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THE FLUORINATION OF 2,4,5-TRICHLORO-6-METHYLPYRIMIDINE; EXPERIMENTAL STUDY AND CNDO/2 CALCULATION

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SUMMARY

A study of the kinetics and mechanism of the fluorination of 2,4,5-trichloro-6-methylpyrimidine (TCMP) to form 2,4-difluoro-5-chloro-6-methylpyrimidine (DFCMP) in polar aprotic solvents with KF or NaF has been performed. The rate constants of the fluorination under various conditions were measured. This fluorination proceeds as a pseudo-first-order consecutive reaction. The values of the activation enthalpy $\Delta H^{\ddagger}$, the activation entropy $\Delta S^{\ddagger}$ and Arrhenius activation energy ΔEa were evaluated and the influence of solvents, catalysts and fluorinating agents was discussed. The CNDO/2 method has been applied to the calculation of the reaction path of the fluorination and the energy levels of the components. The calculated results agree well with experimental observation.

INTRODUCTION

At present, fluorinated six-membered heterocyclic nitrogen compounds have got many applications in both biochemistry and dye-chemistry [1] .

Fluorinated heterocyclic compounds are usually obtained by fluorine/chlorine exchange reactions on the corresponding chlorinated compounds. 2,4-Difluoro-5-chloro-6-methylpyrimidine can

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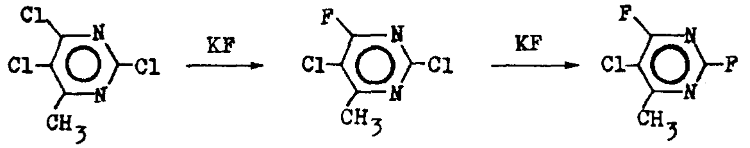
be synthesized by fluorination of 2,4,5-trichloro-6-methylpyrimidine(TCMP), 4-fluoro-2,5-dichloro-6-methylpyrimidine(FDCMP) is produced as an intermediate when alkali metal fluorides e.g. NaF, KF, are used as fluorinating agents[2]. It is necessary to carry out these fluorinations in polar aprotic solvents.

To date there are few literature studies on the kinetics and mechanism of fluorination of chloropyrimidine derivatives. In this paper the fluorination of TCMP is investigated. Tetramethylenesulfone(TMSO), dimethylsulfoxide(DMSO) and nitrobenzene(NB) are used as reaction solvents and NaF and KF are used as fluorinating agents. The results of semiempirical MO (CNDO/2) calculation, especially on the fluorination process of TCMP were described.

MECHANISM AND RATE EXPRESSION

The synthesis of DFCMP proceeds by a selective fluorine/chlorine exchange reaction, i.e. the fluorination of TCMP. Thus, the reaction which is a typical consecutive reaction may be as follows:

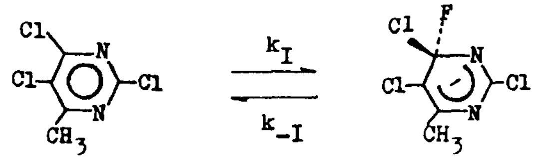


A (TCMP) B (FDCMP) C (DFCMP)

(1)

From current knowledge of nucleophilic aromatic substitution, it can be assumed that the reaction mechanism includes two steps. The reaction mechanism may be shown as eqs.(2) and (3). For a bimolecular nucleophilic aromatic substitution(or Sn$_2$Ar) step 1 is usually a very slow equilibrium process while step 2 is very fast so that step 1 becomes the rate-determining step. The steady-state

Step 1:



(2)

Step 2:

(3)

approximation can be applied here, so that the rate expressions of the fluorination can be deduced as follows:

$$\ln(C_{AO}/C_A) = k_1 t \qquad (4)$$

$$C_B = C_{BO}e^{-k_2 t} + k_1 C_{AO}\left(\frac{e^{-k_1 t} - e^{-k_2 t}}{k_2 - k_1}\right) \qquad (5)$$

$$C_C = C_T - C_{BO}e^{-k_2 t} + C_{AO}\left(\frac{k_1 e^{-k_2 t} - k_2 e^{-k_1 t}}{k_2 - k_1}\right) \qquad (6)$$

where C_{AO}, C_{BO} is initial concentration of component ($t = 0$ min), and total concentration C_T equals $C_{AO} + C_{BO}$.

$$C_B^{max} = \frac{k_1 C_{AO}}{k_2} e^{-k_1 t_{max}} \qquad (7)$$

The rate constants k_1 and k_2 are determined from the concentration of various components (C_{AO}, C_{BO}, C_A, C_B, C_C) which can be measured by gas chromatography (GC). If the values of k_1 and k_2 remain constant during the fluorination, the assumed reaction mechanism is verified. The reaction rate of the fluorination depends upon the concentration of fluoride anion. The greater the quantity of fluoride anion, the faster the reaction rate. Although the properties of polar aprotic solvents (e.g. dielectric constant, dipolarity) can influence the solubility of KF or NaF, the use of a phase transfer catalyst (e.g. a crown ether) can also increase the concentration of fluoride anion.

