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MNDO (Modified Neglect of Diatomic Overlap) Study of the Nucleophilic Substitution Reactions of Chloropyrimidines

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In the case of the reaction of 2,4-dichloro-6-R-pyrimidines with methoxide anion, in which R is a methoxycarbonyl, chlorine, hydrogen, phenyl or methyl group, the replacement reaction of a chlorine atom with a methoxy group occurs predominantly at the 4-position, whereas the substitution takes place mainly at the 2-position when R is a methoxy group. The effect of the substituent at the 6-position on the reactivity of the chlorine atom of the chloropyrimidines was studied by using a semiempirical molecular orbital method (MNDO method). It was proved that the reaction process from the reactants to the Meisenheimer-type complex plays an important role in determining the direction of the progress of the reaction.

Keywords chloropyrimidine; nucleophilic substitution; MNDO method; methoxide ion

The kinetics of the nucleophilic displacement reactions of several 2- and 4-chloropyrimidines with organic bases, as well as the effect of nuclear methyl (Me) groups on the reactivity of chloropyrimidines, have been studied by Chapman and Rees.[1] They reported that studies with piperidine and morpholine in ethanol indicated a series of regular second-order reactions, and the rate constants show that the chlorine atom (Cl) at the 4-position is more active than the one at the 2-position, and that Me groups decrease the activity in both cases. Forchiassin *et al.*[2] investigated the kinetics of the nucleophilic displacement of 2- and 4/6-halogen substituents in pyrimidines by alkoxide ion. They found that 4,6-dichloropyrimidine underwent monomethoxylation 16 times faster than the parent 4-chloropyrimidine, whereas 4-chloro-6-methyl- and 4-chloro-6-methoxypyrimidine underwent the same reaction, at 0.6 and 0.03 times the rate for the parent respectively. In addition, many theoretical studies[3] have been done on nucleophilic substitutions using a molecular orbital (MO) method.

In this report, we would like to present an MO study on the reactions of 2,4-dichloro-6-R-pyrimidines (**1**—**6**) with methoxide anion (MeO$^-$) shown in Chart 1. As shown in Table I,[4] in the case of the reaction of these chloropyrimidines with MeO$^-$, in which R is a methoxycarbonyl (CO_2Me), Cl, hydrogen (H), phenyl (C_6H_5), or Me group, the replacement reaction of Cl with a methoxy (OMe) group occurs predominantly at the 4-position. On the other hand, when there is an OMe group at the 6-position, the substitution reaction occurs mainly at the 2-position.

By means of the MO method, we investigated the reason why, only in the case of the reaction of 2,4-dichloro-6-methoxy-pyrimidine, the order of the reactivity of Cl at the 2- and 4-position is reversed, compared with the other examples of the same reactions, as shown in Table I. To elucidate the differences of the substituent effects between an OMe group and the others at the 6-position, we adopted the modified neglect of diatomic overlap (MNDO) method[5] for the calculation of the energies of these reactions. The MNDO method is much faster than the *ab initio* MO method for large systems and has been shown to give reasonably accurate energies and structures for heterocyclic compounds and ions.[5]

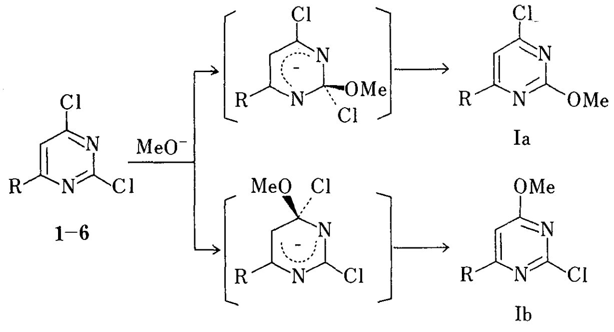
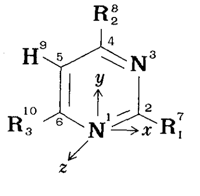


Chart 1

TABLE I. The Ratio of the Products in the Monomethoxylation of 2,4-Dichloro-6-R-pyrimidines with MeO$^-$

Compd. No. R	**1** CO_2Me	**2** Cl	**3** H	**4** C_6H_5	**5** Me	**6** OMe
Ia : Ib	4 : 96	8 : 92	15 : 85	16 : 84	24 : 76	92 : 8



