Pyridinolyses of *O*-Propyl and *O*-Isopropyl Phenyl Phosphonochloridothioates in Acetonitrile

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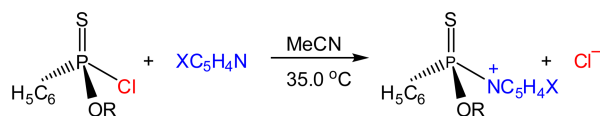
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Continuing the kinetic studies on the pyridinolyses of the phosphonochloridothioates, the nucleophilic substitution reactions of *O*-propyl (**4**) and *O*-isopropyl (**5**) phenyl phosphonochloridothioates with X-pyridines have been carried out kinetically in acetonitrile (MeCN) at 35.0 ± 0.1 °C (Scheme 1). The kinetic results of the present work are compared with those of the pydidinolyses of Y-*O*-aryl methyl [**1**; Me(YC$_6$H$_4$O)P(=S)Cl],[1a] *O*-methyl phenyl [**2**; Ph(MeO)P(=S)Cl],[1b] *O*-ethyl phenyl [**3**; Ph(EtO)P(=S)Cl],[1b] Y-*O*-aryl phenyl [**6**; Ph(YC$_6$H$_4$O)P(=S)Cl][1c] and Y-*S*-aryl phenyl [**7**; Ph(YC$_6$H$_4$S)P(=S)Cl][1d] phosphonochloridothioates, based on the reactivities, selectivity parameters, free energy correlations and reaction mechanisms.

Results and Discussion

The second-order rate constants [k_2 (M^{-1} s^{-1})] of the pyridinolyses of **4** and **5** in MeCN at 35.0 °C are summarized in Table 1, together with the selectivity parameters, ρ_X and β_X. The pyridinolysis rates of **4** are 1.4-1.7 times faster than those of **5**. The substituent effects of the nucleophiles on the rates are in consistent with those for a typical nucleophilic substitution reaction with a positive charge development at the nucleophilic N atom in the transition state (TS). The free energy correlations for both **4** and **5**, however, exhibit biphasic concave upwards with a break point at X = H (Fig. 1). Similarities of the substituent effects of X on the pyridinolysis rates between **4** and **5** strongly suggest that the pyridinolyses of both **4** and **5** proceed through the same mechanism. The magnitudes of β_X [= 2.09 (**4**) and 2.01(**5**)] values with more basic pyridines (X = 4-MeO, 4-Me, 3-Me, H) are ca. four times greater than those [β_X = 0.48(**4**) and 0.47(**5**)] with less basic pyridines (X = H, 3-Ph, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN). The magnitudes of

Table 1. Second-Order Rate Constants ($k_2 \times 10^3$/M^{-1} s^{-1}) and Selectivity Parameters (ρ_X and β_X) of the Reactions of *O*-Propyl (**4**) and *O*-Isopropyl (**5**) Phenyl Phosphonochloridothioates with X-Pyridines in MeCN at 35.0 °C

X	$k_2 \times 10^3$/M^{-1} s^{-1} (**4**)	$k_2 \times 10^3$/M^{-1} s^{-1} (**5**)
4-MeO	1200 ± 10	729 ± 1
4-Me	157 ± 1	91.4 ± 0.1
3-Me	17.4 ± 0.2	12.3 ± 0.1
H	3.22 ± 0.01	2.35 ± 0.01
3-Ph	2.36 ± 0.01	1.54 ± 0.03
3-Cl	0.350 ± 0.004	0.236 ± 0.001
3-Ac	0.312 ± 0.001	0.203 ± 0.001
4-Ac	0.129 ± 0.002	0.0923 ± 0.0007
3-CN	0.0925 ± 0.0001	0.0702 ± 0.0002
4-CN	0.0444 ± 0.0003	0.0326 ± 0.0002
$-\rho_X$	9.51 ± 0.05[a,b]/2.82 ± 0.03[c,d]	9.15 ± 0.04[a,g]/2.77 ± 0.02[c,h]
β_X	2.09 ± 0.02[a,e]/0.48 ± 0.16[c,f]	2.01 ± 0.01[a,i]/0.47 ± 0.17[c,j]