RESULTS

1) The reactions were performed in DMSO or TMSO using KF or NaF as fluorinating agent.

a. Experimental data (see Table I, and Table II)

b. Kinetic curves of the fluorination

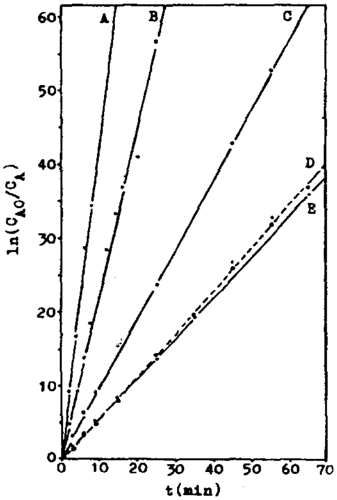


Fig. 1. The relation of ln(C_{A0}/C_A) - t. (DMSO, KF). A - 412.2 K, B - 400.2 K, C - 392.4 K, D - 363.2 K (crown ether), E - 381.2 K.

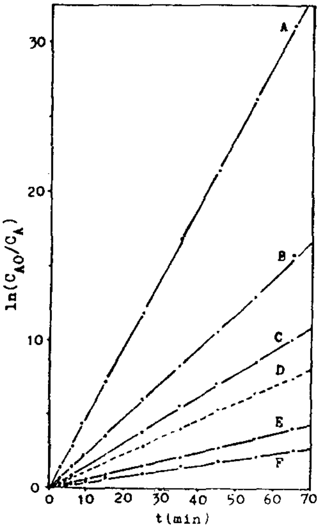


Fig. 2. The relation of ln(C_{A0}/C_A) - t. (TMSO, KF). A - 402.2 K, B - 393.4 K, C - 384.2 K, D - 361.7 K (crown ether), E - 372.2 K, F - 361.1 K.

TABLE I

The values of k_1 and k_2 under various conditions*

Dimethyl sulfoxide, KF			Tetramethylenesulfone, KF			Dimethyl sulfoxide, NaF		
T (K)	$\bar{k}_1 \times 10^{-3}$	$\bar{k}_2 \times 10^{-3}$	T (K)	$\bar{k}_1 \times 10^{-3}$	$\bar{k}_2 \times 10^{-3}$	T (K)	$\bar{k}_1 \times 10^{-3}$	$\bar{k}_2 \times 10^{-3}$
381.2	56.36	21.2	361.1	3.821	1.65	402.9	12.44	1.81
392.4	99.68	36.8	372.2	6.049	2.19	415.4	31.41	5.23
400.2	230.8	101	384.2	15.57	4.36	422.7	54.67	12.5
412.2	448.6	318	393.4	23.69	6.43			
			402.2	47.75	13.5			

* The unit of the rate constant(k) is min^{-1}.

TABLE II

The values of ΔEa, ΔH^{*} and ΔS^{*}*

	ΔEa_1	ΔH_1^{*}(393K)	ΔS_1^{*}(393K)
DMSO, KF	9.364	8.583	-56.29
DMSO, NaF	10.61	9.815	-56.20
TMS, KF	7.740	6.959	-56.86

* The unit of ΔEa and ΔH^{*} is kcal. and ΔS^{*} is cal/K·mol.

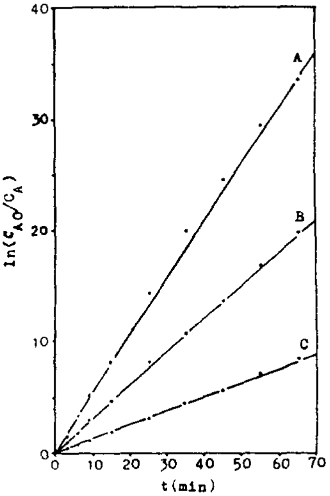


Fig. 3. The relation of ln(C_{A0}/C_A) - t. (DMSO, NaF). A - 422.7K, B - 415.4K, C - 402.9K.

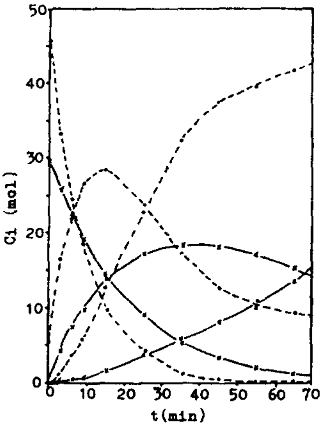


Fig. 4. The relation of Ci - t. —— 402.2K, TMSO + KF. ---- 392.2K, DMSO + KF.

