[Chem. Pharm. Bull.
22(9)2123—2130(1974)]

UDC 547.491.4.04 : 547.7.03.04

Studies on Organic Sulfur Compounds. XVII.[1] Ambident Reactivities of Alkoxycarbonyl Isothiocyanates with Heterocyclic Bases

Takashi Matsui[2a] and Mitsuo Nagano[2b]

Agricultural Chemicals Research Laboratories[2a] and Central Research Laboratories,[2b] Sankyo Co., Ltd.

(Received March 7, 1974)

Ambident reactivities of alkoxycarbonyl isothiocyanates (**2**) with heterocyclic amines were discussed from the concept of charge and frontier controlled interactions which is a qualitative interpretation of the hard and soft acids and bases (HSAB) principle. The calculated charge densities indicate hard nucleophiles have the tendency to attack on the carbonyl carbon atom and soft nucleophiles on the isothiocyanato moiety of **2**.

To clarify the difference in basic behavior of heterocyclic amines, correlations existing in the ionization data of pyridinium and thiazolium ions were analyzed using the dual substituent parameters of F (field) and R (resonance). It seems likely that the F effect results mostly from charge controlled interactions and the R effect from electron transfer interactions between the nearly degenerate overlapping orbitals. It was suggested that the magnitude of the F and R factors of the regression equations can be an indication of the charge and frontier controlled interactions between the two interacting molecules and the F effect may have an important role in determining the pathway of approach in the initial stage of the reactions.

The concept of hard and soft acids and bases (HSAB)[3] which found its first application in coordination chemistry was shown to be useful in organic chemistry.[4]

Hudson[5] and Saville[6] applied this concept to muti-center chemical reactions. Many chemical bonds of differing type and strengths can be regarded as representing partnerships between acids and bases. Most acceptor (acid) and donor (base) molecules can be placed in the category of Hard or Soft. The HSAB principle states that hard acids prefer to coordinate to hard bases and soft acids prefer to coordinate to soft bases.

Klopman[7] showed the quantum chemical perturbation equation reproduces the qualitative features of HSAB concept and emphasized the importance of charge and frontier controlled effects, connected with charge transfer or partly covalent bonding in the transition state. Hard and soft behavior depends upon the energy of the frontier orbitals.[8]

Fukui, *et al.*[9] pointed out the important role of the orbital overlapping interaction of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) in explaining the formation of new bonds and the weakening of old bonds in the chemical interaction between two molecules. When the difference in energy of these orbitals is large and very little electron transfer occurs, the reaction will be controlled by the total charges on the two reagents. This is called a charge controlled hard–hard interaction. On the other hand, when two frontier orbitals are nearly degenerate and strong electron transfer

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[1] Part XVI: T. Matsui, M. Nagano, J. Tobitsuka, and K. Oyamada, *Chem. Pharm. Bull.* (Tokyo), **22**, 2118 (1974).

[2] Location: *Hiromachi, Shinagawa-ku, Tokyo.*

[3] R.G. Pearson, *J. Am. Chem. Soc.*, **85**, 3533 (1963); *J. Chem. Education*, **45**, 581, 643 (1968).

[4] R.G. Pearson and J. Songstad, *J. Am. Chem. Soc.*, **89**, 1827 (1967).

[5] R.F. Hudson, *Struct. Bonding* (Berlin), **1**, 221 (1966).

[6] B. Saville, *Angew. Chem. Intern. Ed. Engl.*, **6**, 928 (1967).

[7] G. Klopman, *J. Am. Chem. Soc.*, **90**, 223 (1968).

[8] K. Fukui, T. Yonezawa, and H. Shingu, *J. Chem. Phys.*, **20**, 722 (1952); **22**, 1433 (1954).

[9] *a)* K. Fukui and H. Fujimoto, *Bull. Chem. Soc. Japan*, **41**, 1989 (1968); **42**, 3399 (1969); *b)* H. Fujimoto, S. Yamabe, and K. Fukui, *ibid.*, **44**, 2936 (1971).

occurs, the reaction is called a frontier controlled soft–soft interaction. It occurs only in reactions between nucleophiles of low electronegativity and electrophiles of high electronegativity with a good overlap of the interacting orbitals. Hard-hard interactions turn out to be charge–controlled and soft–soft interactions are frontier-controlled.

