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5각-이종원자 방향족 고리화합물과 이소프로필 양이온간의 친전자 치환반응에 관한 이론적 연구(1)

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Theoretical Studies on Electrophilic Substitution of Five-membered Heteroaromatic Compounds with Isopropyl Cation[1]

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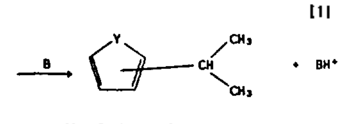
요 약. 5각-이종원자 방향족 고리화합물들인 푸란, 피롤 그리고 티오펜과 이소프로필 양이온간의 친전자성 치환반응에 관하여 MNDO 방법을 사용하여 이론적으로 연구하였다. α, β 그리고 이종원자 위치의 선택성들은 정전기적 상호작용에 의하여 조절되는 것이 아니라, 친전자체의 LUMO와 이종원자 방향족 고리화합물의 HOMO간의 전하전이 안정화(Charge transfer stabilization) 효과에 의하여 주로 결정됨을 알 수 있었다. 한편 α와 β 위치에 대한 반응성의 순서는 피롤>푸란>티오펜의 순서를 가지며 이러한 순서는 기체상 및 용액상 실험결과와 잘 일치하는 것이다.

ABSTRACT. Theoretical studies on the electrophilic substitution reactions of five-membered heteroaromatic compounds, furan, pyrrole and thiophene, with isopropyl cation were carried out using the MNDO method. The results indicated that site selectivities of α, β and hetero-atoms are not controlled by electrostatic interactions but are determined mainly by charge trasfer stabilization between the HOMO of heteroaromatics and the LUMO of the electrophile. The reactivity order for α and β positions was pyrrole > furan > thiophene, in agreement with the solution-phase as well as the gas-phase experimental results.

Electrophilic substitution of five-membered heteroaromatic compound has been extensively studied experimentally[2] and theoretically[3]. The results of these studies agree on a reactivity order of pyrrole > furan > thiophene and a predominant α-substitution in general in solution[2]. However the reactivity scales and positional selectivity of the heteroaromatic compounds vary dramatically with the reaction medium[2,4], so that no plausible explanation has yet been offered as to the intrinsic factors controlling reactivity scale and positional selectivity.

In this work, we investigated the reactivity features of simple five-membered heteroaromatic compounds, furan, pyrrole and thiophene, toward electrophilic substitution by isopropyl cation, (1),



(1)

Y = O, NH or S.
B = a base, or other substrate molecule.

In commemoration of the 60th birthday.

Table 1. Positional activation barriers (ΔH^{*}), heavy atom charge densities(q), HOMO-LUMO energy gaps ($\Delta\epsilon_{FMO}$) and the AO-coefficients in the HOMO of furan

position	H^{*a}	q^{b}	$\Delta\epsilon_{FMO}{}^{c}$	AO-coefficients
O	9.3	-0.127	2.171	-0.467
C_{α}	6.6	-0.013	0.994	0.597
C_{β}	7.5	-0.132	0.994	0.379

[a] $\Delta H^{*} = \Delta H_f(\mathrm{TS}) - \{\Delta H_f(\mathrm{furan}) + \Delta H_f(\mathrm{isopropyl\ cation})\}$ in kcal/mol. [b] Charge densities of heavy atoms are in electronic charge unit. [c] $\Delta\epsilon_{FMO}$ = LUMO (isopropyl cation) - HOMO(furan) in eV.

theoretically using the MNDO method [5], in order to unravel the intrinsic factors by comparing with the experimental results of gas-phase studies reported by Speranza *et al.*[6]

In reaction (1), the second step corresponods to a deprotonation process, which is fast in all cases, and hence will have no effect on the reactivity. We have therefore investigated the recation (1) by MO method up to the formation of the intermediate [1], which is the rate determining step.

CALCULATIONS

The calculations were carried out using the standard MNDO procedure[7] with full optimization of all geometrical variables. Transition states (TS) were located by the recation coordinate method,[8] refined with the gradient norm minimization method[9] and characterized by confirming only one negative eigenvalue in the Hessian matrix[10].

