A Theoretical Study of Neighboring-Group Participation in Thione-to-Thiol Rearrangement of Xanthates. Molecular Orbital Calculation Using a Conductor-Like Screening Model (COSMO) Approach

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The transition structures of the thione-to-thiol rearrangement of *O*-(2-dimethylaminoethyl and 2-methylthio-) *S*-methyl xanthates in several solvents were located by semiempirical molecular orbital method (PM3) using the conductor-like screening model (COSMO) approach. Each transition state transforms into the ion-pair intermediate with a three-membered ring structure (aziridinium or thiiranium), indicating that the rearrangement proceeds through an ionic intermediate with the anchimeric assistance of the neighboring group. The intermediary structures in gas phase are also analyzed by *ab initio* and density functional theory calculations.

Key words xanthate; neighboring-group participation; PM3; thione-to-thiol rearrangement; *ab initio*; ion pair

In the field of pericyclic reactions, it has recently become possible to calculate the details of transition-state (TS) geometries and energies rather than rely upon the approximate descriptions deduced from experimental data. Extensive investigations on nonionic reactions have been performed at different levels of theory.[1]

During the course of the study on synthetic design using sequential pericyclic reactions[2a—c] of *O*-(2-alkenyl or 2,4-alkadienyl) *S*-(2-alkenyl) dithiocarbonates (xanthates) *via* [3,3]-sigmatropic (*i.e.*, allylic thione-to-thiol) rearrangement as a key step,[2d,e] we clarified that *ab initio* and density functional theory (DFT) calculations[3a] reproduced the reaction behaviors.[2b,4] On the other hand, semiempirical molecular orbital (MO) methods are indispensable for large reaction systems. For the study of the asymmetric [3,3]-sigmatropic rearrangement of *O*-cinnamyl *S*-methyl xanthate in cyclodextrin cavities,[4] we examined the applicability of the semiempirical AM1 and PM3 MO methods[5a,b] to the reaction of xanthates. (See Chart 1)[5c]

The [3,3]-sigmatropic rearrangement reactions of allylic xanthates can be treated as gas-phase reactions because they are not sensitive to the change in solvent polarity.[2d] In contrast to the gas-phase MO calculation, the calculation of solvent-sensitive reactions has just begun. In our opinion, the *ab initio* or DFT structure optimization including solvent effect (self-consistent reaction field [SCRF] method)[3b] is still time-consuming at present. In semiempirical MO methods, the

conductor-like screening model (COSMO) approach[6] enables considerable progress in the computational treatment of solvation effects. However, the application to ionic reactions of sulfur compounds has been investigated far less.

With regard to the ionic rearrangement reaction of xanthates, Taguchi *et al.*[7a—c] studied the thermal thione-to-thiol rearrangement of xanthates induced by anchimeric assistance from the dialkylamino or alkylthio group adjacent to the xanthate group. The reactions are assumed to proceed through ion-pair intermediates (IM)[7a—c,8] on the basis of the kinetic data[9,10] (see Chart 2a).

On the other hand, Yoshida reported that *O*,*S*-dimethyl xanthate reacted with triethylamine to give the quaternary salt, during which the thione-to-thiol rearrangement occurred.[11] This suggests the possibility that the rearrangement of *O*-(2-dimethylaminoethyl) *S*-methyl xanthate may proceed through the base-catalyzed reaction mechanism triggered by the intermolecular nucleophilic attack of the dimethylamino nitrogen on the *O*-alkyl carbon of the xanthate (see Chart 2b).

Based on this background, we reinvestigated the rearrangement reactions using the PM3 molecular modeling technique[12] combined with the COSMO approach to clarify the overall character of the neighboring-group participation involving the structural features of the ionic IMs, which had remained an open question.

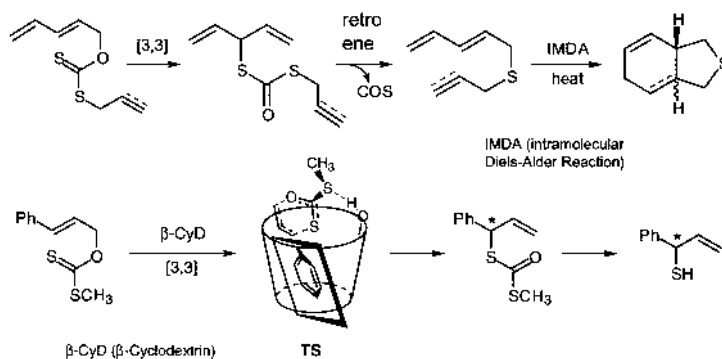This paper describes theoretical evidence of the presence

Chart 1

of aziridinium and thiiranium IMs in the thione-to-thiol rearrangement of xanthates bearing a β-anchimeric group and the applicability of the COSMO approach to the rearrangement reactions of xanthates.