The above concept seems to be useful for understanding the ambident reactivities of alkoxycarbonyl isothiocyanate (**2**) and the differences in basic behavior of heterocyclic amines.

The experimental results previously reported[1,10] have shown the nucleophilic reaction of 2-aminothiazole (**1**) with **2** gives thiazolo[3,2-*a*]-s-triazin-4-thio-2-one (**3**), N-alkoxycarbonyl-N′-(2-thiazolyl)thiourea (**4**), and alkyl N-(2-thiazolyl)carbamate (**5**). Under similar conditions, 2-aminopyridine (**6**) afforded ethyl 4-(2-pyridyl)-3-thioallophanate (**7**) in a good yield. However, 4-aminopyridine (**8**) afforded no addition product, but gave only ethyl N-(4-pyridyl)carbamate (**9**).

In this paper we wish to discuss the differences among those heteroaromatic amines and mechanism of the ambident reactivities of **2** from the concept of charge and frontier controlled interactions.

Method

The CNDO/2 method[11,12] has been applied to the calculation of electronic structure of **1**, methoxycarbonyl isothiocyanate (**2a**), and aminopyridines. As a basis set for sulfur atoms, only 3*s*, 3*p* Slater orbitals are used.[13] The parametrization is just the same as was given by Pople.[12] Because the geometries of the molecules have not been determined, the bond angles and bond lengths are selected from experimental data.[12,14]

The charge densities are defined from the following equation:

$$q_A = 2\sum_i^{\text{on } A} C_i^2$$

where q_A is the charge densities on atom A; C_i is the coefficient of atomic orbital i; and $\sum^{\text{on} A}$ denotes the summation over the specified orbitals belonging to the A atom.

The calculated charge distribution is shown in Fig. 1a—c together with atom coordinate system. The figures given near the atoms are net charge densities of the atoms. The frontier electron densities are indicated by the size of the circle located at the atom. The dotted line is that of the LUMO.

The magnitude and directions of the calculated dipole moment are designated by the arrows.

The multiple regression analysis[15] on the ionization data of pyridinium and thiazolium ions was executed using the IBM Scientific Subroutine Package programs, by which multiple regression coefficient, correlation coefficient (r), t-value (t), and F-value (Fn_1,n_2) for analysis of variance can be calculated.

Results and Discussion

Differences in Charge Distribution

The calculation is still a very crude approximation, but the results obtained are sufficient for qualitative and even some quantitative interpretation.[16]

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[10] M. Nagano, T. Matsui, J. Tobitsuka, and K. Oyamada, *Chem. Pharm. Bull.* (Tokyo), 20, 2618, 2626 (1972).

[11] *a*) J.A. Pople, D.P. Santry, and G. Segal, *J. Chem. Phys.*, 43, S129 (1965); *b*) J.A. Pople and G.A. Segal, *ibid.*, 43, S136 (1965); 44, 3289 (1966).

[12] J.A. Pople and D.L. Beveridge, "Approximate Molecular Orbital Theory," McGraw-Hill Book Co., 1970.

[13] When 3d orbitals were included, no convergence was obtained in the calculation of charge densities of **2a**.

[14] *a*) L.E. Sutton, "Table of Interatomic Distances and Configurations in Molecules and Ions," The Chemical Society, London, 1958; *b*) G.C. Dousmams, T.M. Sanders, Jr., C.H. Townes, and H.J. Zeiger, *J. Chem. Phys.*, 21, 1416 (1953).

[15] C.A. Bennet and N.L. Franklin, "Statistical Analysis in Chemistry and the Chemical Industry," John Wiley & Sons, 1954.

[16] It has been suggested that the chemical reactivity index, the frontier electron densities, obtained from the CNDO MO functiom can be a suitable measure for an intramolecular comparison of the chemical reactivities; H. Fujimoto, S. Sugihara, S. Yamabe, and K. Fukui, *Bull. Chem. Soc. Japan*, 44, 2565 (1971).