RESULTS AND DISCUSSION

Isopropylation of Furan. The three conceivable isopropylation processes of furan, i.e., isopropylations on the α and β carbons and on the oxygen atom, are considered, and the results relevant to the reactivity are summarized in *Table* 1. In this *table*, the HOMO of oxygen is the π-lone pair orbital, and that of α and β is the π-bond orbital between C_{α} and C_{β}. The LUMO of the isopropyl cation is the vacant p-orbital. Reference to *Table* 1 reveals that the positional reactivity is in the order $\alpha > \beta > O$ according to the activation barriers(ΔH^{*}) required for the isopropylation on each position. We note that this positional selectivity dose not agree with that expected from the positional charge densities of the unperturbed furan molecule, i.e., $\beta > O > \alpha$. Accordingly electrostatic interaction between the electrophile and the reaction center is not a significant factor determining the site selectivity. The transition state (TS) structures shown in *Fig.* 1 indicate that the 'chelating' properties of the electrophile producinig the electrostatic adduct [II] by attack on a bidentate substrate, furan, is not substantiated as suggested by Speranza *et al.*[6, 11]

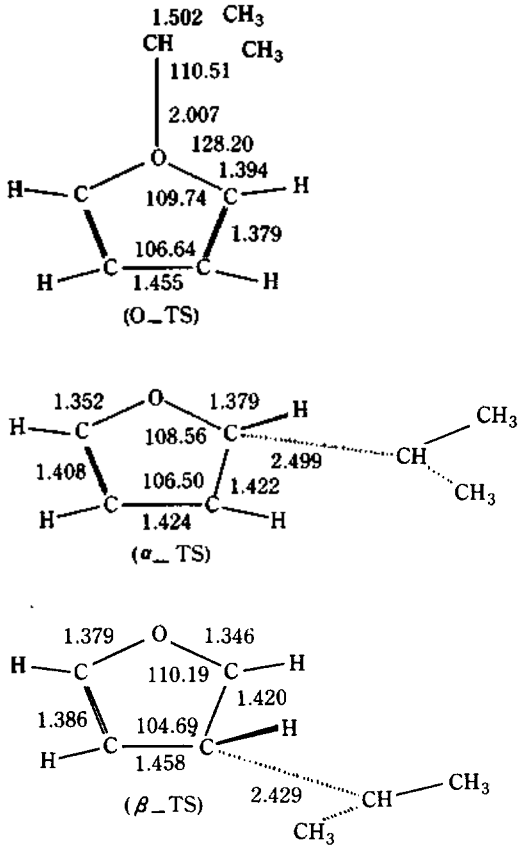
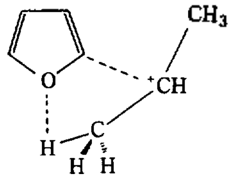


Fig. 1. Geometries for the TSs in the isopropylation processes of Furan.

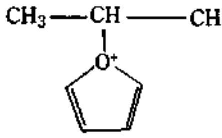


[II]

Of the four major intermolecular interactions[12] i.e., electrostatic E_{es}, polarization E_{pol}, exchange repulsion E_{ex}, and charge transfer E_{ct} intractions, the last type of interaction, E_{ct}, is known to be operationally important in determinig reactivity, and can be approximated as[13]

$$E_{ct} \cong \frac{H_{ij}^2}{\Delta \varepsilon_{FMO}} \tag{2}$$

where $\Delta\varepsilon_{FMO} = \varepsilon_{LUMO} - \varepsilon_{HOMO}$ and H_{ij} is the interaction matrix element between orbitals i and j, which is proportional to the overlap, S_{ij}, between two orbitals[14]. This will be, in turn, proportional to the AO coefficients of the two interacting atoms in orbitals i and j. Examination of *Table* 1 shows that the reactivity trend expected from the charge transfer stabilization is indeed consistent with the gas-phase experimental (α:β: O = 52:22:26) as well as the theoretical (based on barrier heights) results of enhanced α-reactivity ; the α position has lower $\Delta\varepsilon_{FMO}$ as well as a greater AO coefficient, and the oxygen atom has a substantially large interfrontier energy gap, $\Delta\varepsilon_{FMO}$, compared to α and β. The inconsistency of the reactivity expected from our calculations for β and O (β > O) with the gas-phase results[6](O > β) may probably arise from the indirect detection method adopted in the gas-phase experiment for O-isopropylated species[III].