2) Catalysis: The reaction rate can be increased by the use of 18-crown ether-6 (0.2g) as catalyst. Comparable experimental data are shown in Table III, Fig. 1 and Figure 2.

For the reaction condition: solvent — NB, fluorinating agent -- KF and temperature -- 383.2K, there was no reaction and FDCMP was not detected by GC after 2 hrs. Once the crown ether (0.2g) was added, the reaction was speeded up and DFCMP can be immediately detected. The colour of the reaction liquid became dark.

DISCUSSION

Reaction and mechanism

The fluorination mechanism for the first process is proved since the experimental data are satisfied by eq.(4) and the values of k_1 maintained constant.

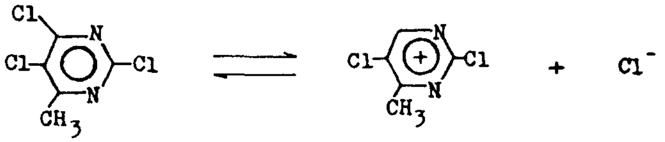
TABLE III

Effect of Catalysis on the Fluorination

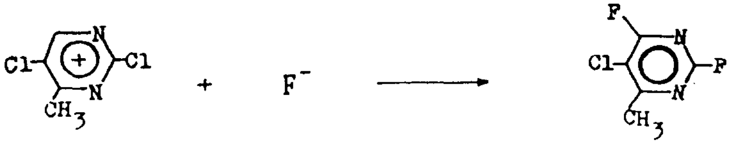
Solvents	T (K)	Crown ether (0.2g)	$\bar{k}_1(\mathrm{min}^{-1})$	$\bar{k}_2(\mathrm{min}^{-1})$
DMSO	381.2	No	0.05636	0.0212
	363.2	Yes	0.05592	0.0138
TMS	361.1	No	0.003821	0.00165
	361.7	Yes	0.01184	0.00348
NB	383.2	No	hardly react	
	383.2	Yes	react fast	

* The fluorinating agent is KF.

If the reaction proceeds as follows:



(8)



(9)

we would also get a pseudo-first-order reaction expression. The value of $\Delta S_1^{\ddagger}$ must be positive since the number of different particles and the degree of randomness increase. In the Sn$_2$Ar mechanism (eqs. 2, 3), the value of $\Delta S^{\ddagger}$ must be negative because the degree of randomness decreases. Thus, the value of $\Delta S^{\ddagger}$ in Table II is a strong evidence for the Sn$_2$Ar mechanism.

Further, the values of $\Delta S_1^{\ne}$ under various conditions are similar. This proves that the reaction mechanism for fluorination and the structures of the activated complexes are independent with the fluorinating agents, although the fluorination is easier with KF than NaF because of the difference of the solvation.

The experiments showed that however fast the first sample (t = 0) was taken, FDCMP can still be detected by GC. It is very clear that there is a very fast process of fluorine/chlorine exchange reaction at the beginning of the fluorination and then the reaction tends to become smooth and steady.

Influence of solvents

Polar aprotic solvents must be used for the fluorination. In hydroxylic (or protic) solvents there is strong hydrogen bonding of the fluoride anion so that its nucleophility becomes very weak, and, for example, the pyrimidine will be hydrolysed.

Polar aprotic solvent compounds (especially DMSO, TMSO) contain polar groups (e.g. S = O) which can readily solvate the metal cation. A 'free' and 'exposed' fluoride anion with high reactivity is produced and its concentration is increased, because of high solubility of the fluorides. On the other hand, the pyrimidines readily dissolve in these solvents too. However, NB does not solvate so strongly and fluorination only occurs at high temperatures and with long reaction times. Fluorination with a Sn_1Ar mechanism is unlikely, because the formation of the carbocation (eq. 8) must be through use of electron-attracting solvents to produce the heterolytic cleavage or heterolysis of C–Cl bond, while the polar aprotic solvents are electron-donating which are unsuitable for the heterolysis of the C–Cl bond of TCMP. Further, if the reaction were Sn_1Ar, there would be two kinds of 'free' or 'exposed' anion (i.e. F^- and Cl^-) with high reactivity, therefore, this reaction system would be in a high energy level. However, if the reaction is by a Sn_2Ar mechanism (eqs. 2,3), the 'free' and 'exposed' fluoride anion reacts with pyrimidine to form the relatively stable activated complex with a lower energy for the reaction system. A reaction will generally proceed along the path having an energy minimum, so that the reaction mechanism of the fluorination in polar aprotic solvents must be bimolecular nucleophilic aromatic substitution.