[a]More basic pyridines; X = (4-MeO, 4-Me, 3-Me, H). [b]Correlation coefficient, r = 0.999. [c]Less basic pyridines; X = (H, 3-Ph, 3-Cl, 3-Ac, 4-Ac, 3-CN, 4-CN). [d]r = 0.999. [e]r = 0.999. [f]r = 0.977. [g]r = 0.999. [h]r = 0.999. [i]r = 0.999. [j]r = 0.976.

selectivity parameters with more basic pyridines are considerably larger than with less basic pyridines, indicating

Figure 1. Brönsted plots [log k_2 *vs* pK_a(X)] of the reactions of *O*-propyl (**4**) and *O*-isopropyl (**5**) phenyl phosphonochloridothioates with X-pyridines in MeCN at 35.0 °C.
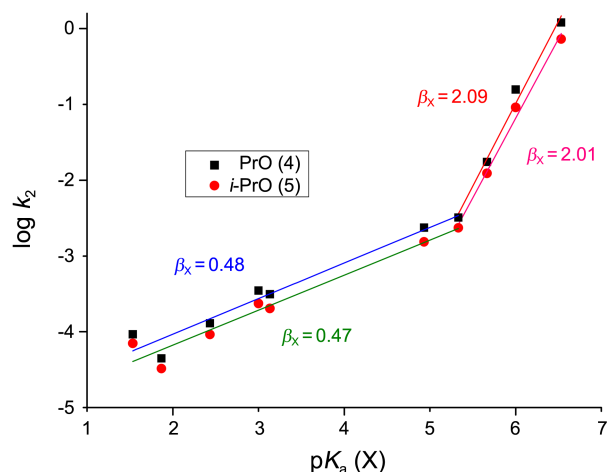

Scheme 1. Pyridinolyses of *O*-propyl (**4**) and *O*-isopropyl (**5**) phenyl phosphonochloridothioates in MeCN at 35.0 °C.

Table 2. Summary of the Second-Order Rate Constants, NBO Charges at the Reaction Center P Atom, Summations of the Taft Steric Constants of Ph and R_i [$\Sigma E_S = E_S(Ph) + E_S(R_i)$], Brönsted Coefficients, CICs and Free Energy Correlations for Substituent X and Y Variations of the Reactions of **1-7** with X-Pyridines in MeCN

Substrate	$10^3 k_2{}^a$	charge at P	$-\Sigma E_S{}^c$	β_X	ρ_{XY}	X variation	Y variation
1: Me(YC$_6$H$_4$O)P(=S)Cl	14.3^b	1.432^b	$< 2.48^b$	$0.66\text{-}1.04/2.08\text{-}2.38^d$	$-1.76/0/2.80/0^e$	discrete^f	Λ^h
2: Ph(MeO)P(=S)Cl	6.87	1.472	2.48	$1.42/0.46^d$	–	V^g	–
3: Ph(EtO)P(=S)Cl	5.47	1.478	2.55	$1.39/0.46^d$	–	V^g	–
4: Ph(PrO)P(=S)Cl	3.22	1.479	2.84	$2.09/0.48^d$	–	V^g	–
5: Ph(*i*-PrO)P(=S)Cl	2.35	1.488	2.95	$2.01/0.47^d$	–	V^g	–
6: Ph(YC$_6$H$_4$O)P(=S)Cl	11.2^b	1.462^b	4.96^b	0.87-0.95	-0.46	linear	linear
7: Ph(YC$_6$H$_4$S)P(=S)Cl	1.10^b	0.999^b	$> 4.96^b$	$1.42\text{-}1.49/0.46\text{-}0.55^d$	$0/0.97/1.42/0.44^e$	V^g	V$_{min}{}^i$

^{a}The second-order rate constant with unsubstituted pyridine at 35.0 °C. ^{b}The value with Y = H. ^{c}Summations of the Taft steric constants. ^{d}More/less basic pyridines. ^{e}*a*-block(stronger nucleophiles and weaker electrophiles)/*b*-block(weaker nucleophiles and weaker electrophiles)/*c*-block(stronger nucleophiles and stronger electrophiles)/*d*-block(weaker nucleophiles and stronger electrophiles). ^{f}Biphasic discrete two plots, neither concave upwards nor downwards. ^{g}Biphasic concave upwards. ^{h}Biphasic concave downwards. ^{i}Biphasic concave upwards with a minimum point.

greater degree of bond formation with more basic pyridines than with less basic pyridines in the TS.