Chart 2

Results and Discussion

MO Calculation Semiempirical MO calculations were run through the ANCHOR II interface using MOPAC6.0 on a Fujitsu S4/2 workstation (WS) or through the CS Chem3D Pro interface using MOPAC97 on a Macintosh G3 personal computer.[12a] The *ab initio* and DFT computations[3a] were carried out on a Scientists' Paradise Dragon AXP5A/433 computer or a Convex Exemplar SPP-1000 parallel computer in the Kumamoto University Information Processing Center.

The ground states (GSs) of *O*-(2-dimethylaminoethyl and 2-methylthioethyl) *S*-methyl xanthates (**1a, b**) and their rearrangement products and IMs were optimized by the EF routine implemented in the MOPAC program packages using MNDO-PM3 (PM3) approximation.[12a] The TSs for the rearrangement were located by the TSs location routine. In the COSMO method, the effective radius of the solvent molecule (RSOLV) is set to the default value.[12b]

The fully optimized geometries calculated by the AM1 or PM3 method were used as starting geometries for the *ab initio* and DFT calculations. Graphic analysis of the MO calculation data was performed on a Macintosh G3 or 8500/150
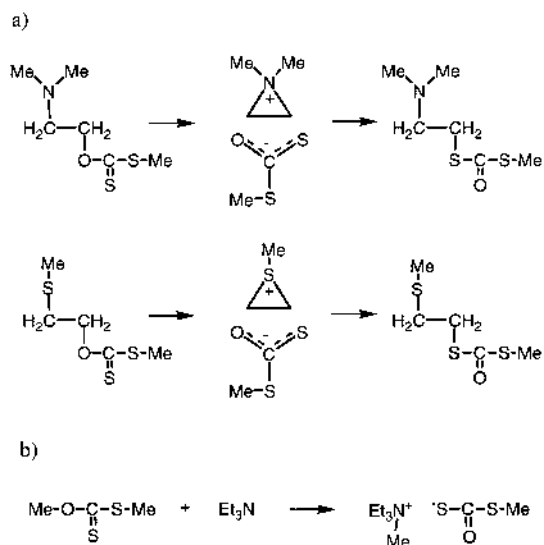
Table 1. Energetics of Reactants, TSs and IMs Involved in Thione-to-Thiol Rearrangement of *O*-(2-Dimethylaminoethyl and 2-Methylthioethyl) *S*-Methyl Xanthates (**1a, b**) in Gas Phase

Geometry	Method	$\Delta Hf^{a)}$	$E^{b)}$	Energy difference$^{c)}$
1a				
	PM3	−3.58		0.0
	RHF/3-21G		−1153.1559	0.0
	RHF/3-21G*		−1153.3747	0.0
	RHF/6-31G*		−1159.0765	0.0
	B3LYP/6-31G*		−1162.7985	0.0
TS for **1a**				
	PM3	48.08		51.66
	RHF/3-21G*		−1153.3074	42.19
	B3LYP/6-31G*		−1162.7422	35.33
IM for **1a**				
	PM3	22.31		25.89
	RHF/3-21G		−1153.1067	30.90
	RHF/3-21G*		−1153.3105	40.28
	RHF/6-31G*		−1159.0272	30.90
	B3LYP/6-31G*		−1162.7485	31.35
2a				
	PM3	−36.95		−33.37
	RHF/3-21G		−1153.1581	1.37
	RHF/3-21G*		−1153.3786	−2.50
	RHF/6-31G*		−1159.0956	−11.99
	B3LYP/6-31G*		−1162.8176	−12.04
1b				
	PM3	−7.14		0.0
	RHF/3-21G		−1455.1925	0.0
	RHF/3-21G*		−1455.5190	0.0
	RHF/6-31G*		−1462.5414	0.0
TS for **1b**				
	PM3	41.80		48.94
IM for **1b**				
	PM3	21.57		28.71
	RHF/3-21G		−1455.0964	60.33
	RHF/3-21G*		−1455.4144	65.58
	RHF/6-31G*		−1462.4609	50.50
2b				
	PM3	−36.00		−28.86
	RHF/3-21G		−1455.1972	−2.95
	RHF/3-21G*		−1455.5246	−3.50
	RHF/6-31G*		−1462.5614	−12.55

a) kcal/mol. *b*) Hartree. *c*) Difference from GS, kcal/mol.

personal computer.