Solvent effect theories which were developed by Kirkwood et al were used here qualitatively. According to the model of Laidler-Landskroner[4].

$$\ln(k) = \ln(k_o) + \frac{\varepsilon^2}{2kT}\left(\frac{1}{D} - 1\right)\sum\left(\frac{Z_i^2}{b_i}\right) + \frac{3}{8}\,\frac{\varepsilon^2}{kT}\left(\frac{2}{D} - 1\right)\sum\frac{\vec{\mu}_i^{\,2}}{b_i^3} \tag{10}$$

The rates of fluorination in DMSO and in TMSO have been compared.

$$\ln\frac{k_{DMSO}}{k_{TMSO}} = \frac{\varepsilon^2}{2kT}\left(\frac{1}{D_{DMSO}} - \frac{1}{D_{TMSO}}\right)\left(\frac{Z_F^2}{b_F} - \frac{Z_\ddagger^2}{b_\ddagger}\right) + \frac{3\varepsilon^2}{8kT}\left(\frac{2}{D_{DMSO}} - \frac{2}{D_{TMSO}}\right)\left(\frac{\vec{\mu}^{\,2}_{TCMP}}{b^3_{TCMP}} - \frac{\vec{\mu}_\ddagger^{\,2}}{b_\ddagger^3}\right) \tag{11}$$

$$\ln\left(\frac{k_{DMSO}}{k_{TMSO}}\right) = \frac{\varepsilon^2}{kT}\left(\frac{2}{D_{DMSO}} - \frac{2}{D_{TMSO}}\right)(-1.601) \tag{12}$$

The term $\left(\frac{1}{D_{DMSO}} - \frac{1}{D_{TMSO}}\right)$ is negative, so a reasonable result which fits the experimental data ($k_{DMSO} > k_{TMSO}$) has been obtained. In eq.(11) $\vec{\mu}_{TCMP}$ and $\vec{\mu}_\ddagger$ are the dipole moments of the reactant and activated complex (d_{F-C} = 2.93 Å, d_{Cl-C} = 1.70 Å) respectively, and b, the radius of the species ($b_{TCMP} = b_\ddagger$ = 4.60Å, b_F = 1.33 Å).

When we deal with the same problem by use of the model of Hiromi[5], we fail to get a reasonable result.

$$\ln(k) = \ln(k_o) + \frac{\varepsilon^2}{2kT}\left(\frac{1}{D} - \frac{1}{D_o}\right)\left(\frac{L_A}{b_A} + \frac{L_B}{b_A} - \frac{L_\ddagger}{b_\ddagger}\right) \tag{13}$$

The L s are the charge configuration functions. $L_\ddagger$ = 3.148, L_{F^-} = 2, L_{TCMP} = 0.05118, b is as same as above.

$$\ln\left(\frac{k_{DMSO}}{k_{TMSO}}\right) = \frac{\varepsilon^2}{2\,kT}\left(\frac{1}{D_{DMSO}} - \frac{1}{D_{TMSO}}\right)\left(\frac{L_A}{b_A} + \frac{L_B}{b_B} - \frac{L_{\ddagger}}{b_{\ddagger}}\right) \quad (14)$$

$\left(\frac{L_A}{b_A} + \frac{L_B}{b_B} - \frac{L_{\ddagger}}{b_{\ddagger}}\right) = 0.83$, so the rate in TMSO should be faster than that in DMSO. The value of L depends sensitively upon how much the charge is embedded within the sphere. It is found that a suitable coordinate could be chosen to force the value of L to become large enough to get a result which is in accord with the experimental data. Reliable theory for a quantitative description of solvent effects[6], especially for polar aprotic solvents has not been developed. The values of $\vec{\mu}_i$ and charge distribution used here were calculated by the CNDO/2 method.

Influence of crown ether as catalyst

Crown ether is very effective catalyst used in the fluorination. The reaction rate can be increased by adding the crown ether under all conditions (see Table III). However, the lower the polarity of solvent, the greater the catalysis effect, and this effect is extremely obvious in NB.

The crown ether ties up the K^+, i.e. solvates the alkali metal[3] portion of salt KF, leaving the F^- anion much freer or 'exposed' to attack the pyrimidine ring. This makes F^- anion a strong nucleophile. Since the strong solvation of DMSO or TMSO for the K^+ has made the F^- anion free and 'exposed' to a large extent, the reaction rate of fluorination is mainly dependent upon the activation enthalpy $\Delta H^{\ddagger}$ claimed for the attack of F^- anion to the pyrimidine ring. Therefore, the adding crown ether in DMSO or TMSO is not very useful to decrease the $\Delta H^{\ddagger}$. Because NB has weak solvation for the K^+ ion, the action of the crown ether in NB is very important.