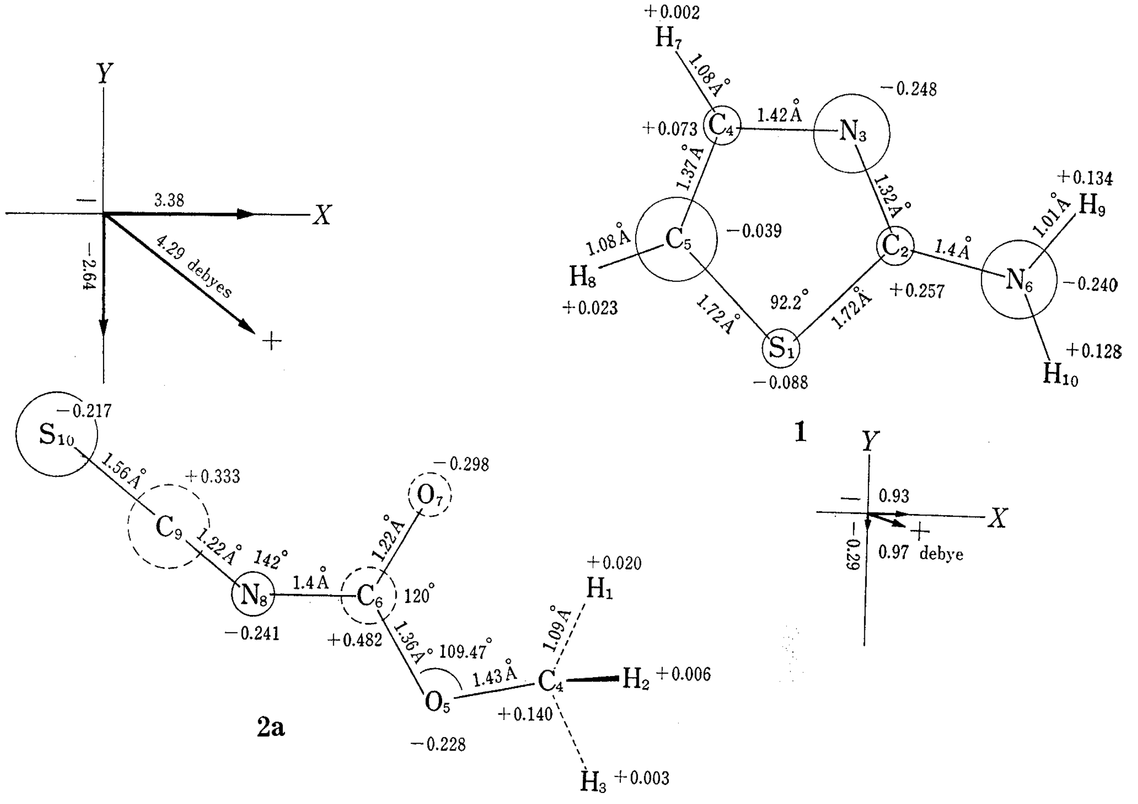
All of the frontier orbitals consist of *Pz* (π) orbitals. The calculation shows two electrophilic centers for **2a**. The total electron densities of **2a** are the most deficient at the carbonyl carbon atom. The largest frontier electron densities of the LUMO is at the isothiocyanato carbon. The LUMO of **2a** is antibonding between N_8 and C_9 and between C_9 and S_{10}, but is bonding between C_6 and N_8. The results indicate hard nucleophilies have the tendency to attack on the carbonyl carbon and soft nucleophiles on the isothiocyanato moiety.

Remarkable differences among heteroaromatic amines are in the distribution pattern of charge densities,[17] especially in the dipole moment of the molecules and in the frontier electron densities of the ring nitrogen atoms, which supposedly influence the interacting orbital at the attacking position. The N_1 atom of 3-aminopyridine has little the HOMO density. Consequently it may behave like aniline. It is noted the ring nitrogen atom of 2-aminothiazole has the largest charge density among those of the heterocycles. However, the charge densities are not enough to account for the differences between the *ortho* and *para* substituted pyridines.

