \quad (1)$$

where X^- is called the nucleophile, $R_1R_2R_3ZY$ the substrate and Y^- the leaving group. The substrate structure, the nature of the nucleophile, of the reaction center Z and of the leaving group, and the nature of the solvent are important factors of the overall rate of reaction.

Now, experiments[1] are available for studying solvated ions in the gas-phase, it is possible to explore the transition state in the kinetics of the ion-molecule reactions from the solvent-free case to the solution one, which shows that the reaction proceeds with inversion of configuration at the carbon atom in the gas phase just like in solution. Such experiments often offer a valuable starting point for theoretical *ab initio* computations. A variety of theoretical methods[2-11] have been used to check if the theory is able to give a correct picture of the experimental results.

In terms of Salem's[2] and Fukui's[3] treatment of the Walden inversion, on the basis of the frontier orbital approximation, it is postulated that the reaction evolution is mainly determined by the interaction between the highest occupied molecular orbital (HOMO) of the nucleophilic reagent X^- and the lowest unoccupied molecular orbital (LUMO) of the substrate and in this way it is possible to explain the switch from the inversion to retention of configuration by increasing the overlap of the HOMO with the orbital of the reaction center involved in the LUMO. The more complicated influence of the leaving group Y is also explained. But the limits of such a model are clear: it cannot give energy values and reaction barrier values comparable with the experimental ones.

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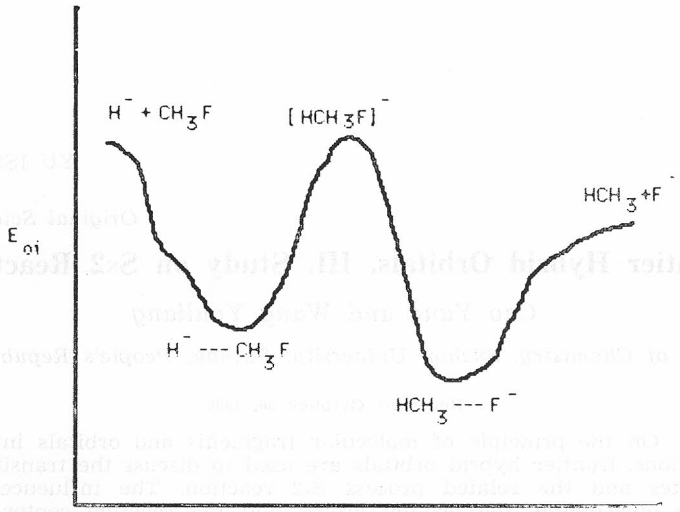

Figure 1. Reaction coordinate for the gas-phase displacement reaction

$$X^- + CH_3Y \rightarrow XCH_3 + Y^-.$$

Therefore, the reactivity studies are increasingly carried out by *ab initio* computations.

A number of *ab initio* molecular orbital calculations[4-7] of S_N2 transition states have already appeared in the literature and are consistent with the reaction coordinate depicted in Figure 1, which is characterized by two energy minima, corresponding to reactant (*1*) and product (*3*) ion-molecule clusters, separated by a central barrier (*2*) corresponding to the S_N2 transition state.

In parts 1 and 2 of these series,[12] the name »Frontier Hybrid Orbitals« was proposed to describe the directional, characteristic hybrid orbitals of a fragment, and applied to discussing the electronic structure and chemical bond of octahedral ML_5 framents and the molecules built up of these fragments. In the present work, on the basis of orbital interactions, the frontier hybrid orbitals are developed to describe the transition states and the related process of S_N2 reaction.

THEORY AND CALCULATIONS METHOD

According to the principle of orbital interactions and molecular fragments,[13-14] S_N2 reaction can be considered as the process of interaction between three frontier hybrid orbitals of fragments (or groups) X^-, $R_1R_2R_3Z^+$, and Y^-, which are represented by h_x, h_z, and h_y. Where h_x and h_y are lone-pair orbitals, respectively, and h_z is an empty orbital. The S_N2 reaction includes the form of X—Z bond and the break of Z—Y bond. In the reaction process, the lone-pair on orbital h_x enters the empty orbital h_z to make the X—Z bond form, and the lone-pair on orbital h_y exits orbital h_z to make the Z—Y bond break. So, the ion-molecules $[XZR_1R_2R_3Y]^-$ in the process of reaction are the structures of three-center four-electron bonding, and the most stable one is the transition state Therefore, we can discuss the transition state and the related process of S_N2 reaction in terms of the interactions of the three frontier hybrid orbitals.