Table 2 lists the second-order rate constants ($k_2 \times 10^3$/M^{-1} s^{-1}) with unsubstituted pyridine at 35.0 °C, natural bond order (NBO) charges in the gas phase at the reaction center P atom in the substrate [B3LYP/6-311+G(d,p) level of theory], summations of the Taft steric constants[2] of Ph and R_i [$\Sigma E_S = E_S(Ph) + E_S(R_i)$],[3] Brönsted coefficients (β_X), cross-interaction constants (CICs; ρ_{XY})[4] and free energy correlations for the substituent X and Y variations in the nucleophiles and substrates, respectively, of the pyridinolyses of the seven phosphonochloridothioates of **1-7** in MeCN. In view of the pyridinolysis rates of **1-6**,[5] the rates do not show linear correlation with the positive NBO charge at the reaction center P atom. These indicate that the inductive effects of the two ligands do not play any role to decide the pyridinolysis rates of the phosphonochloridothioates.

Figure 2 shows the Taft plot according to 'log $k_2 = \delta\Sigma E_S + $ C'. Note that the numbering of the substrates of **1-6** follows the sequence of the size of the two ligands.[2] The pyridinolysis rates of **2-5** with phenyl and alkoxy ligands are inversely proportional to the size of the two ligands,
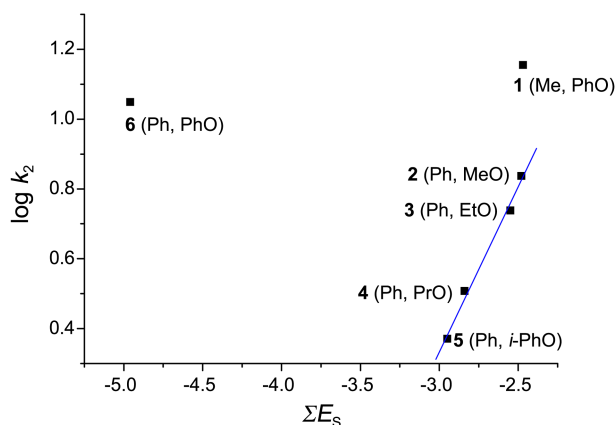
Figure 2. Taft plot of log k_2 *vs* ΣE_S for the reactions of **1-6** with C$_5$H$_5$N in MeCN at 35.0 °C. The substrate number and two ligands are displayed next to the corresponding point. The substrates of **2-5** give good linearity of $\delta = 0.937$ with r = 0.996.

indicating that the steric effects of the two ligands are major factor to decide the rates. The pyridinolysis rates of **1** and **6** with phenoxy ligand show positive deviations from the Taft plot of **2-5**, and the rate of **1** is faster than that of **6**. The anilinolysis rates of the phosphonochloridothioates show the similar trend.[6] Moreover, the same trends were also observed for the pyridinolyses of the chlorophosphates [(R$_1$O)(R$_2$O)P(=O)Cl-type][7] and chlorothiophosphates [(R$_1$O)(R$_2$O)P(=S)Cl-type],[8] and for the anilinolyses of chlorophosphates[9] and chlorothiophosphates.[9c,d,10] Thus, the authors conclude that the substrates with phenoxy ligand(s) of *a* group differ from those without phenoxy ligand(s) of *b* group regarding the steric effects of the two ligands on the aminolysis rates.