Basic Behavior of Heterocycles *vs.* pK_a Values

The previous interpretations of the basic properties of the molecules were mainly based on their pK_a values. However, the difference in basic behavior of heterocycles can not be explained from pK_a values only as was pointed out in the previous paper.[1,10]

To clarify the difference between *ortho* and *para* substituted pyridines, correlations existing in the ionization data of pyridinium ions were analyzed using the dual substituent parameter.[18-21] The general approach of Swain and Lupton[21] who defined the *F* (field) and *R* (resonance)



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2a

Fig. 1a. Calculated Charge Densities and Dipole Moments

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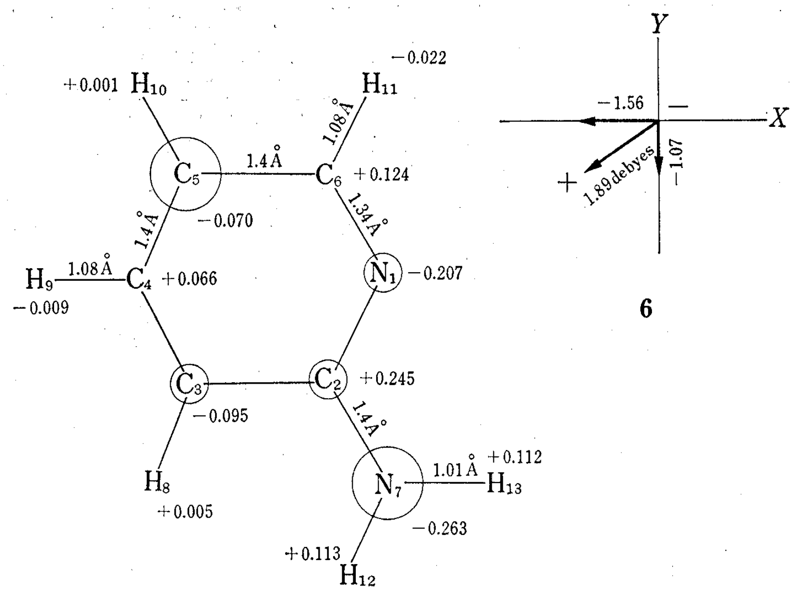
17) Theoretical studies on the electronic structures of aminopyridines have been done by several authors and similar results have been reported.[26]

18) R.W. Taft and I.C. Lewis, *J. Am. Chem. Soc.*, **80**, 2436 (1958).

19) *a*) M.J.S. Dewar and P.J. Grisdale, *J. Am. Chem. Soc.*, **84**, 3539 (1962); *b*) M.J.S. Dewar, R. Golden, and J.M. Harris, *ibid.*, **93**, 4187 (1971).

20) Y. Yukawa and Y. Tsuno, *Nippon Kagaku Zasshi*, **86**, 873 (1965).

21) C.G. Swain and E.C. Lupton, *J. Am. Chem. Soc.*, **90**, 4328 (1968).



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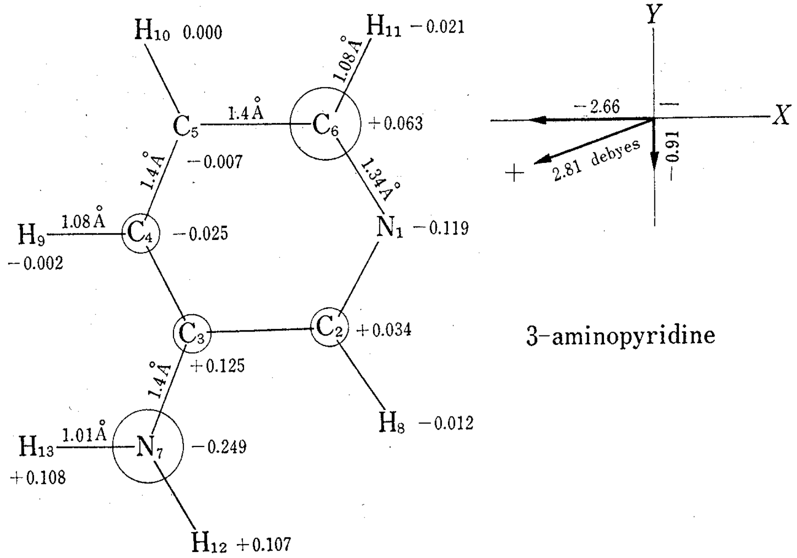