The gas-phase energetics of GS (**1a, b**), IM, TS, and product (**2a, b**) involved in the reactions are listed in Table 1.

PM3 Geometries The TS models for the rearrangement of *O*-(2-dimethylaminoethyl and 2-methylthioethyl) *S*-methyl xanthates (**1a, b**) were obtained by the reaction-path calculation method and the TSs (TSa, b) were optimized by using the TS keyword. As the rearrangements take place only in polar solvents, the transition structures in several solutions were calculated using the COSMO approach. The heats of formation and important structural data are summarized in Tables 2a, b and the transition and IM structures of **1a, b** in water ($\varepsilon=78.5$) are depicted in Figs. 1a, b.

To compare the effect of solvent polarity on the calculated reaction barriers with that of a typical nonionic concerted reaction, the [3,3]-sigmatropic rearrangement of *O*-allyl *S*-methyl xanthate[2d,e] (**1c**) (Chart 3) was also analyzed by the PM3/COSMO method. The results are shown in Table 2c.

In the gas-phase TS geometry of **1a** shown in Fig. 2, strong intramolecular hydrogen bonding exists between one of the α hydrogens and the thiocarbonyl sulfur (Cα–H··S=, 1.791 Å), in which the Cα–H bond considerably elongates to 1.218 Å compared with the normal value (1.097 Å). The Cα–O bond (2.124 Å) to be broken is also longer than those observed in polar solvents.

As shown in Fig. 1a, the strong Cα–H··S= hydrogen bonding in gas phase disappears in solvents, and most of the bond lengths and angles of the five-membered ring formed by the hydrogen bonding are relaxed considerably. The corresponding Cα–H··S= distance changes from 1.791 to 2.713 Å and the O–C–S angle expands from 121.5° to 125.8°.

The intrinsic reaction coordinate (IRC) calculations starting from the transition structure confirmed the presence of a three-membered ring (aziridinium) IM (IMa) at the end of the IRC. As shown in Fig. 1a, the anionic moiety dissociates away from the α carbon beyond 3.0 Å in aqueous solution ($\varepsilon=78.5$).

***Ab Initio* and DFT Geometries** To compare the result of the semiempirical calculations, the GS, TS, and IM geometries of **1a** were calculated by the *ab initio* and DFT methods[3a] at some levels of theory. All the *ab initio* and DFT calculations refer to the gas phase, and therefore the sovent effect on the rearrangement reaction has not been investigated.

The GS and IM structures were obtained using the PM3-optimized structures as starting geometries. The RHF/3-21G* and B3LYP/6-31G* transition structures of **1a** were successfully located using the CALCALL option. The angles of S–C–C of the aziridinium rings of the TS and IM structures are 71.6° and 61.8°, respectively. IM IMa is 1.91 kcal/mol more stable than TS TSa. It is interesting to note that the gas-phase IM structure is symmetrical, in which the plane of the aziridinium ring and that of the dithiocarbonate anion moiety cross at right angles and the thiocarbonyl sulfur forms weak hydrogen bonds with the two methylene hydrogens. The calculations of the IM at several levels of theory gave essentially the same geometry.

The DFT calculation (Beckel3LYP) at the 6-31G* level gave a similar result to the HF/3-21G* structures (see Fig. 3). The reaction barrier in gas phase is 35.33 kcal/mol, and the IM is 3.98 kcal/mol more stable than TS.

The gas-phase stabilization energies on going from TS to IM in 3-21G* and B3LYP/6-31G* calcualtions are 1.91 and 3.98 kcal/mol, respectively, significantly smaller than the corresponding PM3 stabilization energy (25.77 kcal/mol).

In spite of all our efforts, the TS of **1b** could not be located.

Table 2a. GS and TS Heats of Formation (ΔHf), Dipole Moments (DM), and Geometries of **1a** in Several Solvents Calculated by the PM3 Method

| Solvent | ε | ΔHf (kcal/mol), DM (Debye) | | TS structural feature | | |
		GS	TS	C–C–N< (°)	Cα–O (Å)	=S–H–C (Å)
Gas	1.0	−3.58 (1.13)	48.08 (8.43)	79.2	2.124	1.791
C$_6$H$_{12}$	2.0	−7.45 (1.36)	38.56 (11.8)[a]	77.7	2.066	2.400
Et$_2$O	4.3	−10.72 (1.72)	28.42 (12.0)	80.6	2.028	2.546
EtOAc	6.0	−11.73 (1.92)	25.41 (12.0)	81.6	2.019	2.585
Me$_2$CO	20.7	−14.03 (2.50)	18.97 (12.2)	83.9	2.005	2.676
MeCN	35.9	−14.49 (2.63)	17.75 (12.3)[b]	84.3	2.013	2.737
H$_2$O	78.5	−14.86 (2.76)	16.66 (12.4)	84.7	2.000	2.713

a) IM, ΔHf=−1.531 kcal/mol. *b*) IM, ΔHf=−18.834 kcal/mol.