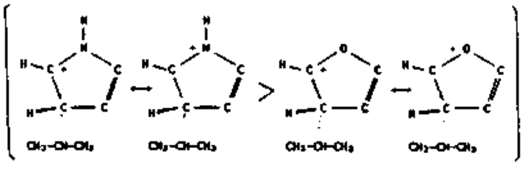
[III]

Moreover the site selectivity between β and O is not large and disagreement may not be significant. In any case, the barrier height differences between the three processes are only 1-3 kcal/mol so that all three processes can take place competitively as experimentally observed.

Table 1. Positional activation barriers (ΔH^{*}), heavy atom charge densities(q), HOMO-LUMO energy gaps ($\Delta\varepsilon_{FMO}$) and the AO-coefficients in HOMO of pyrrole

position	ΔH^{*a}	q^b	$\Delta\varepsilon_{FMO}{}^c$	AO-coefficients
N	2.3	-0.224	1.179	0.550
C_α	1,9	-0.028	0.417	-0.603
C_β	-0.2	-0.130	0.417	-0.369

[a] $\Delta H^{*} = \Delta H_f(\mathrm{TS}) - \{\Delta H_f(\mathrm{fyrrole}) + \Delta H_f(\mathrm{isopropyl\ cation})\}$ in kcal/mol. [b] Charge densities of heavy atoms are in electronic charge unit. [c] $\Delta\varepsilon_{FMO}$ = LUMO (isopropyl cation) - HOMO(pyrrole) in eV.



Scheme 1.

Isopropylation of Pyrrole. For three isopropylation processes, on N, α and β carbons, activation enthalpies, charge densities, interfrontier energy gaps and AO coefficients are given in *Table* 2. The site selectivity for pyrrole is seen to be β > α > N based on the activation barriers (ΔH^{*}), the β carbon being the most reactive site ; this is different from the most reactive site of α carbon for furan, but nevertheless the factor controlling the site selectivity is not charge densities in both isopropylations of furan and pyrrole. The N atom has the greatest negative charge of -0.224 but the reactivity is the least so that electrostatic attraction between two reactants is not an important factor in the reaction. Here again the FMO energy gaps are lower for the α- and β-carbons than that for the N atom indicating importance of an FMO interaction in the isopropylation of pyrrole. However, the AO coefficient of the HOMO is greater for α than for β in contrast to a greater reactivity of β than α. This can be rationalized by a greater resonance effect of π-lone pair on N In pyrrole due to the weaker electronegativity compared to O in furan, for which the position was the most reactive site; the developing positive charge in substitution of the isopropyl cation can be more effectively stabilized at the α-position in pyrrole by resonance than in fuan as shown in *Scheme* 1. This effect is reflected in the TS structure for pyrrole in *Fig.* 2: the H artom on N can be coplanar with the pyrrole ring in the TS when pyrrole is β-isopropylated due to the resonance structure (*Scheme* 1) as in the ground state. In contrast,