$R_1 = H, Cl$
$R_2 = H, Cl$
$R_3 = H, Cl, Me, OMe, CO_2Me, C_6H_5$

Fig. 1. The Numbering of Atoms of Chloropyrimidines with the Cartesian Coordinate System

Computational Procedure

The numbering of atoms of chloropyrimidine derivatives with the Cartesian coordinate system is shown in Fig. 1. All numerical values in the following section were obtained using the MNDOM program[7] with standard parameters.[5,8] All equilibrium geometries were determined by minimizing the total energy with respect to all geometrical variables using the standard DFP (Davidon-Fletcher-Powell) algorithm.[9] All energy minima for the displacement reactions were generated by determining the energies of the complex "superion" at fixed C^2–O (or C^4–O) distances while optimizing all other variables. The difference in the heat of formation, $\Delta\Delta H_f$ was obtained from the heat of formation of the superion

Table II. The Heats of Formation (ΔH_f) and the LUMO Energies of Chloropyrimidines

Compd. No.	R_1	R_2	R_3	ΔH_f (kcal mol^{-1})	LUMO energies (eV)
1	Cl	Cl	CO_2Me	−52.4	−1.609
2	Cl	Cl	Cl	16.6	−1.421
3	Cl	Cl	H	22.1	−1.104
4	Cl	Cl	C_6H_5	45.3	−1.007
5	Cl	Cl	Me	12.7	−1.053
6	Cl	Cl	OMe	−24.1	−1.006
7	Cl	H	H	28.3	−0.733
8	Cl	H	Me	18.8	−0.702
9	Cl	H	OMe	−13.2	−0.632
10	H	Cl	H	27.9	−0.726
11	H	Cl	Me	18.6	−0.685
12	H	Cl	OMe	−18.2	−0.659
13	H	Cl	Cl	21.6	−1.078

ΔH_f(superion) by subtracting that of substrate ΔH_f(substrate) and of MeO$^-$ ΔH_f(reagent).

$$\Delta\Delta H_f = \Delta H_f(\text{superion}) - (\Delta H_f(\text{substrate}) + \Delta H_f(\text{reagent}))$$

Results and Discussion

It can be generally said that in nucleophilic substitution reactions a substrate is more easily attacked by a nucleophilic reagent with the lowering of the energy level of the lowest unoccupied molecular orbital (LUMO), and an electron-releasing group raises the energy level of the LUMO of a substrate compared with that of the unsubstituted parent compound, while an electron-withdrawing group has an opposite effect.

The heats of formation and the LUMO energies of the chloropyrimidines are shown in Table II.

As shown in Table II, when a 2-chloro- or 4-chloropyrimidine has an Me or OMe group at the 6-position, the orbital energy level of the LUMO is higher than that of the parent chloropyrimidine, which has no substituent at the 6-position; the reactivity of Cl at the 2- or 4-position is reduced by a substituent such as Me or OMe group at the 6-position.

When there is a substituent such as a C_6H_5, Me or OMe group at the 6-position of 2,4-dichloropyrimidine, the energy levels of the LUMO are higher than that of the parent 2,4-dichloropyrimidine, whereas the energy levels of the LUMO are lowered by a substituent such as CO_2Me or Cl. However, the differences of the reactivity depending on the substituents at the 6-position can not be explained in terms of the LUMO amplitudes and energies in the ground states of these compounds.

Next, we investigated the change of the energies along the reaction path. The reaction profile for the reaction of 2,4-dichloropyrimidine with MeO$^-$ and the structures of the corresponding superion at each point are shown in Fig. 2. The heat of formation is plotted on the ordinate and the distance between the oxygen atom of MeO$^-$ and the carbon atom of the pyrimidine nucleus on the abscissa, *i.e.*, as the reaction coordinate. It is clear from this reaction profile that the reaction is exothermic. When MeO$^-$ approaches the pyrimidine nucleus, the energy of the system is lowered first to the point of W_1, and then the reaction proceeds further *via* the transition state B_1 to the stable point, *i.e.*, the intermediate M. The energy difference between the reactants and the intermediate M is rather large (average value: *ca.* 40—50 kcal mol^{-1}), so that the reaction proceeds easily *via* the second transition state B_2 to give the products. In this reaction the process passing through the point B_1 is the rate-determining step, and the subsequent process to give the products occurs easily.