Table 2b. GS and TS Heats of Formation (ΔHf), DM and Geometries of **1b** in Several Solvents Calculated by the PM3 Method

| Solvent | ε | ΔHf (kcal/mol), DM (Debye) | | TS structural feature | | |
		GS	TS	C–C–SMe (°)	Cα–O (Å)	=S–H–C (Å)
Gas	1.0	−7.14 (1.94)	41.80 (6.10)	82.9	2.109	1.774
C$_6$H$_{12}$	2.0	−7.14 (1.94)	33.93 (9.36)	81.4	2.100	2.279
Et$_2$O[a]	4.3	−11.21 (2.23)	23.88 (9.85)	84.0	2.047	2.487
EtOAc	6.0	−12.51 (2.36)	20.74 (10.2)	85.0	2.032	2.535
Me$_2$CO	20.7	−15.26 (2.74)	14.13 (10.2)	87.5	2.005	2.642
MeCN	35.9	−15.81 (2.84)	12.82 (10.2)	88.0	2.000	2.664
H$_2$O[b]	78.5	−16.22 (2.93)	11.93 (10.2)	88.3	2.000	2.682

a) RSOLV=1.5: ΔHf (GS)=−9.87 kcal/mol; ΔHf (TS)=26.61 kcal/mol. *b*) RSOLV=1.5: ΔHf (GS)=−14.16 kcal/mol; ΔHf (TS)=15.78 kcal/mol.
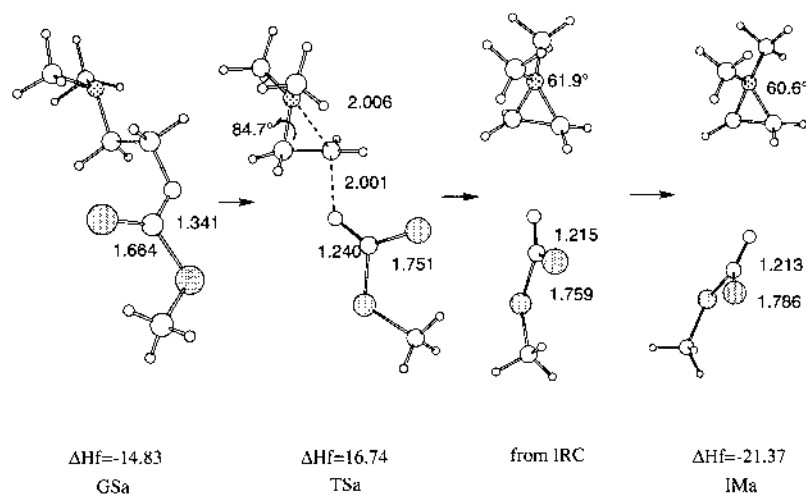
Fig. 1a. GS, TS, and IM Structures and Heats of Formation (kcal/mol) for the Rearrangement of **1a** Calculated by the PM3/COSMO Method (ε=78.5)
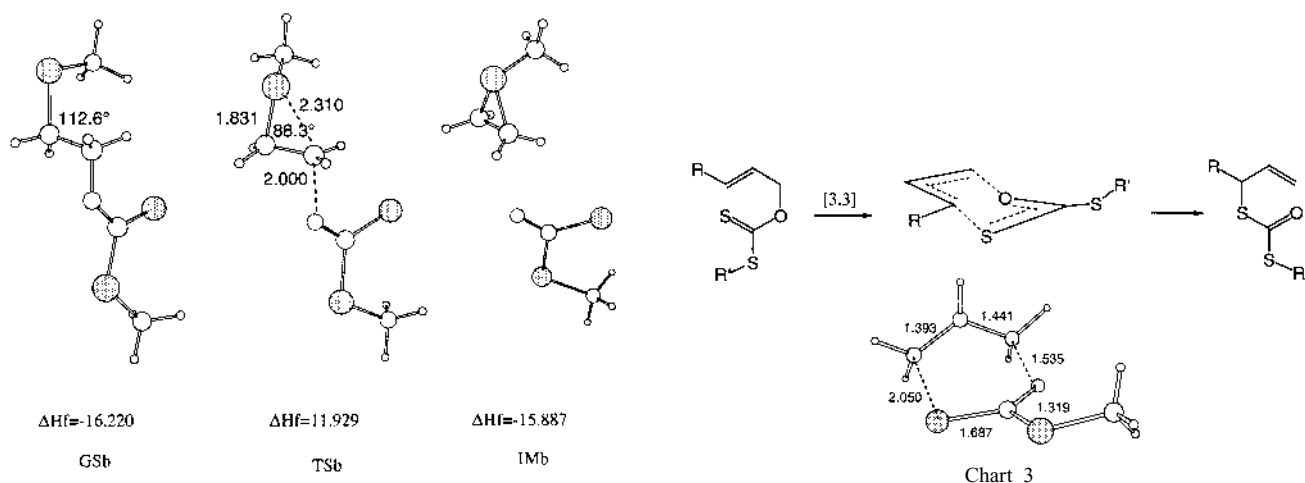
The important bond lengths (Å) and angles are shown.