3-aminopyridine

Fig. 1b

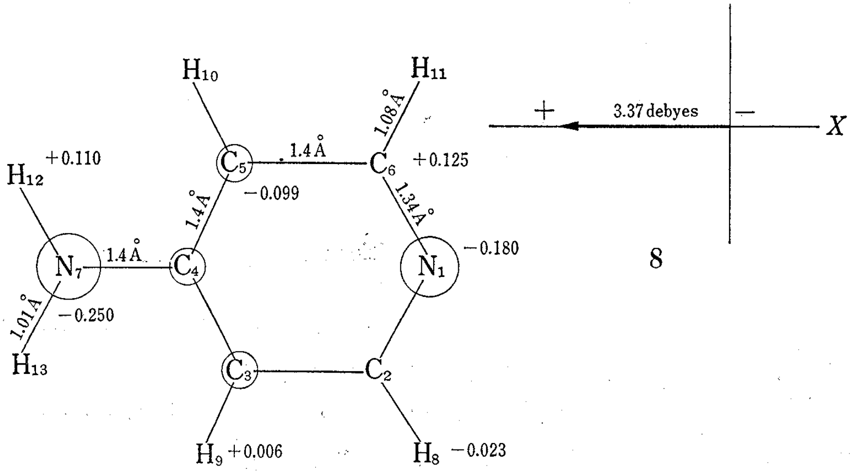

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Fig. 1c

TABLE I. Calculated Charge Densities on Nucleophilic Nitrogen Atoms and Dipole Moments of Heterocyclic Bases

Heterocyclic base	Orbital	Energy level (eV)	Charge densities		Dipole moment (in debye unit)	
			q_{ringN}	q_{aminoN}	Calcd.	Obsd.
Pyridine	HOMO[a]	−13.86[b]	0.000[b]	—	2.15	2.2[c]
	π		1.060	—		
	σ		4.084	—		
2-Aminopyridine	HOMO[a]	−11.53	0.185	0.688	1.89	2.17[d]
	π		1.159	1.897		
	σ		4.048	3.366		
3-Aminopyridine	HOMO[a]	−11.42	0.041	0.714	2.81	3.19[d]
	π		1.022	1.912		
	σ		4.097	3.337		
4-Aminopyridine	HOMO[a]	−11.81	0.459	0.743	3.37	3.79[d]
	π		1.128	1.896		
	σ		4.052	3.354		
2-Aminothiazole	HOMO[a]	−10.95	0.326	0.407	0.97	
	π		1.281	1.876		
	σ		3.967	3.364		

[a] Frontier electron densities of P_z orbitals
[b] The usual CNDO/2 calculation shows the lone pair orbital is the HOMO of pyridine. However, the experimental results have shown the HOMO is the π orbital; see M.I. Al-Joboury and D.W. Turner, *J. Chem. Soc.*, **1964**, 4434
[c] D.G. Leis and B.C. Curran, *J. Am. Chem. Soc.*, **67**, 79 (1945).
[d] ref. 26

parameters[22] seems to give the best orthogonality and avoids the pitfall of muticollinearity[23] for analyzing the substituent effect.

The multiple regression equations obtained from the ionization data[24] of *o*, *m*, and *p*-substituted pyridinium ions are as follows[25];

$$o\text{-p}K_a = -6.16F - 2.19R + 5.18, \qquad r=0.992,\ F_{2,5}=151.18$$
$$(t=-14.51)\ (t=-4.22)$$
$$m\text{-p}K_a = -3.77F - 1.88R + 5.18, \qquad r=0.991,\ F_{2,5}=130.61$$
$$(t=-12.71)\ (t=-5.19)$$
$$p\text{-p}K_a = -2.55F - 5.70R + 5.21, \qquad r=0.989,\ F_{2,5}=108.73$$
$$(t=-5.88)\ (t=-10.80)$$

The base strength of heterocyclic amines can be related to the energy of protonation. If the entropy of protonation is assumed to be constant or proportional to the energy of protonation, the energy change of the systems may be represented by the following equation:

$$\Delta E \propto \Delta \text{p}K_a = \alpha F + \beta R$$

where ΔE is the energy change; α and β are the regression coefficients of F and R parameters.

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[22] Some corrections may be necessary for F and R values; see M. Charton, *Prog. Phys. Org. Chem.*, **10**, 85 (1973).