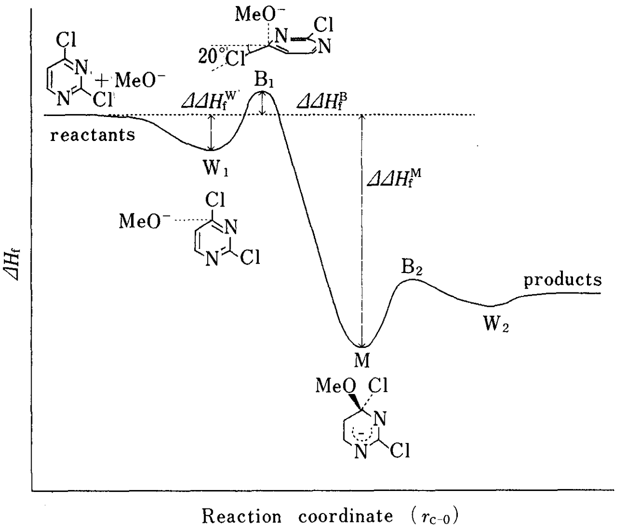


Fig. 2. The Reaction Profile for the Reaction of 2,4-Dichloropyrimidine with MeO$^-$ and the Structures of the Superions W_1, B_1 and M

Our attention was focussed on the energy change of the system from the reactants to the intermediate M. The symbols $\Delta\Delta H_f^W$, $\Delta\Delta H_f^B$ and $\Delta\Delta H_f^M$ stand for the differences between the heat of formation of the reactants and that of the corresponding superion W_1, B_1 or M, respectively. $\Delta\Delta H_f^W$ is the stabilization energy of the system with the approach of MeO$^-$ to the pyrimidine nucleus; as this value becomes lower the system is more stable. $\Delta\Delta H_f^B$ is the energy barrier of this reaction, and the reaction proceeds more easily to pass over the point B_1, and to reach the intermediate M with the lowering of this value. $\Delta\Delta H_f^M$ stands for the stability of the Meisenheimer-type complex. In the case of the superion W_1, the structures of the reagent and the substrate remain almost unchanged. At the point of the transition state B_1, the oxygen atom of MeO$^-$ is located right over the carbon atom that participates in the reaction, on the plane of the pyrimidine nucleus. The bond-length between this carbon atom and the chlorine atom is elongated, and the angle θ between this C–Cl bond and the plane of the pyrimidine nucleus is *ca.* 20°. In M the carbon atom participating in the reaction has the sp^3 structure, and this superion is regarded as a Meisenheimer-type complex.

Reaction of 2-Chloro- and 4-Chloro-6-R-pyrimidines with MeO$^-$ Table III shows the values of $\Delta\Delta H_f^W$, $\Delta\Delta H_f^B$ and $\Delta\Delta H_f^M$ in the reactions of 2-chloro- and 4-chloro-6-R-pyrimidines with MeO$^-$. When an Me group is located at the 6-position, all the values of $\Delta\Delta H_f^W$, $\Delta\Delta H_f^B$ and $\Delta\Delta H_f^M$ of **8** and **11** are higher than those of the corresponding parent chloropyrimidines **7** and **10**, *i.e.* the reactivities of **8** and **11** decrease compared with those of **7** and **10**. In the case of the 6-methoxy derivatives **9** and **12**, the values of $\Delta\Delta H_f^W$ increase and those of $\Delta\Delta H_f^M$ decrease, whereas the value of $\Delta\Delta H_f^B$ decreases in the case of **9**, and increases in **12** compared with those of **7** and **10**. Although the values of $\Delta\Delta H_f^B$ of **9** and **12** are similar, these values show that the

TABLE III. $\Delta\Delta H_f^W$, $\Delta\Delta H_f^B$ and $\Delta\Delta H_f^M$ Values in the Reaction of 2-Chloro- and 4-Chloro-6-R-pyrimidines with MeO$^-$ (kcal mol^{-1})

	2-Cl-6-R-pyrimidines				4-Cl-6-R-pyrimidines			
Compd. No.	**7**	**8**	**9**	**3**	**10**	**11**	**12**	**13**
R	H	Me	OMe	Cl	H	Me	OMe	Cl
$\Delta\Delta H_f^W$	−9.4	−9.2	−6.0	−11.1	−8.5	−7.3	−5.7	−6.2
$\Delta\Delta H_f^B$	5.8	6.2	4.8	0.7	4.4	4.7	4.9	−0.6
$\Delta\Delta H_f^M$	−49.5	−49.1	−50.9	−57.8	−51.0	−50.3	−51.1	−58.7