Fig. 1b. GS, TS, and IM Structures and Heats of Formation (kcal/mol) for the Rearrangement of **1b** Calculated by the PM3/COSMO Method (ε=78.5)

The important bond lengths (Å) and angles are shown.

Chart 3

Table 2c. GS and TS Heats of Formation (ΔHf), DM and Geometries of **1c** in Several Solvents Calculated by the PM3 Method

| Solvent | ε | ΔHf (kcal/mol), DM (Debye) | | TS structural feature | |
		GS	TS	Cα–O (Å)	=S–H–C (Å)
Gas	1.0	19.80 (0.87)	36.39 (2.57)	1.535	2.050
C_6H_{12}	2.0	16.36 (1.30)	33.19 (3.15)	1.544	2.062
Et_2O	4.3	13.34 (1.90)	30.41 (3.81)	1.554	2.074
EtOAc	6.0	12.33 (2.17)	29.50 (4.07)	1.558	2.078
Me_2CO	20.7	10.19 (2.88)	27.49 (4.73)	1.566	2.080
MeCN	35.9	9.77 (3.05)	27.06 (4.89)	1.566	2.078
H_2O	78.5	9.41 (3.20)	26.75 (5.01)	1.567	2.077

Rearrangement Mechanism As described above, *O,S*-dimethyl xanthate reacts with triethylamine to give the quaternary salt, during which the thione-to-thiol rearrangement occurs. The reaction with triethylamine is limited only to *O*-methyl and *O*-ethyl *S*-alkyl xanthates because of the S_N2-type steric reason. In this connection, we clarified that pyridine *N*-oxides and 4-dimethylaminopyridines are reactive catalysts.[13] In the rearrangement of **1a**, an intermolecular reaction mechanism of this type has not yet been ruled out. However, based on the present theoretical evidence together with the results of **1b**, we can safely say that the neighboring-group participation of the adjacent dimethylamino group is operative in the rearrangement of **1a**.

The structure of the anionic moiety of the IMs should be

mentioned. The structure of the anion has been ambiguous.[7a—c] In particular, it is not clear whether the negative charge delocalizes over the O–C–S moiety or localizes on the sulfur atom. Inspection of the interatomic C–O and C–S distances of the dithiocarbonate anion calculated in sev-

eral polar solvents ($\varepsilon > 6.0$) suggests that the negative charge clearly localizes on the sulfur atom. The frontier orbital consideration also supports this result. Based on these data, we wish to propose that the reaction would follow scheme b) in Chart 5, in which the ion pairs of the xanthates should be drawn as IM2.

Solvent Effect As can be seen in Tables 2a, b, TSa and TSb are more effectively stabilized than the corresponding GSs by solvent-ionizing power. For example, in **1a**, the stabilization energies of the GS and TS when the solvent is changed from cyclohexane to acetonitrile are *ca*. 7 and 21 kcal/mol, respectively. The xanthate **1b** showed a similar trend. In sharp contrast to these, both the GS and TS of **1c** are almost equally stabilized by *ca*. 10 kcal/mol (Table 2c). The reaction barriers ($\Delta\Delta Hf$) were estimated from the heats of formation (ΔHf) of GSs and TSs of **1a—c**,[14a] (see Table 3).
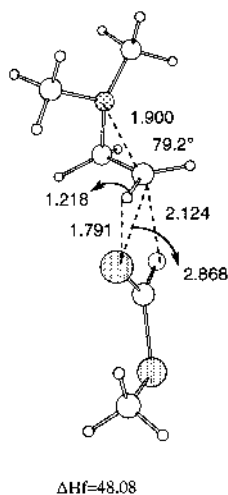