[23] C. Hansch, A. Leo, S.H. Unger, K.H. Kim, D. Nikaitani, and E.J. Lien, *J. Med. Chem.*, **16**, 1207 (1973).

[24] A. Albert, "Physical Methods in Heterocyclic Chemistry," Vol. I, ed. by A.R. Katritzky, Academic Press, New York, 1963, p. 1. The ionization data lacking in those of *para* substituents and of hydroxy substituents were deleted from the regression analysis.

[25] Similar equations have been obtained using σ_I and σ_R^+ parameters for pyridinium ions. However, the ortho ionization data are fitted with poorer precision and irregular in the ρ_R sequence.[30b]

The variation of the equations must be really a reflection of the protonation at the N_1 ring nitrogen atom of the pyridines.[26] However, the coefficients of F and R parameters have no correlations with any of π or σ charge densitites of the N_1 atoms (see Table I).

Some ambiguities exist in the field or inductive effect.[27] F and R parameters seem to be significant in correlations with ionization data, but often fail to be significant in correlations with electron densities or C^{13}-NMR shifts.[28]

If seems likely the F effect is related to the geometry of the molecules and depends on the length between the N_1 reaction site and the pyridine substituent, and the R effect correlates with the HOMO electron densities of the N_1 atoms.

If the above is true, it may be probable that the F effect results mostly from the classical charge controlled interactions, inclusive of the core–core repulsive force,[29] and the R effect from the electron transfer interactions between the nearly degenerate overlapping orbitals, inclusive of the lone pair orbitals.[26]

There is the possibility that the magnitude of the F and R factors can be an indication of the charge and frontier controlled interactions between the two interacting molecules. It must be noted the F effect except in alkyl substituents usually acts as a repulsive force to the positively charged atoms or molecules.

For the reasons mentioned above, the N_1 atoms of *ortho*-substituted pyridines may supposedly suffer a relatively large F effect[30] from the substituents and hardly approach electrophiles having a positive charge. On the contrary, the F effect of *para*-substituents may be less operative at the N_1 atoms of pyridines, which easily attack electrophiles. The high basicity of 4-aminopyridine may result partly from its small F effect and partly from its large R effect at the N_1 nitrogen atom.

From the ionization data[10] of 5-substituted-2-aminothiazoles, the following regression equation was obtained;

$$\begin{aligned} pK_a &= -3.29F - 3.76R + 5.19, \qquad r=0.997,\ F_{2,3}=239.62 \\ &\quad (t=-15.76)\ (t=-4.44) \end{aligned}$$

The difference in basic behavior of heterocycles may be explained by the variations of F and R factors in the equations.

Mechanism of Ambident Reactivities

When solute–solvent interactions and steric effects are essentially similar in all the reaction systems, the rate determining factors in nucleophilic reactions are considered to be the approach of the nucleophile and the stabilization of the transition state by the electron donating conjugation with the electrophile.[31]

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26) It has been shown that the mono-protonation occurs on the ring nitrogen atoms of pyridines and quite large charge redistributions take place in the protonation of aminopyridines, where about 0.7 e charge migrates to the attached proton; H. Konishi, H. Kato, and T. Yonezawa, *Theoret. Chim. Acta* (Berl.), **19**, 71 (1970).

27) *a*) Dewar and his co-workers have stated the long-range effects of substituents are due solely to a combination of the mesomeric and field effects, the classical inductive effect being wholly unimportant[19b]; *b*) see also, M. Charton, *Prog. Phys. Org. Chem.*, **10**, 180 (1973).

28) Unpublished data.

29) Vaughan and O'Donnel have shown that the total molecular protonation energy, inclusive of the energy from the core-core repulsive interactions, is a more reliable index of the relative base strengths of five membered heterocycles; J.D. Vaughan and M. O'Donnel, *Tetrahedron Letters*, **1968**, 3727.

30) *a*) Charton has shown that the electrical effect of *o*-substituted pyridines is abnormal and rate and equilibrium data for these systems generally correlate with σ_m and/or σ_I; M. Charton, *J. Am. Chem. Soc.*, **86**, 2033 (1964); see also *b*) S. Ehrenson, R.T.C. Brownlee, and R.W. Taft, *Prog. Phys. Org. Chem.*, **10**, 59 (1973).