TABLE IV. The LUMO Energies and the Coefficients of p_z Orbitals in the LUMO of 2-Chloro- and 4-Chloro-6-R-pyrimidines at $\theta=0°$ and $20°$

	2-Cl-6-R-pyrimidines							
Compd. No.	**7**		**8**		**9**		**3**	
R	H		Me		OMe		Cl	
θ	0°	20°	0°	20°	0°	20°	0°	20°
E_{LUMO}[a)]	−0.733	−0.825	−0.702	−0.782	−0.631	−0.706	−1.104	−1.150
Coeff.								
N^1	−0.228	−0.221	−0.068	−0.091	−0.310	−0.275	−0.331	−0.267
C^2	0.594	0.573	0.545	0.541	0.591	0.589	0.559	0.582
N^3	−0.228	−0.248	−0.346	−0.338	−0.148	−0.198	−0.082	−0.170
C^4	−0.316	−0.263	−0.121	−0.104	−0.429	−0.331	−0.163	−0.255
C^5	0.574	0.546	0.551	0.528	0.545	0.518	0.562	0.546
C^6	−0.317	−0.309	−0.486	−0.450	−0.185	−0.232	−0.457	−0.331

	4-Cl-6-R-pyrimidines							
Compd. No.	**10**		**11**		**12**		**13**	
R	H		Me		OMe		Cl	
θ	0°	20°	0°	20°	0°	20°	0°	20°
E_{LUMO}[a)]	−0.726	−0.789	−0.685	−0.736	−0.659	−0.700	−1.078	−1.130
Coeff.								
N^1	−0.354	−0.419	−0.064	−0.441	−0.390	−0.409	−0.186	−0.452
C^2	0.530	0.387	0.548	0.084	0.498	0.393	0.574	0.267
N^3	−0.009	0.159	−0.313	0.388	0.050	0.140	−0.199	0.273
C^4	−0.520	−0.572	−0.161	−0.550	−0.575	−0.579	−0.333	−0.590
C^5	0.550	0.443	0.565	0.132	0.506	0.442	0.596	0.309
C^6	−0.106	0.108	−0.488	0.446	0.005	0.139	−0.349	0.277

a) The LUMO energies are in eV.

OMe group at the 6-position lowers the reactivity of Cl at the 4-position of **12**, while in **9** this group plays a role in facilitating the removal of Cl at the 2-position. The value of $\Delta\Delta H_f^W$ decreases in the case of **3** and increases in **13**, whereas the values of $\Delta\Delta H_f^B$ and $\Delta\Delta H_f^M$ decrease appreciably in both **3** and **13**, *i.e.* Cl at the 6-position greatly enhances the reactivities of **3** and **13**.

Based on the differences in the values of $\Delta\Delta H_f^B$, we can summarize the results of the calculation shown in Table III as follows.

In the case of 2-chloro-6-R-pyrimidines Me at the 6-position decreases the reactivity of Cl at the 2-position, OMe at the 6-position increases it a little, and Cl at the 6-position increases it remarkably. In the case of 4-chloro-6-R-pyrimidines both Me and OMe at the 6-position decrease the reactivity of Cl at the 4-position, whereas Cl at the 6-position increases it. Moreover, when we compare the $\Delta\Delta H_f^B$ value of 2-chloro- with that of 4-chloropyrimidine having the same substituent at the 6-position, the $\Delta\Delta H_f^B$ values of **10**, **11** and **13** are smaller than those of **7**, **8** and **3**, whereas this value of **12** is nearly equal to that of **9**.

In 1969 Forchiassin *et al.*[2)] reported the enthalpy changes ΔH^* in the methoxydechlorination of some 2-chloro-4-R-pyridines and 4-chloro-6-R-pyrimidines, in which R(H, Cl, or OMe) is located in the *meta* position with respect to the reaction center and in a conjugative position with respect to the aza group. We investigated the correlation of these ΔH^* values with our $\Delta\Delta H_f^B$,[10)] and obtained a linear relationship between ΔH^* and $\Delta\Delta H_f^B$ with the correlation coefficient $r=0.881$. This relation shows that our experimental results shown in Table I can be reasonably explained in terms of the values of $\Delta\Delta H_f^B$. Moreover, it appears that our reaction is under kinetic control, because in addition to the above relation, the differences between the enthalpy changes of the reactants and those of the products alone could not explain the reactivity differences between the compounds shown in Table I.