ΔHf=48.08

Fig. 2. Gas-Phase Transition Structure for the Rearrangement of **1a** and Heats of Formation (kcal/mol) Calculated by the PM3/COSMO Method ($\varepsilon = 1.0$)
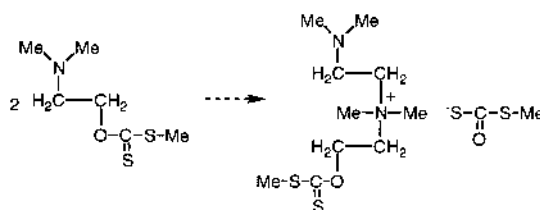
The important bond lengths (Å) and angles are shown.

Chart 4

E=-1153.3747　　　　　　E=-1153.3074　　　　　　E=-1153.3105

GS (3-21G*)　　　　　　　TS (3-21G*)　　　　　　　IM (3-21G*)

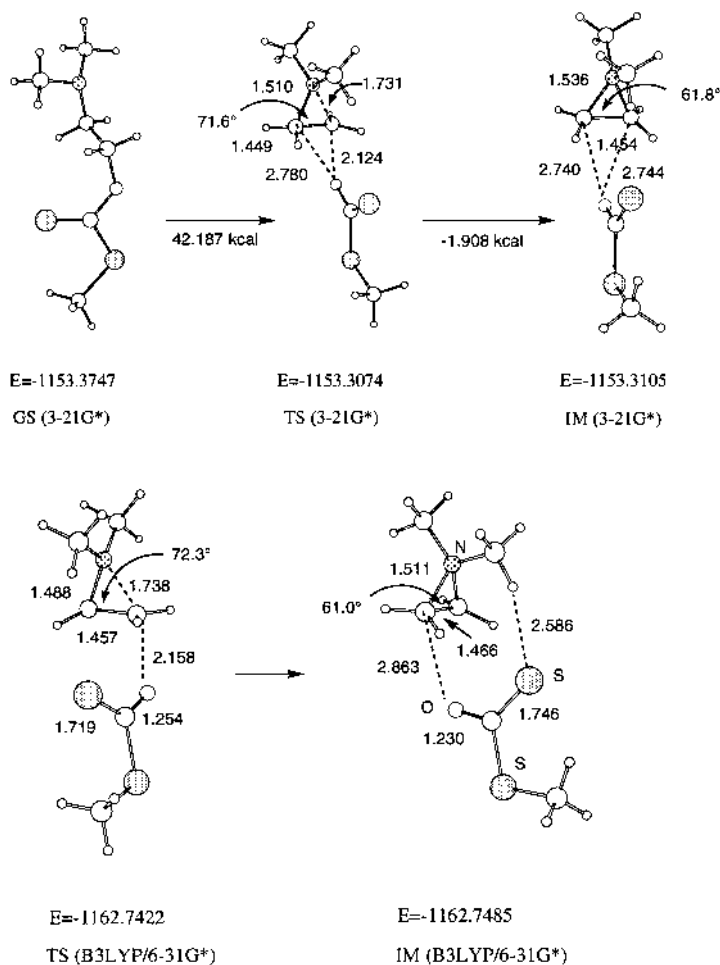E=-1162.7422　　　　　　　E=-1162.7485

TS (B3LYP/6-31G*)　　　　IM (B3LYP/6-31G*)

Fig. 3. 3-21G* and B3LYP/6-31G* Structures and Energies (Hartrees) of TS and IM for the Rearrangement of **1a**
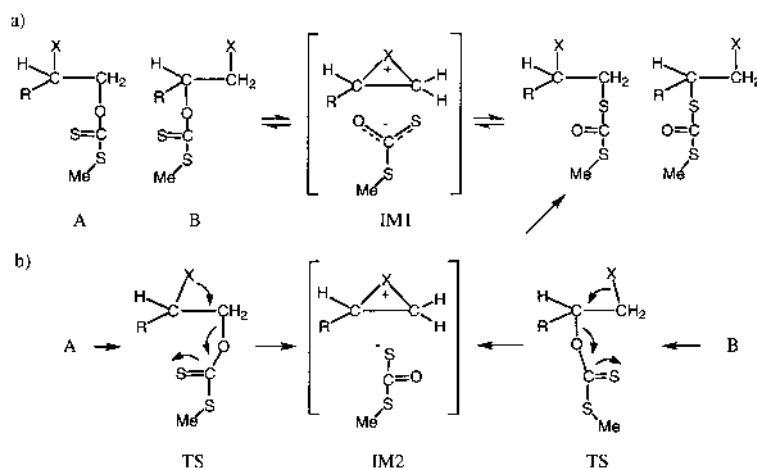
The important bond lengths (Å) and angles are shown.