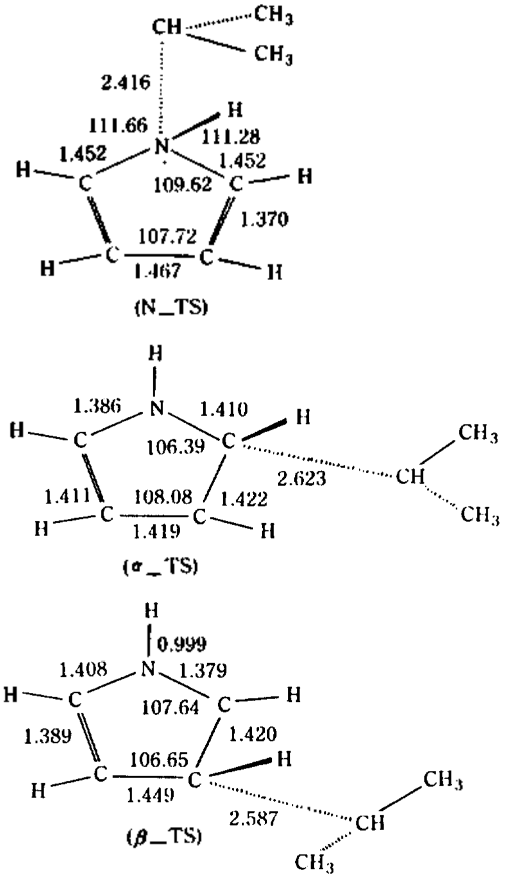


Fig. 2. Geometries for the TSs in the isopropylation processes of Pyrrole.

however the N atom has more sp^3 character in the TS of the α-isopropylation sine orbitals of C_α can not overlap with π-lone pair of the N-atom due to change over from sp^2 to sp^3. Thus in the α-isopropylation, the sp^3 character of N increases as the ground state proceeds to the TS and as a result the H atom on N is lifted ca. 20° off from the ring plane in the TS. The greater resonance stabilization in the β-isopropylation leads to a greater selectivity of β- over α-position. our results are therefore in complete agreement with the gas-phase results of α : β : N = 20:70:10 by Speranza *et al.*[6] The barrier height differnences are 0.3-2 kcal/mol (*Table* 2) so that the isopropylation on the three positions can be competitive as experimentally found.

Table 3. Positional activation barriers (ΔH^*), heavy atom charge densities(q), HOMO-LUMO energy gaps ($\Delta\epsilon_{FMO}$) and the AO-coefficients in HOMO of thiophene

position	ΔH^{*a}	q^b	$\Delta\epsilon_{FMO}{}^c$	AO-coefficients
S	-2.3	0.312	1.462	-0.747
C_α	8.3	-0.256	1.359	0.596
C_β	9.3	-0.082	1.359	0.380

[a] $\Delta H^* = \Delta H_f(TS) - \{\Delta H_f(\text{Thiophene}) + \Delta H_f(\text{isopropyl cation})\}$ in kcal/mol. [b] Charge densities of heavy atoms are in electronic charge unit. [c] $\Delta\epsilon_{FMO}$ = LUMO (isopropyl cation) - HOMO(thiophene) in eV.

Isopropylation of Thiophrene. As in the two proceding cases, charge density on the three reactive positions, α, β, and S, in thiophene are also not important in determining the site selectivity as can be seen in *Table* 3; the site selectivity is S > α > β, in contrast to both furan and pyrrole. The activation enthalpy is the lowest and hence the reactivity is the greatest at the S atom, despite its positive charge of +0.312 ; here again electrostatic interaction is not an important factor determining the site selectivity, nor the FMO gap is in favor of a greater reactivity of the S atom. We note, however, that the AO coefficient is the largest for S, which may be due to a greater size being a second row element, resulting in a greater polarizability of S compared to the first row elements of C, N or O; the interaction between the LUMO of the isopropyl cation, which is a vacant p-orbital, and the greater lobe of S will therefore increase significantly so that the site selectivity of S becomes the greatest. The α position is more reactive than the β position since S has a net positive charge in the ground state so that the developing positive charge at α in the β-isopropylation causes destabilization due to a repulsive electrostatic interaction with the positive S atom in the TS (*Fig.* 3)

Speranza *et al.*[6] reported the site selectivity of thiophene for the isopropylation as α:β: S: = 40: 38: 22, which indicates that our theoreticals results ap-