The authors proposed a stepwise mechanism with a rate-limiting bond formation (or a concerted S$_N$2 mechanism) for the pyridinolyses of **6** based on the negative value of ρ_{XY}.[4] In the case of the pyridinolyses of **1** and **7**, four values of ρ_{XY} were obtained because both the Hammett plots for substituent X and Y variations are biphasic. In **1**, a stepwise mechanism with a rate-limiting bond formation was proposed with *a*-block based on the negative ρ_{XY} value, and a stepwise mechanism with a rate-limiting leaving group departure from the intermediate was proposed with *b*-, *c*- and *d*-blocks based on the positive and null ρ_{XY} values.[11] In **7**, a stepwise mechanism with a rate-limiting leaving group departure from the intermediate was proposed with all blocks, *a*-, *b*-, *c*- and *d*-blocks based on the positive and null ρ_{XY} values.[11] The authors proposed a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate for the pyridinolyses of **2** and **3**, the same mechanism for the pyridinolyses of **7**, based on the very similar trends of the β_X values and free energy relationships with X. In the present work of the pyridinolyses of **4** and **5**, a stepwise mechanism with a rate-limiting leaving group departure from the intermediate is proposed based on the same reason as in **2**, **3** and **7**. Taking into account the considerably larger values of $\beta_X = 2.09$(**4**) and 2.01(**5**) compared to those of $\beta_X = 1.42$(**2**), 1.39(**3**) and 1.42-1.49(**7**) with more basic pyridines, the extents of the degree of bond formation
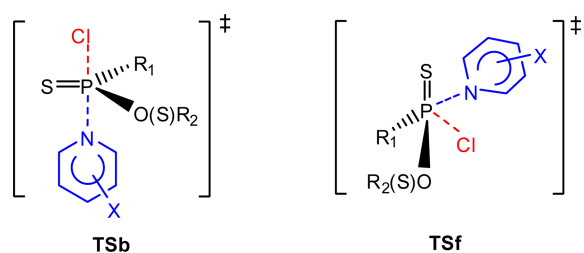
Scheme 2. Backside attack TSb and frontside attack TSf for the reactions of phosphonochloridothioates with X-pyridines.

Table 3. Activation Parameters[a] for the Reactions of *O*-Propyl (**4**) and *O*-Isopropyl (**5**) Phenyl Phosphonochloridothioates with Pyridine (C_5H_5N) in MeCN

Substrate	$t/^oC$	$k_2 \times 10^3$ /$M^{-1} s^{-1}$	$\Delta H^{\neq}$ /kcal mol^{-1}	$-\Delta S^{\neq}$ /cal mol^{-1} K^{-1}
4: Ph(PrO)P(=S)Cl	35.0	3.22 ± 0.01		
	40.0	4.51 ± 0.01	11.6 ± 0.1	32 ± 1
	45.0	6.03 ± 0.01		
5: Ph(*i*-PrO)P(=S)Cl	35.0	2.35 ± 0.01		
	40.0	3.08 ± 0.01	9.2 ± 0.1	40 ± 1
	45.0	3.88 ± 0.03		

[a]Calculated by Eyring equation.

of **4** and **5** are greater than those of **2**, **3** and **7** in the TS.

In view of biphasic concave upward free energy correlations for substituent X variations of **2-5**, and **7**, the greater β_X values with more basic pyridines than those with less basic pyridines indicate a frontside attack TSf with more basic pyridines and a backside attack TSb with less basic pyridines (Scheme 2). It is worthy of note that the magnitudes of ρ_X and β_X values involving a frontside attack TSf are greater than those involving a backside attack TSb.[12]

Activation parameters, enthalpies and entropies of activation, are determined for the pyridinolysis (with C_5H_5N) of **4** and **5** in Table 3. The enthalpies of activation is relatively small and entropies of activation is relatively large negative values in consistent with the typical aminolyses of P=S systems.