Chart 5

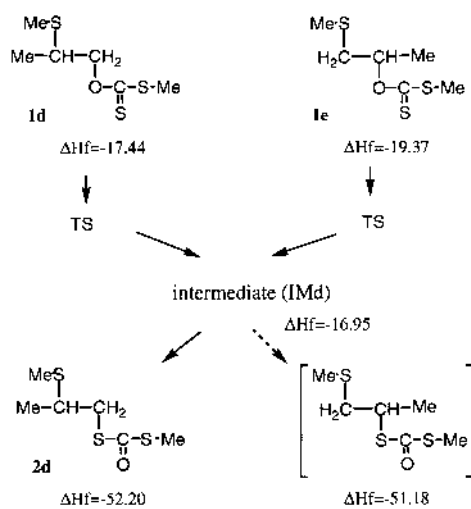Table 3. Reaction Barriers[a] and DM Differences with Change in Solvent Polarity for Thione-to-Thiol Rearrangement of **1a**—**c**

Solvent	ε	$\Delta\Delta$Hf (kcal/mol), ΔDM (Debye)[b]		
		1a	**1b**	**1c**
Gas	1.0	51.66 (7.30)	48.94 (4.20)	16.59 (1.70)
C_6H_{12}	2.0	46.01 (10.4)	41.07 (7.42)	16.82 (1.85)
Et_2O	4.3	39.14 (10.2)	35.10 (7.62)	17.07 (1.91)
EtOAc	6.0	37.14 (10.1)	33.25 (7.57)	17.17 (1.89)
Me_2CO	20.7	33.00 (9.73)	29.39 (7.41)	17.29 (1.85)
MeCN	35.9	32.24 (9.65)	28.63 (7.40)	17.30 (1.84)
H_2O	78.5	31.52 (9.60)	28.15 (7.30)	17.34 (1.80)
Solvent sensitivity parameter,[b] $a\times10^2$				
		40.3	13.0	6.31

a) The reaction barriers ($\Delta\Delta$Hf) are simply estimated from ΔHf (TS)$-\Delta$Hf (GS), kcal/mol. *b*) ΔDM$=$DM (TS)$-$DM (GS). *c*) Least-square slope of line (log $k=$ aE_T+b) derived from plots of log k against E_T values in various solvents.[2e,9]

COSMO calculation in MeCN

Chart 6

The differences in the reaction barriers when the solvent is changed from cyclohexane to acetonitrile for **1a** and **1b** are -13.8 and -12.4 kcal/mol, respectively, whereas that of **1c** is only -0.48 kcal/mol. This is in accordance with the reaction behavior that the rearrangements of **1a** and **1b** could not be observed in nonpolar solvents (*n*-hexane or benzene)[9] and the allylic xanthate (**1c**) easily isomerizes to the dithiol ester even in nonpolar solvents at room temperature.

From the COSMO calculations, we can make a rough estimation that the rearrangement *via* an ionic IM would show a large rate enhancement with the change in solvent polarity and the allylic rearrangement *via* a nonionic TS is not affected by changes in solvent polarity.[14b] The DM changes from GSs to TSs and their solvent polarity dependencies support this assumption (see Tables 2, 3). The DM difference between the GS and TS of **1c** is not affected by the change in solvent polarity.

To compare the calculation data with the experimental ones, the solvent sensitivity parameters for **1a**—**c** are added to Table 3. The solvent sensitivity parameters were defined by use of the least-square slope of line derived from plots of log k against the E_T values.[2e,9] The order of sensitivity is **1a**≫**1b**>**1c**. Strictly speaking, the PM3 calculation using the COSMO continuum solvation model does not interpret the solvent effect deduced from the solvent sensitivity para-

meters for **1a**—**c**. The reason is because some specific interactions between xanthates and solvents like hydrogen bonding are not included in the calculation.

Rearrangement of Unsymmetric Xanthates In unsymmetrical xanthates,[7b,c] neighboring-group participation may often lead to molecular rearrangement. The xanthate (**1d**) rearranged to the corresponding dithiolcarbonate (**2d**) upon heating. On the other hand, the isomeric xanthate (**1e**) yields the skeletally rearranged dithiolesters (**2d**), in which the neighboring group breaks away from the atom to which it was originally attached in the substrate. These indicate that the rearrangements proceed through a common IM (IMd). Presumably, the IM thiiranium ion is attacked preferentially at the primary α-carbon atom rather than at the secondary β-carbon atom. The observed reaction behavior was reproduced by the PM3/COSMO method (Fig. 4).