As described above, in the transition state B_1 the angle θ between the C–Cl bond and the plane of the pyrimidine nucleus is *ca.* 20°. We examined the differences between the coefficients of the p_z AOs in the LUMOs of chloropyrimidines with $\theta=0°$ and $\theta=20°$.[11)]

As shown in Table IV and Fig. 3, the LUMO energies of all compounds **7**, **8**, **9**, **3**, **10**, **11**, **12** and **13** decrease when θ changes from 0° to 20°, but the order of the LUMO energy levels remains unchanged, and it would be

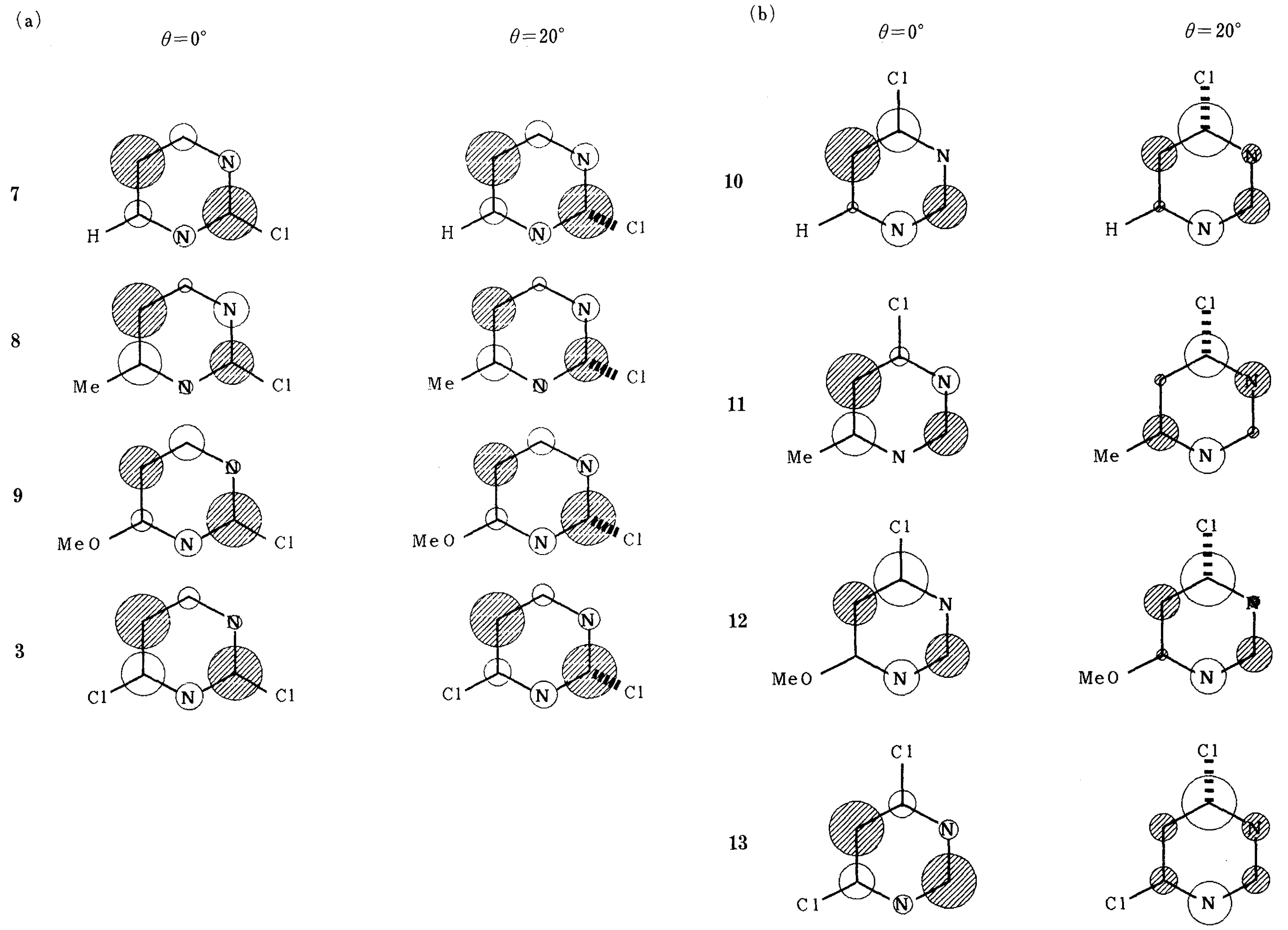


Fig. 3. The LUMOs of 2-Chloro- (a) and 4-Chloro-6-R-pyrimidines (b) at $\theta=0°$ and $\theta=20°$