Application of CNDO/2 calculation to the fluorination process

The properties of the compounds in the ground state

The great merit of the CNDO/2 method is its capability for prediction of the equilibrium geometry of the molecules, fairly correct charge distributions and dipole moments. Although it fails to predict binding energies of the molecules, the calculated values of binding energy need only be modified[7] by a multiplying factor p_E in order to yield experimentally observed or thermochemical binding energy values, i.e.

$$E_{B.E.(actual)} = p_E * E_{B.E.(CNDO/2)} \qquad (15)$$

The molecules studied in this work are listed in Table IV together with computed dipole moments, heats of formation, calculated and actual binding energies.

The data included in Table IV shows that if the value of p_E is 0.345 to 0.365, the results of the calculation can be improved.

The fluorination pathways and the structure of reaction intermediate (or T.S.).

That nucleophilic aromatic substitution proceeded by the two-step mechanism is widely accepted by organic chemists. When X

TABLE IV

Binding Energy, Heats of Formation, and Dipole Moment of the Compounds, Calculated by CNDO/2 Method

Compounds	Binding* Energy (CNDO/2)	Modified* Binding Energy	Actual * Binding Energy	Dipole‡ Moment	Heat of* Formation
Benzene	3945.42	1369.06	1369.81	0.0000	-5285.78
2,4,5-Cl-py	4333.64	1499.44	1497.00	2.4877	-5659.31
2-F-4,5-Cl-py	4306.39	1524.46	1524.50	2.7721	-5621.97
4-F-2,5-Cl-py	4304.72	1523.87	1524.50	2.6098	-5620.32
2,4-F-5-Cl-py	4277.11	1552.76	1552.00	2.9048	-5582.60

* kcal/mol. ‡ debyes

(leaving group) and Nu (attacking group) are oxygenated groups (e.g. OCH_3) the complexes (normally called the Meisenheimer complex) are stable enough to identify. When the substrate is poorly activated, the complex is so unstable that it can not be seen. In such cases, a MO study of the molecular properties provide a useful alternative until suitable experimental techniques are developed.

The errors which occur using the semi-empirical MO methods are unimportant when dealing with qualitative problems. The methods used here are not expected to reproduce absolute values for change in total energy of fluorination process but they are good in showing tendencies.

The changes of the total energy of the system containing TCMP and F^- anion are listed in Table V, VI and Fig. 5.

The structure of the reaction intermediate which occurs during fluorination may be as follows: F-C bond length is 1.33 Å, Cl-C, 1.70 Å and angle F-C-Cl is in range 104.47 - 99.47°. Figure 6 shows the minimum energy pathway for fluoride anion attacking the pyrimidine ring.

One effect of ignoring solvation energies (in gas phase) is that the energy of the reaction is calculated to be higher than that of the intermediate. This phenomenon, which was described by H.F.Beer[8] dealing with Wheland Intermediates using a CNDO/2 method, is reasonable since the complex allows a major redistribution of the negative charge.

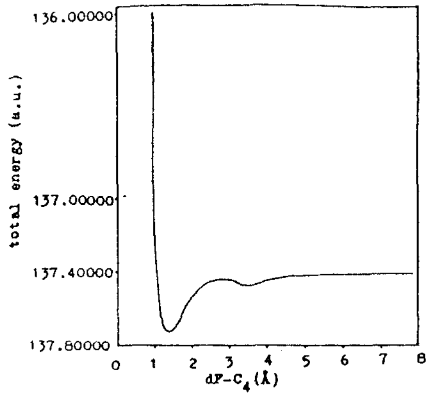


Fig. 5. Energy-bond length relationship.

TABLE V

Geometries and Energies of TCMP-F Calculated by CNDO/2 Method

R_{F-C4}	$\angle FC_4Cl$	R_{Cl-C4}	-E, au	R_{F-C2}	$\angle FC_2Cl$	R_{Cl-C2}	-E, au
1.730	109.47	1.700	137.61091	1.730	109.47	1.700	137.60199
1.330	109.47	1.700	137.73511	1.330	109.47	1.700	137.72329
1.730	109.47	2.100	137.49000				
1.330	109.47	2.100	137.64000				
1.530	109.47	1.700	137.70768	1.530	109.47	1.700	137.69666
1.130	109.47	1.700	137.50000				
0.930	109.47	1.700	136.61000				
0.530	109.47	1.700	128.28000				
1.330	104.47	1.700	137.73790	1.330	104.47	1.700	137.72606
1.330	114.47	1.700	137.72422	1.330	114.47	1.700	137.71730
1.330	99.47	1.700	137.73747	1.330	99.47	1.700	137.72562
1.330	94.47	1.700	137.73311	1.330	94.47	1.700	137.72091
1.530	104.47	1.700	137.71199	1.530	104.47	1.700	137.70070

Distances in Ångströms, and angles in degrees.