In summary, the kinetic studies on the reactions of *O*-propyl (**4**) and *O*-isopropyl (**5**) phenyl phosphonochloridothioate with X-pyridines have been carried out in acetonitrile at 35.0 ºC. The free energy correlations with X in the nucleophiles are biphasic concave upwards with a break point at X = H for both substrates. The steric effects of the two ligands are major factor to decide the rate. A stepwise mechanism with a rate-limiting leaving group departure from the intermediate is proposed based on the β_X values and biphasic concave upward free energy relationship for both substrates. The biphasic concave upward free energy relationships are rationalized by a frontside nucleophilic attack TSf with more basic pyridines and a backside attack TSb with less basic pyridines for both substrates.

Experimental Section

Materials. GR grade pyridines and HPLC grade MeCN

(water content < 0.005%) were used for kinetic studies without further purification. *O*-Propyl (**4**) and *O*-isopropyl (**5**) phenyl phosphonochloridothioates were prepared as reported earlier.[6c]

Kinetic Procedure. Rates and selectivity parameters were obtained as previously described.[1] Initial concentrations for the reactions of both **4** and **5** were as follows; [substrate] = 5 × 10^{-3} M and [XC_5H_4N] = (0.10-0.30) M.

Product Analysis. *O*-Propyl (**4**) and *O*-isopropyl (**5**) phenyl phosphonochloridothioates were reacted with excess pyridine, respectively, for more than 15 half-lives in MeCN at 35.0 ºC. Solvent was removed under reduced pressure. The product was isolated after treatment with ether and acetonitrile, and then dried under reduced pressure. The analytical and spectroscopic data of the products are summarized as follows:

[(C_6H_5)(PrO)P(=S)NC_5H_5]$^+$Cl$^-$. Colorless liquid; ^{1}H-NMR (400 MHz, MeCN-d_3) δ 0.87-0.96 (m, 3H), 1.66-1.1.67 (m, 2H), 2.53-2.56 (m, 2H), 7.95-8.74 (m, 10H); ^{13}C-NMR (100 MHz, MeCN-d_3) δ 12.62, 23.94, 60.52, 118.6, 128.5, 131.5, 142.3, 142.8, 144.7, 147.2; ^{31}P-NMR (162 MHz, MeCN-d_3) δ 11.25 (1P, s, P=S); LC-MS (EI, *m/z*), 313(M$^+$).

[(C_6H_5)(*i*-PrO)P(=S)NC_5H_5]$^+$Cl$^-$. Colorless liquid; ^{1}H-NMR (400 MHz, CDCl$_3$ and TMS) δ 2.17-2.19 (m, 6H), 3.52-3.58 (m, 1H), 8.00-8.92 (m, 10H); ^{13}C-NMR (100 MHz, CDCl$_3$ and TMS) δ 30.78, 52.83, 104.4, 127.0, 130.7, 141.0, 145.4, 152.7; ^{31}P-NMR (162 MHz, CDCl$_3$ and TMS) δ 78.94 (1P, s, P=S); LC-MS (EI, *m/z*), 313 (M$^+$).

References and Notes

1. (a) Guha, A. K.; Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 1375. (b) Hoque, M. E. U.; Lee, H. W. *Int. J. Chem. Kinet.* **2013**, *45*, 337. (c) Lumbiny, B. J.; Adhikary, K. K.; Lee, B. S.; Lee, H. W. *Bull. Korean Chem. Soc.* **2008**, *29*, 1769. (d) Adhikary, K. K.; Lumbiny, B. J.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 3743.

2. (a) Taft, R. W. *Steric Effect in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956; Chapter 3. (b) Exner, O. *Correlation Analysis in Chemistry: Recent Advances*; Chapman, N. B., Shorter, J., Eds; Plenum Press: New York, 1978; p 439.

3. The Taft steric constants of E_S(R) are as follows: E_S(R) = 0(Me), –0.07(Et), –0.36(Pr), –0.47(*i*-Pr), –2.48(Ph). Note that the steric constants of alkoxy, phenoxy and thiophenoxy (R$_i$O types) are not available. Thus, the authors estimate that the summations of the Taft steric constants of **1** and **7** are slightly less than 2.48 and slightly larger than 4.96, respectively.