1. Depending on the energies of the three frontier hybrid orbitals h_x, h_y, and h_z, which are represented by E_x, E_y, and E_z, respectively, the reactivity can be determined. In general, the larger the energy difference between the orbitals h_z and h_y, the more easily the break of bond Z—Y: and the smaller the energy difference between the orbitals h_x and h_z, the more easy the creation of bond X—Z. The orbital energy of the empty h_z is lower than that of the occupied h_x or h_y. Thus, if the difference between E_x and E_z is smaller than that between E_y and E_z, the substitution reaction will take place and it is expected to be exothermic.

2. When the energy differences are approximately equal, the reactivity primarily depends on the overlap integrals between orbitals h_x and h_z, and between h_y and h_z, which are indicated by S_{xz}, and S_{yz}, respectively. The larger the S_{xz}, the more easily X can attack Z. And the smaller the S_{yz}, the more easily Y can leave Z. It is well known that the hybrid orbital is directional. In order to create a stable X—Z bond and break the Z—Y bond, the nucleophile X must attack the reaction center Z in the opposite direction to Z—Y bond. Thus, orbitals h_x and h_z can overlap efficiently, and it explains the mechanism of the Walden inversion.

3. Quantitatively, the frontier hybrid orbital interaction energy of the transition state and ion-molecule complex can be calculated with the process of reaction. The bond orbital of the three-center four-electron bond in $[XZR_1R_2R_3Y]^-$ complex is defined as

$$\Psi_i = c_{ix}\, h_x + c_{iy}\, h_y + c_{iz}\, h_z \tag{2}$$

where c_{ix}, c_{iy}, and c_{iz} are the mixing coefficients. At the first-order approximation level, h_x and h_y are considered to be the same in the process, but h_z changes, which are determined on the method described in part 1 of this series. The bond orbital energy is

$$E_i = \langle \Psi_i \,|\, H^{eff} \,|\, \Psi_i \rangle \tag{3}$$

which can be solved by the variation principle, to obtain the following secular determinant

$$\begin{vmatrix} H_{xx} - E & H_{xy} & H_{xz} - S_{xz}E \\ H_{xy} & H_{yy} - E & H_{yz} - S_{yz}E \\ H_{xz} - S_{xz}E & H_{yz} - S_{yz}E & H_{zz} - E \end{vmatrix} = 0 \tag{4}$$

With the solution of this secular equation, the total orbital interaction E_{oi} can be calculated by the following formula

$$E_{oi} = 2\,E_1 + 2\,E_2 \tag{5}$$

where E_1 and E_2 are the bond orbital energies of the two occupied Ψ_1 and Ψ_2. The calculated results for reaction $H^- + CH_3F \rightarrow HCH_3 + F^-$ are shown in Figure 2, which is very similar to Figure 1.

In part 1 of this series, the frontier hybrid orbitals were calculated and discussed on the CNDO/2 approximation level. But in the present work, the *ab initio* STO-3G method was used to calculate the frontier orbitals of

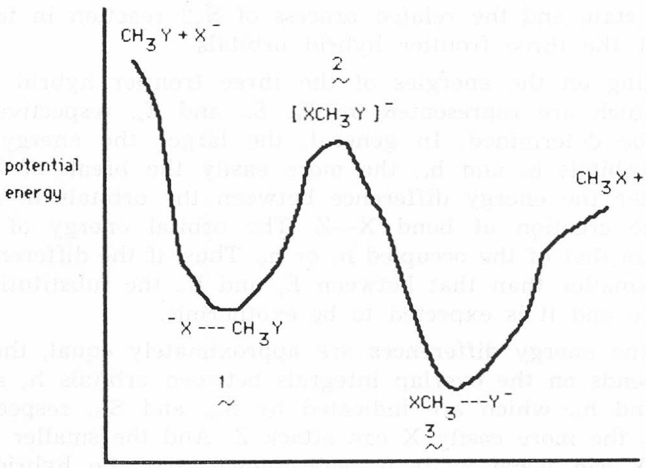

Figure 2. The total frontier hybrid orbital interaction of the reaction process depicted in Fig. 1.

fragments, by using the GAUSSIAN-82 program.[15] Calculations were carried out in a Digital VAX 11/750 computer at The Normal University of East China.