The reactants first associate to form a charge/dipole complex with virtually no change in the geometry of the TCMP (Fig. 6). When the distance of F-C is large, fluoride anion attacks the ring in the direction of Cl-C bond axis as well as in the plane of the ring (also see Table VII). As shown in Fig. 6, the bonding between the fluoride anion and the pyrimidine ring is electrostatic in nature, due to charge/dipole interaction. We must pay attention

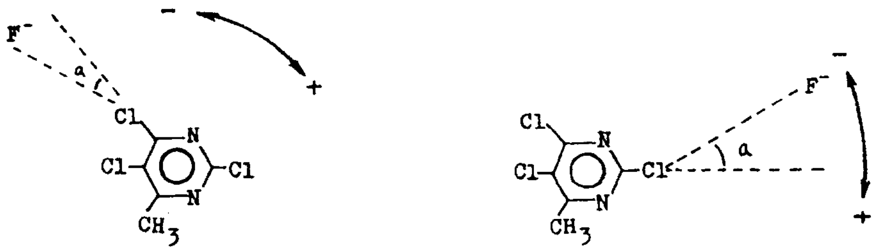


Fig. 6. Variation in TCMP geometries.

TABLE VI

Geometries and Energies of TCMP-F Calculated by CNDO/2 Method

R_{F-C4}	$\angle$FCO	$\angle$ClCO	-E, au	R_{F-C2}	$\angle$FCO'	$\angle$ClCO'	-E, au
7.730	0.00	0.00	137.42507	7.344	0.00	0.00	137.42440
4.730	0.00	0.00	137.42749	4.730	0.00	0.00	137.42559
3.730	0.00	0.00	137.46477	3.730	0.00	0.00	137.45932
3.730	10.23	0.00	137.45738	3.730	10.23	0.00	137.45212
3.330	0.00	0.00	137.46829	3.330	0.00	0.00	137.45737
3.330	10.23	0.00	137.46978	3.330	10.23	0.00	137.45886
3.330	10.23	10.23	137.44863	3.330	10.23	10.23	137.43939
2.930	10.23	0.00	137.02975				
2.930	10.23	10.23	137.32200				
2.930	30.23	0.00	137.43118	2.930	40.23	0.00	137.42390
2.930	30.23	10.23	137.43189	2.930	40.23	10.23	137.42625
2.930	50.23	0.00	137.43411	2.930	50.23	0.00	137.42856
2.930	50.23	10.23	137.43138				
3.130	10.23	0.00	137.38301	3.130	10.23	0.00	137.36762
3.130	30.23	0.00	137.44364	3.130	30.23	0.00	137.43074
3.130	40.23	0.00	137.43644	3.130	40.23	0.00	137.42892
2.730	50.23	10.23	137.43703	2.730	50.23	10.23	137.43009
2.730	50.23	20.23	137.43020	2.730	50.23	20.23	137.42697
2.530	50.23	0.00	137.42943	2.730	50.23	0.00	137.42573
2.530	50.23	10.23	137.43798	2.530	50.23	0.00	137.41780
2.530	50.23	20.23	137.43935	2.530	50.23	20.23	137.43518
2.530	50.23	30.23	137.43245	2.530	50.23	30.23	137.42859
2.130	50.23	20.23	137.48048	2.130	50.23	30.23	137.48178
2.130	50.23	30.23	137.48702	2.130	50.23	20.23	137.47486
2.130	50.23	40.23	137.47822	2.130	50.23	40.24	137.47586
1.730	50.23	30.23	137.61499	1.730	50.23	30.23	137.60556
1.730	50.23	40.23	137.62517	1.730	50.23	40.23	137.61587
1.730	50.23	50.23	137.61963	1.730	50.23	50.23	137.61020
1.530	50.23	40.23	137.71163				
1.530	50.23	50.23	137.71384				

Distances in Ångströms, angles in degrees.

TABLE VII

The F^- anion attacking energies to pyrimidine ring

4-position of pyrimidine				2-position of pyrimidine			
D_{F-C} = 4.730Å		D_{F-C} = 3.330Å		D_{F-C} = 4.730Å		D_{F-C} = 3.330Å	
a	energy	a	energy	a	energy	a	energy
0	-137.42749	0	-137.46978	0	-137.42559	0	-137.45886
+20	-137.42649	+20	-137.42649	+20	-137.42525	+20	-137.44154
-20	-137.42691	-20	-137.44941	-20	-137.42483	-20	-137.44057