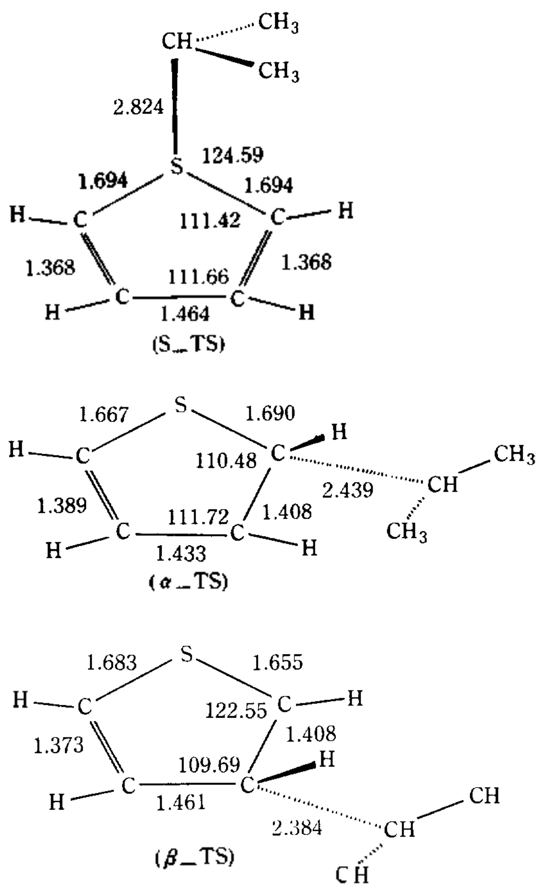
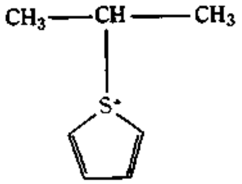


Fig. 3. Geometries for the TSs in the isopropylation processes of Thiophene.

pear to be inconsistent with the gas-phase experimental results. Howervr, in view of the facts that the direct measurement of the adduct,[IV],[15] was impossible experimentally, and the gas-phase work was conducted under kinetically controlled condition so that the possibility of subsequent migration of the isopropyl group from S to α or β can not be precluded, the experimental selectivity order for S may not represent a true situation; therefore, it is likely that our theoretical order observed is correct. As to the relative order of reactivity for α and β, our results are consistent with those of the gas-phase results.



[IV]

Comparison of the Reactivities of the Three Heteroarommatic Compounds. The reactivities of isopropylation for the three heteroaromatics considered in this work are in the order pyrrole > furan > thiophene as far as the α and β-positions (*Table* 1 and 3) are concerned, which is in agreement with the reactivity order for condensed phase reactions.[2,4] The major factor controlling the reactivativity order is seen to be the FMO energy gaps, which are 0.417, 0.974 and 1.359 eV for pyrrole, furan and thiophene, respectively. On the other hand the reactivity order for adduct formation on the heteroatom is thiophene > pyrrole > furan, for which no condenesed phase experimental results are available but is in good agreement with the gas-phase results of Speranza *et al.*[6] This is reasonable since in eq. (2) both $\Delta\varepsilon_{FMO}$ and H_{ij} are imporant foro charge-transfer stabilization of TSs so that the HOMO-LUMO interaction energy involving S can be more stabilizing since the AO coefficient is the greatest, i.e., H_{ij} is the greatest, for S although $\Delta\varepsilon_{FMO}$ is the smallest for N.

We have seen that the FMO interaction (E_{ct}) is more important than the electrostatic interaction (E_{es}) for the isopropylation of the five-membered heteroaromatics. This may be due to a substantial distance ($r \simeq 2.5$ Å) involved between two reaction centers of the reactants in the TS reducing the Coulombic interaction energy. We have shown heats of formation and bonding distances in the stationary species in *Table* 4. Even thought the electrostatic term, E_{es}, is in general more important at a long distance,[12] the contribution at the TS seems very small relative to that of the short range effect, charge transfer term E_{ct}, due

Table 4. Heats of formation (ΔH_f) of the stationary point species and the bonding distances between reaction centers in the TSs

Compound		ΔH_f				Distance (Å)
		Reactant[a]	Reactant complex	TS	Product	
	O			201.42	188.09	2.007
Furan	C_α	192.08[b]	188.06	198.72	157.74	2.499
	C_β			199.42	163.73	2.429
	N			235.68	207.23	2.416
Pyrrole	C_α	233.43	229.12	235.34	185.87	2.623
	C_β			233.24	188.76	2.587
	S			224.87	203.30	2.823
Thiophene	C_α	227.53	223.53	235.49	196.58	2.439
	C_β			236.49	204.02	2.384

[a] Reactants are heteroaromatic compounds and isopropyl cation. [b] Values are in kcal/mol.

to relatively small charges involved in the isopropylation of five-membered heteroaromatics.

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