31) It has been shown that the substituent effect can be rationalized in terms of the importance of the approach of a nucleophile in S_N2 reactions; J. Hayami, N. Tanaka, and A. Kaji, *Bull. Chem. Soc. Japan*, **46**, 954 (1973).

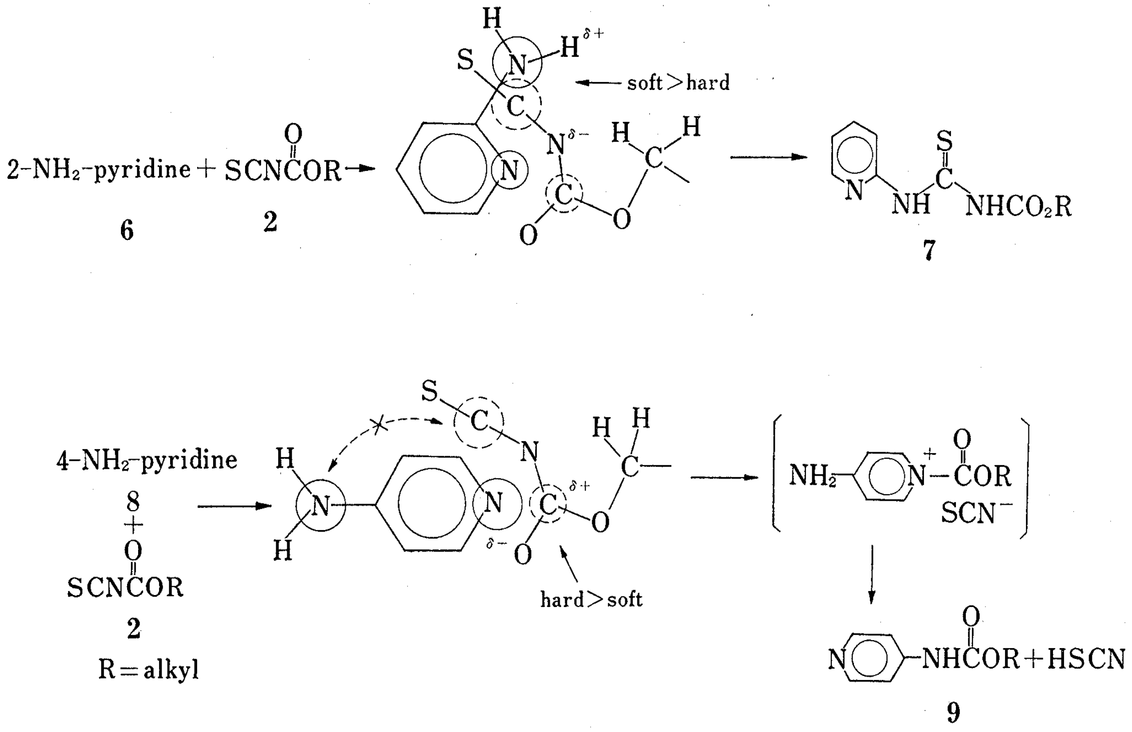

Chart 1

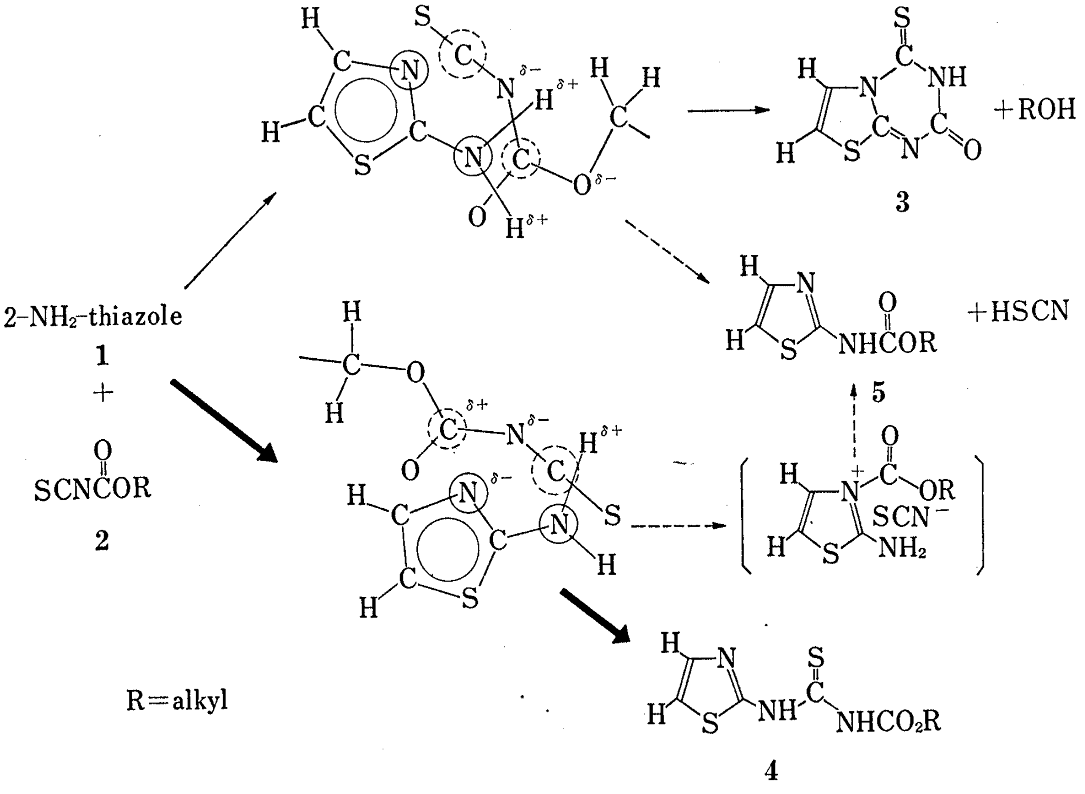

Chart 2

In the initial stage of the reactions the *F* effect or dipole-dipole interactions which result from the charge controlled interactions may play a dominant role, by which the interacting molecules approach each other. But in the transition state of the reactions the orbital overlapping interactions which result mostly from the frontier controlled interactions may become important.

From the results obtained in the above calculations the interactions between **2** and the heterocyclic amines can be estimated as graphically shown in Chart 1, 2.

In the case of 2-aminopyridine it is probable that the orbital overlapping interactions at the amino substituent can be predominant (Chart 1) and afford the addition product in a reasonable good yield.[1] On the contrary, the N_1 atom of 4-aminopyridine may have strong orbital overlapping at the carbonyl carbon atom of **2** and electron transfer may occur at this place which results in the formation of pyridinium salt, whereas the amino substituent can hardly approach the isothiocyanato moiety (see Chart 1) and makes no orbital overlapping in the initial stage of the reaction. The intermolecular orbital overlapping between the amino substituent and the carbonyl carbon of pyridinium ions may result in the further rearrangement of the pyridinium salt and the formation of **9**.

In the nucleophilic reaction of **1**, the situation is somewhat complicated. The calculated dipole moment of **1** is so small that the two ways of approach may have the possibility as shown in Chart 2. Both the N_3 ring nitrogen and the N_6 amino substituent of **1** make the orbital overlapping at the isothiocyanato moiety and the carbonyl carbon atom of **2** and electron transfer may occur at the various positions of the interacting molecules which result in the formation of **3**, **4**, and **5**. Further intramolecular cyclization occurs in **4** by heating.[10,32] It is interesting the cycloaddition products analogous to **3** can be obtained only from the thiazoles having the substituent of negative F value at the C_5 position.

From the above discussion we come to the conclusion that the difference in basic hehavior of heterocyclic bases and the ambident reactivities of **2** are understandable from the concept of the hard–hard charge controlled and soft–soft frontier controlled interactions between the two interacting molecules and the F (field) effect may also have an important role in determining the pathway of approach, which is greatly affected by the geometry of the molecules and the pattern of charge distribution.

Acknowledgement The authors are grateful to the staffs of the computer room of Central Research Laboratories for operating a NEAC 2200 Model 375 system on which most of the calculations were carried out.

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32) M. Nagano, T. Matsui, J. Tobitsuka, and K. Oyamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 74 (1973).