TABLE VIII

Net Charge for TCMP-F System, Calculated by CNDO/2 Method

		Distances of $F-C_4$					
No.	Atoms	7.730	3.730	3.130	2.130	1.730	1.330
1	Cl	-0.0785	-0.1099	-0.1323	-0.1166	-0.1402	-0.1595
2	C	0.0134	0.0157	0.0192	-0.0103	-0.0544	-0.0833
3	C	0.2215	0.1349	0.1189	0.3287	0.4004	0.4614
4	N	-0.2295	-0.2449	-0.2845	-0.2976	-0.3644	-0.4245
5	C	0.2913	0.2852	0.2998	0.3056	0.3244	0.3342
6	N	-0.2400	-0.2708	-0.3177	-0.3096	-0.3699	-0.4174
7	C	0.1532	0.1359	0.1151	0.1352	0.1364	0.1268
8	Cl	-0.0400	0.0744	0.1246	-0.1212	-0.1950	-0.2515
9	Cl	-0.0948	-0.1354	-0.1577	-0.1525	-0.1711	-0.1890
10	C	-0.0525	-0.0484	-0.0416	-0.0429	-0.0414	-0.0387
11	H	0.0033	-0.0064	-0.0159	-0.0133	-0.0193	-0.0258
12	H	0.0263	0.0116	0.0027	0.0063	-0.0012	-0.0097
13	H	0.0263	0.0096	-0.0030	-0.0011	-0.0059	-0.0108
14	F	-1.0000	-0.8515	-0.7276	-0.7107	-0.4985	-0.3122

Distances in Ångströms, and angles in degrees.

to the fact that there are larger negative charges on the pyrimidine ring than on its substituents. When the fluoride anion approaches the ring, F and Cl repel one another. These make fluoride anion attacking pathway change the original direction and turn the angles out of the plane of TCMP ring. But Cl atom does not change until the distance of F-C becomes less than 2.93 Å, because the conjugate effect makes the energy of the system lower. In the process of fluorination there is an energy barrier which is due entirely to the renewal of the conjugated system. The barrier is small that fluorination of TCMP would take place rapidly in the gas phase as it is a exothermal reaction. The negative charges on the N_1 and N_3 atoms are very large when the distance F-C is 1.330Å, evidently there is a charge transfer during the process of fluoride anion attacking the ring (see Table VIII).

When the distance of C-F is 7.730 Å, the net charge on F is -1, while the charge on the ring, is zero and when the distance of C-F is 1.330 Å, the net charge on F is -0.3122, while the charge on the ring, is -0.6878. It is reasonable that a σ-complex can be written as:  ., and coincident with the early idea.

The minimum energy of pathway, in which a fluoride anion approaches C_4 of the pyrimidine ring, is lower than that of fluoride anion approach to C_2 of the ring. If the usual pattern of nucleophilic reaction is followed, the C_2-position shall be more active because the charge on C_2 is more positive. But the experimental fact (also see ref. [2]) showed the C_4-position to be more active when using KF or NaF as a fluorinating agent. The result of the calculation agreed with the experimental values so the fact of more activity for the C_4-position is quite reasonable.

EXPERIMENTAL

Materials

Nitrobenzene (NB): The commercial product (c.p.) was dried by adding anhydrous calcium chloride and vacuum distilled. Dimethyl sulfoxide (DMSO): The commercial product (c.p.) was dried by adding calcium hydride and vacuum distilled. Tetramethylenesulfone (TMSO): TMSO (industrial) was purified by the repeated addition of NaOH followed by vacuum distillation. The pure product was dried by the addition of calcium hydride and then redistilled. Fluorinating agents: Anhydrous potassium and sodium fluoride were dried and ground to fine particle (100 Mesh), and then kept under vacuum.

2,4,5-Trichloro-6-methylpyrimidine(TCMP)[9] : 6-methyluracil was synthesized by the reaction of acetoacetic ester with urea in n-hexanol and converted to TCMP by two-step chlorination(using first sulfonyl chloride, then phosphoryl chloride) following by vacuum distillation. Yield: 65%.

2,4-Difluoro-5-chloro-6-methylpyrimidine(DFCMP): 50g of TCMP was charged into a reaction vessel with 78g of anhydrous KF and 20g NB. The reaction contents were heated to reflux(208°C). After 7 hrs the temperature dropped to 174 C. 30g of DFCMP were obtained by the fractional distillation. Yield: 71%.

4-Fluoro-2,5-dichloro-6-methlpyrimidine(FDCMP): 30g of TCMP was charged into a reaction vessel with 40g anhydrous KF and 100g of TMSO. The reaction proceeded at 140°C for 1 hr, then pure FDCMP was obtained by repeated fractional distillation. Yield: 40%. The product was examined by GC and MS(M^+= 182).