RESULTS AND DISCUSSION

A. Reaction $X^- + CH_3F \rightarrow XCH_3 + F^-$

In order to study and compare the properties and influence of nucleophile X^- on the substitution reaction, we studied a number of these reactions, using *ab initio* STO-3G calculations. Table I lists the calculated energy differences and overlap integrals between the frontier hybrid orbitals, their composition in the occupied bond orbitals, the orbital interaction change (ΔE_{oi}), and the activation energy (ΔE) of STO-3G *ab initio* computations. ΔE_{oi} and ΔE are calculated by the following formulas

$$\Delta E_{oi} = E_{oi}\,(\mathrm{TS}) - E_{oi}\ (\mathrm{reactants}) \tag{6}$$

$$\Delta E = E\,(\mathrm{TS}) - E\ (\mathrm{reactants}) \tag{7}$$

The results of the energy difference indicate that HCC^-, F^-, NC^-, and CN^- are weak nucleophiles, but H^-, H_2N^-, HO^-, and CH_3O^- are good ones. Combining with the results of the overlap integrals, it is determined that NC^-, and CN^- are weak nucleophiles, and H_2N^-, HO^-, and CH_3O^- are strong ones, and the other groups are general ones. Replacing X by some lower element in the same column of the periodic table, *i. e.*, changing X = OR to X = SR, will generally decrease the reactivity of nucleophile X. The calculated orbital interaction changes are consistent with the activation energy. The results indicate that the transition states of which X are H_2N^-, HCC^-, F^-, NC^-, and CN^- are more stable. This is because the frontier hybrid orbitals of these nucleophiles can form strong three-center four-electron bonds with those of the reaction center and leaving groups.

TABLE I

Calculated frontier hybrid orbital interaction of the transition state for reaction $X^- + CH_3F \rightarrow XCH_3 + F^-$

X	E_x—E_c	S_{xc}	S_c	C_x	C_y	C_z	ΔE_{oi}	ΔE
H	1.22	0.366	0.412	0.203	0.296	0.501	35.70	29.56
H_2N	1.11	0.434	0.414	0.210	0.295	0.495	8.00	15.20
HO	0.73	0.365	0.417	0.227	0.273	0.500	16.50	15.80
HS	—0.16	0.480	0.413	0.218	0.281	0.501	44.78	41.90
CH_3O	1.02	0.510	0.410	0.246	0.251	0.503	26.91	18.78
CH_3S	—0.41	0.563	0.408	0.242	0.259	0.499	43.87	40.97
HCC	—0.72	0.401	0.407	0.255	0.248	0.497	6.85	8.06
F	—0.68	0.406	0.406	0.250	0.250	0.500	9.80	10.1
NC	—0.75	0.372	0.401	0.279	0.221	0.500	6.21	6.53
CN	—1.26	0.395	0.398	0.288	0.218	0.494	10.09	7.32

Note: The values $E_x - E_c$ are in eV, ΔE_{oi} and ΔE are in kcal/mol. S_{xc} is the overlap integral between h_x and h_c. C_x, C_y, and C_z are the composition of h_x, h_y, and h_z in the occupied orbitals of the three-center four-electron bond of transition state $[XCH_3F]^-$, respectively.