4. (a) Lee, I. *Chem. Soc. Rev.* **1990**, *19*, 317. (b) Lee, I. *Adv. Phys. Org. Chem.* **1992**, *27*, 57. (c) Lee, I.; Lee, H. W. *Collect. Czech. Chem. Commun.* **1999**, *64*, 1529.

5. The authors compare the pyridinolysis rates of **1-6** in which the two ligands are R$_1$ and R$_2$O (R = alkyl, phenyl or aryl), because **7** has thiophenoxy ligand (YC$_6$H$_4$S). The positive NBO charges at the reaction center P atom are 1.462 (**6**) and 0.999 (**7**) in the gas phase, and the rate ratio is k_2(**6**)/k_2(**7**) = 10.2. The two substrates have similar ground state structure and the steric effects of the two ligands of **7** on the rate would be slightly larger than those of **6**.

The obtained rate ratio of 10.2 seems to be ascribed to the electronegativity difference between phenoxy oxygen and thiophenoxy sulfur, resulting in great difference of the NBO charges at the reaction center P atom: 1.462(**6**)–0.999(**7**) = 0.463.

6. (a) Hoque, E. M. U.; Guha, A. K.; Kim, C. K.; Lee, B. S.; Lee, H. W. *Org. Biomol. Chem.* **2009**, *7*, 2919. (b) Adhikary, K. K.; Lumbiny, B. J.; Dey, S.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 2628. (c) Barai, H. R.; Hoque, M. E. U.; Lee, M.; Lee, H. W. *Bull. Korean Chem. Soc.* **2013**, *34*, 1096.

7. (a) Guha, A. K.; Lee, H. W.; Lee, I. *J. Org. Chem.* **2000**, *65*, 12. (b) Dey, N. K.; Hoque, M. E. U.; Kim, C. K.; Lee, H. W. *J. Phys. Org. Chem.* **2010**, *23*, 1022. (c) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 3505. (d) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2012**, *33*, 1055. (e) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2012**, *33*, 3441.

8. (a) Hoque, M. E. U.; Dey, S.; Kim, C. K.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 1138. (b) Adhikary, K. K.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 3947. (c) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2012**, *33*, 325. (d) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2012**, *33*, 1085. (e) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2012**, *33*, 3203.

9. (a) Guha, A. K.; Lee, H. W.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **1999**, 765. (b) Lee, H. W.; Guha, A. K.; Lee, I. *Int. J. Chem. Kinet.* **2002**, *34*, 632. (c) Hoque, M. E. U.; Dey, N. K.; Kim, C. K.; Lee, B. S.; Lee, H. W. *Org. Biomol. Chem.* **2007**, *5*, 3944. (d) Dey, N. K.; Hoque, M. E. U.; Kim, C. K.; Lee, B. S.; Lee, H. W. *J. Phys. Org. Chem.* **2008**, *21*, 544. (e) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 3245. (f) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2012**, *33*, 663. (g) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2012**, *33*, 1879.

10. (a) Hoque, M. E. U.; Dey, S.; Guha, A. K.; Kim, C. K.; Lee, B. S.; Lee, H. W. *J. Org. Chem.* **2007**, *72*, 5493. (b) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 4403. (c) Hoque, M. E. U.; Lee, H. W. *Bull. Korean Chem. Soc.* **2012**, *33*, 843.

11. The null ρ_{XY} value can be rationalized by a stepwise mechanism with a rate-limiting leaving group expulsion from the intermediate where the distance between X and Y does not vary from the intermediate to the transition state (TS). The null ρ_{XY} value suggests the absence of the cross-interaction between X and Y. This phenomenon can be occurred: (i) X and Y are too far apart to interact; (ii) the distance between X and Y does not vary. Thus, the null ρ_{XY} value indicates a special stepwise mechanism with a rate-limiting bond breaking where the distance between X and Y does not vary from the intermediate to the TS.

12. Adhikary, K. K.; Lee, H. W.; Lee, I. *Bull. Korean Chem. Soc*. **2003**, *24*, 1135.