expected that the delocalization of an electron from MeO^- on the pyrimidine nucleus would be facilitated with the change of the angle θ, from 0° to 20°. In 2-chloro-6-R-pyrimidines **7**, **8**, **9** and **3**, the LUMO amplitudes remain almost unchanged with the change of the angle θ. On the other hand, in 4-chloro-6-R-pyrimidines **10**, **11** and **13** except **12**, the signs of the coefficients of the AOs on N^3 and C^6 of the pyrimidine nucleus are reversed, and the extent of the change in the coefficients of the AOs of **13** is especially large with the change of the angle θ. These results indicate that an electron from the reagent MeO^- can be easily delocalized in **13**, whereas the delocalization of an electron from MeO^- in **12** is depressed by the substituent OMe at the 6-position, because the extent of the change in the coefficients of the AOs in the LUMO is small in **12**. Especially in **13**, the LUMO amplitudes on the reaction center C^4 and on N^1, which is a "p"-cyclic nitrogen atom with respect to the reaction center C^4, increase appreciably when θ changes from 0° to 20°. This is consistent with the results of the kinetic investigation of Chapman *et al.*[12] on the reactions of chloronitropyridines with amines, which are illustrated by the tautomeric effect of a "p"-cyclic nitrogen atom. From the above results, it can be said that the reactivity of the Cl at the 4-position is enhanced by the substituent Cl and depressed by OMe at the 6-position.

Reaction of 2,4-Dichloro-6-R-pyrimidines with MeO^- The $\Delta\Delta H_f^B$ values in the reaction of 2,4-dichloro-6-R-pyrimidines with MeO^- are shown in Table V. $\Delta\Delta H_f^B$-(2-position) and $\Delta\Delta H_f^B$(4-position) stand for the values of the differences of the heat of formation described before, when the substrate is attacked by MeO^- at the 2- and 4-position, respectively. In the reaction of compounds **1**, **2**, **3**, **4** or **5** with MeO^-, the $\Delta\Delta H_f^B$(4-position) value is lower than $\Delta\Delta H_f^B$(2-position) in each case. These calculation results mean that the 4-position is much more subject to attack by MeO^- than the 2-position in these five compounds. On the other hand, in the reaction of compound **6** with MeO^- the $\Delta\Delta H_f^B$(2-position) value is lower than the $\Delta\Delta H_f^B$(4-position) one; this means that Cl at the 2-position is relatively more reactive to MeO^- than Cl at the 4-position. It can be assumed that the depression of the reactivity of Cl at the 4-position by the influence of OMe at the 6-position brings about the relative enhancement of the reactivity of Cl at the 2-postion.

Table V. $\Delta\Delta H_f^B$ Values in the Reaction of 2,4-Dichloro-6-R-pyrimidines with MeO^- ($kcal\,mol^{-1}$)

Compd. No.	**1**	**2**	**3**	**4**	**5**	**6**
R	CO_2Me	Cl	H	C_6H_5	Me	OMe
$\Delta\Delta H_f^B$ (2-position)	−8.1	−4.1	0.7	0.5	1.1	−0.0
$\Delta\Delta H_f^B$ (4-position)	−9.2	−5.0	−0.3	−0.6	0.1	0.6

Concluding Remarks

The experimental results of the reaction of 2,4-dichloro-6-R-pyrimidines could be reasonably explained in terms of $\Delta\Delta H_f^B$ values. It became apparent that in the reaction of 2,4-dichloro-6-R-pyrimidines with MeO^- the transition state B_1, formed just before the formation of the Meisenheimer-type complex M, plays an important role in determining the direction of the reaction. As found in the study on the reaction of 2-chloro- or 4-chloro-6-R-pyrimidines with MeO^-, the reactivity of Cl at the 4-position is greatly influenced, but that of Cl at the 2-position is little influenced by the substituent at the 6-position. This is the reason why in compound **6** the reactivity of Cl at the 2-position is higher than that of Cl at the 4-position.

A further MO study on the influence of the cyclic nitrogen atom and OMe group on the nucleophilic reactions of aromatic heterocycles using pyridine derivatives as model compounds is under way.

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