TABLE II

Calculated frontier hybrid orbital interaction of the transition state for reaction $X^- + CH_3Y \rightarrow XCH_3 + Y^-$

X	E_x—E_c	Y	E_y—E_c	S_{xc}	S_{cy}	C_x	C_z	C_y	ΔE_{oi}	ΔE
H	1.22	F	—0.68	0.366	0.412	0.203	0.296	0.501	35.70	29.56
H	1.22	HO	0.73	0.360	0.365	0.222	0.274	0.504	34.65	37.78
H	1.22	HS	—0.16	0.357	0.480	0.241	0.259	0.500	42.41	39.00
H	1.22	CN	—1.26	0.370	0.395	0.194	0.305	0.501	25.04	27.31
H	1.22	HCC	—0.72	0.354	0.401	0.211	0.285	0.504	15.09	21.37
H	1.22	CH_3O	1.02	0.359	0.510	0.226	0.277	0.497	34.66	32.92
F	—0.68	HO	0.73	0.417	0.365	0.273	0.226	0.501	16.50	15.80
F	—0.68	HS	—0.16	0.413	0.480	0.283	0.218	0.499	44.78	41.90
F	—0.68	CN	—1.26	0.398	0.395	0.219	0.288	0.493	10.09	7.32
F	—0.68	HCC	—0.72	0.407	0.401	0.247	0.255	0.498	6.85	8.06
F	—0.68	CH_3O	1.02	0.410	0.510	0.254	0.246	0.500	26.91	18.78
F	—0.68	H	1.22	0.412	0.366	0.296	0.203	0.501	35.70	29.56
HO	0.73	F	—0.68	0.365	0.417	0.222	0.273	0.505	16.50	15.80
HO	0.73	CN	—1.26	0.369	0.395	0.220	0.278	0.502	7.62	6.47
HO	0.73	HCC	—0.72	0.358	0.401	0.235	0.267	0.498	6.37	7.02
HO	0.73	CH_3O	1.02	0.371	0.510	0.230	0.269	0.501	13.03	12.78
HO	0.73	H	1.22	0.349	0.366	0.274	0.222	0.504	24.65	14.78

Note: The values $E_x - E_c$, $E_y - E_c$ are in eV, ΔE_{oi}, ΔE are in kcal/mol. S_{xc} and S_{cy} are the overlap integrals between h_x and h_c, and between h_c and h_y, respectively. C_x, C_y and C_z are the composition of h_x, h_y, and h_z in the occupied orbitals of the three-center four-electron bond of transition state $[XCH_3Y]^-$, respectively.

B. Reaction $X^- + CH_3Y \rightarrow XCH_3 + Y^-$

The stereochemical influence of the leaving group was studied by Sommer,[16] who suggested that a classification of leaving groups may be made using the pK_a of the conjugate acid XH. If the pK_a is smaller than 6, X is considered to be a good leaving group. If the pK_a is larger than 10, X is considered to be a poor leaving group. Now let us examine the effects of the leaving group on the substitution reactivity, by using the method mentioned above. Table II lists the calculated results of the transition state for reaction $X^- + CH_3Y \rightarrow XCH_3 + Y^-$, which are very similar to those in Table I. In terms of these results, the influence of the the leaving groups to the substitution reactivity can be discussed. If the energy of h_z is higher than that of h_y, and S_{zy} is smaller than S_{xz}, Y^- is a good leaving group. Thus, the reactivity order of leaving groups can be determined from the results of Tables I and II: $CN^- > NC^- > F^- > HCC^- > CH_3S^- > HS^- > HO^- >$ $> CH_3O > H_2N^- > H^-$.

TABLE III

Claculated frontier hybrid orbital interaction of the transition state for reaction $X^- + SiH_3Y \rightarrow XSiH_3 + Y^-$