F atom of FDCMP was established in position 4 of the pyrimidine ring (the proportion of 4-FDCMP is more than 93%) by ^{19}F NMR (4-F: δ = -12.66). The ^{19}F NMR measurement was carried out with a FX-90Q NMR with a ^{19}F dual sample holder at a measurement frequency of 84.25 MHz. The shifts refer to trifluoroacetic acid(δ = 0 ppm) as internal standard using $(CD_3)CO$ as solvent.

Catalyst: 18-crown ether-6 (AR).

Measurement of Kinetic Data

Reaction and Sampling: A reaction vessel(250 ml) was filled with solvent 100 ml(NB, TMSO or DMSO) and TCMP 10g. The stirred contents of the vessel were heated to a specific reaction temperature(~± 0.1°C). As soon as a fluorinating agent(0.3 mol KF or NaF) was added into the reaction vessel, the first sample(1 ml content) was withdrawn and immediately cooled to 0°C and the values of the initial concentrations C_{A0}, C_{B0}(t = 0) measured. Other samples were withdrawn similarly. The stationary phase used in GC column was fluorogum III : H_3PO_4 : PEG-20000 : 101 silane support = 10:2:1:100. Since all the pyrimidines in the reaction can be detected, concentrations can be calculated by the area normalization method. The relative detector response factors of pyrimidines are TCMP = 0.977, FDCMP = 0.988, and DFCMP = 1.000, respectively. Percentage concentrations were changed into molarities.

Treatment of Data

Calculation of k_1 and k_2: k_1 can be got from eq.(8). From the curves of C_B against t, the values of t_{max} and C_B^{max} can be found and the value of k_2 can be calculated from eq.(7). The activation energy, activation enthalpy and activation entropy of the fluorination can be got from eqs.(16), (17) and (18).

$$\ln k = \ln A - \frac{\Delta Ea}{R\,T} \tag{16}$$

$$\Delta H^{*} = \Delta Ea - RT \tag{17}$$

$$\Delta S^{*} = R\ln\frac{A}{T} - R\ln\frac{e\,k}{h} \tag{18}$$

Eq.(17) and (18) can be obtained from eq.(19).

$$k = \frac{kT}{h}e^{-\Delta G^{*}/RT} = \frac{kT}{h}e^{-\Delta H^{*}/RT}\,e^{\Delta S^{*}/R} \tag{19}$$

CNDO/2 Calculation

Calculations have been carried out using the CNDO/2 method. Standard geometries [10,11] of the molecules considered were used (Fig. 7). The F-C and Cl-C bond lengths were selected as 1.33 Å and 1.70 Å, respectively.

Calculation were performed by use of the CNDO/2 program obtained from Institute of Biochemistry (Shanghai) on a Burroughs 6935 computer at ECICT. Physical properties were calculated by CNDO/2 method as follows [12] :

Binding energy: $$\Delta H_B = E^m - \sum_A E_A^e \tag{20}$$

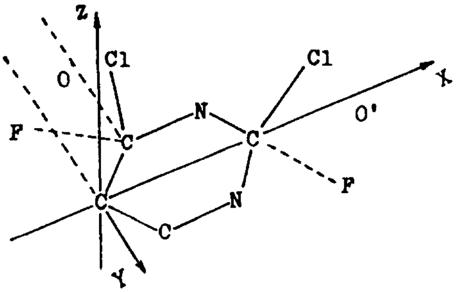


Fig. 7. Standard geometrical projection.

E^m ----- total energy of the molecule; E_A^m ----- the energy of an atom.

Heats of formation: $\Delta H_f = \Delta H_B - \sum_A H_f(A)$ (21)

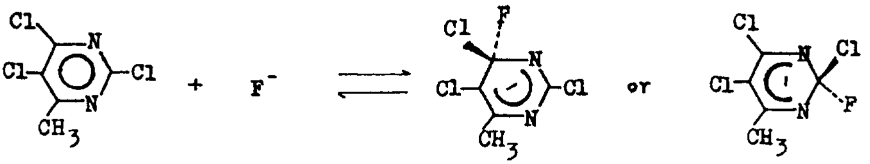
$H_f(A)$ ----- heats of formation of atoms.

Dipole moment: $\vec{\mu} = \vec{\mu}_0 + \vec{\mu}_1$ (22)

$$\vec{\mu}_0 = 2.5416 \sum_A Q_A \vec{R} \quad (23)$$

$$\vec{\mu}_1 = -14.67 \sum_A \zeta_A P_{2sA} \; P_{2p_xA} \quad (24)$$

The fluorination reaction proceeding in the gas phase was hypothesized as:



According to this process, the interaction of fluoride anion with TCMP has been investigated while decreasing the distance between F and C, and while increasing Cl-C bond length. In the discussion of formation of the reaction intermediates, the ring geometries were assumed to be unchanged.

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