Inspection of the IM structure and net charges of α,β-carbon atoms indicates that the attack at the primary α carbon atom is controlled by the steric factor.[15] As shown in Fig. 4, the dithiolcarbonate anion may attack at the α-carbon atom from a less-hindered site.
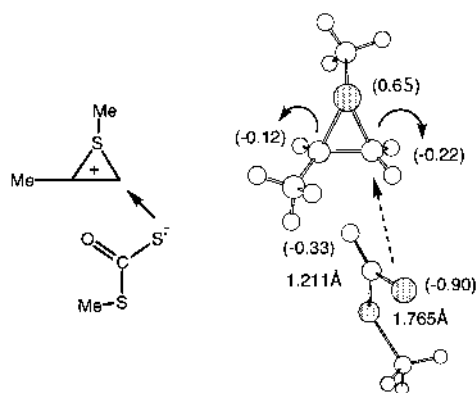
Finally, the anchimeric assistance of ether groups should

Fig. 4. Structure and Net Charges (NC) of the Ion-Pair IM (IMd) for the Rearrangement of a Pair of Position Isomers of the Xanthates (**1d, e**) ($\varepsilon = 78.5$)
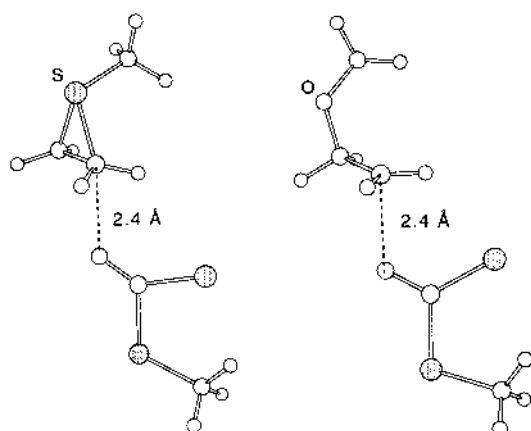

Fig. 5. Structural Changes in **1b** and **1f** along the Dissociation of the C–O Bond Calculated by the PM3/COSMO Method ($\varepsilon = 78.5$)

be described. *O*-(2-Methoxyethyl) *S*-methyl xanthate (**1f**) did not undergo thione-to-thiol rearrangement on heating. The corresponding TS could not be located by the method adopted for **1a** and **1b**, in which the angle of Me–O–CH$_2$– or the bond length of CH$_2$–O(C=S)– was used as a reaction co-ordinate (Fig. 5). The anchimeric assistance of ether oxygen appears to be smaller than those of the dialkylamino and alkylthio groups. The difference in the *n*-HOMO electron densities of the oxygen and sulfur atoms supports this assumption.

In summary, the PM3/COSMO calculations provided theoretical evidence that 2-dimethylaminoethyl and 2-methylthioethyl *S*-methyl xanthates (**1a, b**) rearrange to the corresponding dithiolcarbonates (**2a, b**) by the anchimeric assistance of the neighboring-group with the assistance of the solvent-ionizing power. Although 3d atomic orbitals have not as yet been included in the PM3 treatment, the PM3 MO study using the COSMO technique affords a useful clue for interpretation of the ionic reaction behavior of xanthates bearing an anchimeric group adjacent to the xanthate group.

References and Notes
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12) *a*) PM3 calculations were performed using MOPAC ver. 6.0 (QCPE No. 445) and MOPAC97. Fujitsu Ltd., Tokyo, Japan, 1998; *b*) In the COSMO method, RSOLV is set to the default value (1.0) which is appropriate for water. The effect of this quantity was tested in **1b** (see Table 2b). The keyword NSPA=32 was used to construct a solvent-accessible surface area.
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14) *a*) The PM3 calculated reaction barriers are underestimated. The observed activation energy of **1c** is 25.8 kcal/mol in *n*-hexadecane; *b*) In contrast to the observed solvent effect, the calculated reaction barrier of **1c** slightly decreased with the increase in solvent polarity. This may be due to an additional desolvation energy in the GS compared with the TS.
15) The LUMO electron densities of the carbon atoms of the thiiranium ion of IMd are almost same, indicating that the steric factor is operative in the dominant attack of ⁻SCOSMe on the primary carbon.