X	E_x—E_{si}	Y	E_y—E_{Si}	S_{xSi}	S_{Siy}	C_x	C_y	C_z	ΔE_{oi}	ΔE
H	0.21	F	—1.69	0.302	0.425	0.209	0.291	0.500	—5.58	—8.67
H	0.21	HO	—0.28	0.315	0.478	0.229	0.269	0.502	—4.90	—8.30
H	0.21	HS	—1.17	0.331	0.493	0.237	0.263	0.500	—3.01	—4.82
H	0.21	CN	—2.27	0.322	0.408	0.206	0.293	0.501	—5.74	—7.48
H	0.21	HCC	—1.73	0.317	0.414	0.217	0.280	0.503	—5.73	—5.04
H	0.21	CH_3O	0.01	0.305	0.523	0.232	0.268	0.500	—6.45	—4.32
F	—1.69	HO	—0.28	0.402	0.380	0.281	0.221	0.498	—5.63	—8.36
F	—1.69	HS	—1.17	0.413	0.495	0.282	0.219	0.499	—7.48	—9.25
F	—1.69	CN	—2.27	0.398	0.417	0.226	0.275	0.499	—7.90	—9.54
F	—1.69	HCC	—1.73	0.407	0.415	0.253	0.250	0.497	—2.65	—3.07
F	—1.69	CH_3O	0.01	0.410	0.517	0.258	0.243	0.499	—4.69	—5.83
F	—1.69	H	0.21	0.412	0.302	0.298	0.201	0.501	—5.58	—8.67
HO	—0.28	F	—1.69	0.380	0.402	0.222	0.281	0.497	—5.63	—8.36
HO	—0.28	CN	—2.27	0.389	0.417	0.226	0.275	0.499	—2.65	—3.56
HO	—0.28	HCC	—1.73	0.376	0.441	0.240	0.262	0.498	—2.98	—4.07
HO	—0.28	CH_3O	0.01	0.401	0.530	0.236	0.263	0.501	—3.87	—2.45
HO	—0.28	H	0.21	0.382	0.302	0.246	0.229	0.507	—4.90	—8.30

Note: The values $E_x - E_{Si}$ and $E_y - E_{Si}$ are in eV, ΔE_{oi} and ΔE are in kcal/mol. S_{xSi} and ${}_{siy}$ are the overlap integrals between h_x and h_{Si}, and between h_{Si} and h_y, respectively. C_x, C_y, and C_z are the composition of h_x, h_{Si} and h_z in the occupied orbitals of the three-center four-electron bond of transition state $[XSiH_3Y]^-$, respectively.

C. Influence of the Reaction Center Z

The simplest way to study the influence of the reaction center is by going down the same column in the periodic table, *i. e.*, by replacing Z = C by Z = Si. The valence orbitals have also changed from 2s and 2p for C to 3s and 3p for Si. The calculated results shown in Table III indicate that the energy of the frontier hybrid orbital of fragment SiH_3^+ is higher than that of CH_3^+ by about 1.01 eV. Therefore, most of the calculated groups are good leaving groups. This is because $E_{Si} > E_y$, the electron can easily transfer to the orbital of leaving group to become the lone-pair of Y and to break the Si—Y bond. And this makes the substitution on the reaction center Si give retention of configuration. The results of orbital interaction changes and activation energies shown in Table III are negative, which indicates that the transition state $[XSiH_3Y]^-$ has been found to be more stable than the reactants.

D. Effect of Alpha Substituents

The substituents attached to the reaction center effect the reactivity of S_N2 reactions.[17] The effects are very complicated, and depend on the nature of alpha groups, which can be alkyl, electromeric, conjugative, halogen, oxygen, and other ±I or ±E substituents. In this treatment, the effects of alpha substituents on reactions can be explained by the energy and composition of the frontier hybrid orbitals of $ZR_1R_2R_3^+$, and the stability of the three-center four-electron bond in the transition state. As an example, the reactions $F^- + RCH_3F \rightarrow FRCH_3 + F^-$ (R = H, F. OH, CH_3O) are studitd. The calculated results of ΔE_{oi} for H, F, OH, CH_3O are 9.26, 5.48, 2.41, 10.50 kcal/mol, which show that the three-center four-electron bond in the transition state $[FHOCH_3F]^-$ is very strong, the stability order of the transition states $[FRCH_3F]^-$ is $HO > F > H > CH_3O$. Therefore, the reactivity order for these alpha substituents is $HO > F > H > CH_3O$.

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SAŽETAK

Granične hibridne orbitale. III. Proučavanje kemijskih S_N2 reakcija

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Formalizam graničnih hibridnih orbitala korišten je u razmatranju S_N2 reakcija i njihovih prijelaznih struktura. Proučen je utjecaj α-substituenata.