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The Reaction of α-Carbonyl Sulfides with Bases. I. The Reaction between α-Carbonyl Sulfides with Thiolates

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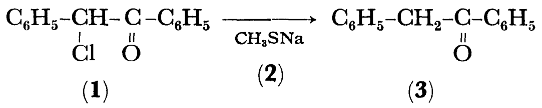
It is found that carbonyl compounds, such as ketones and esters, bearing an alkyl(or aryl)thio group at the α-position, are smoothly reduced to the parent carbonyl compounds by the action of the thiolate anion. α-Halo or α,α-dihalo ketones are similarly reduced with the thiolate, probably *via* the corresponding sulfides. The mechanism of the reaction is discussed.

Since oxygen and sulfur belong to the same group in the periodic table, many similar reactions occur with the oxygen-sulfur analogs. However, there are also some dissimilarities, mainly because of the ability of the sulfur atom to expand its valence shell. The formations of the quadrivalent and sexivalent sulfur compounds are typical examples. As another dissimilarity of the two elements, the behavior toward bases may be cited; elemental sulfur itself and other polysulfides are known to undergo electrophilic cleavage,[1] whereas the dialkyl peroxides have seldom been reported to be cleaved by the bases.[2]

During the course of another study, we have encountered a rather curious reaction: the treatment of α-chlorodeoxybenzoin (**1**) with sodium methanethiolate (**2**) in ethanol gave rise to the formation of deoxybenzoin (**3**) instead of the expected α-(methylthio)deoxybenzoin (**4**). This finding of an unexpected reaction allured us to investigate the scope and the mechanism of the reaction. The purpose of this paper is to present the results of these studies and our conclusion that this unexpected reaction probably occurs *via* a nucleophilic attack of the thiolate ion on sulfur:

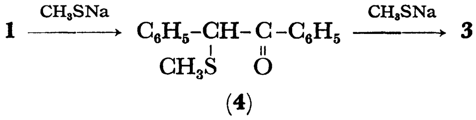


$$C_6H_5\text{-}\underset{Cl}{CH}\text{-}\underset{O}{\overset{}{C}}\text{-}C_6H_5 \xrightarrow[CH_3SNa\ (2)]{} C_6H_5\text{-}CH_2\text{-}\underset{O}{C}\text{-}C_6H_5$$

(**1**) (**3**)

Results and Discussion

The cautious treatment of **1** with one equivalent of **2** in ethanol at 0°C resulted in the formation of **4** in a good yield, whereas the heating of an equimolar mixture of **1** and **2** in ethanol afforded a mixture of **3** and **4**. Thus, it is possible that the formation of **4** is the intervening process in the reduction of **1** to **3**.



$$1 \xrightarrow{CH_3SNa} C_6H_5\text{-}\underset{CH_3S}{CH}\text{-}\underset{O}{C}\text{-}C_6H_5 \xrightarrow{CH_3SNa} 3$$

(**4**)

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[1] A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).

[2] Oxidation of olefins and amines with peroxy acid and Baeyer-Villiger oxidation may be considered to involve the nucleophilic cleavage of the O–O bonds. For cleavage of hydrogen peroxide with various bases, see J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962).

TABLE 1. REDUCTION OF α-ALKYLTHIO CARBONYL COMPOUNDS WITH THIOLATES

Run No.	Substrate	Thiol	Molar ratio[a]	Reaction period (hr)	Yield (%)	Products
1	 $C_6H_5CO\underset{\substack{\vert \\ SC_2H_5}}{C}HC_6H_5$	C_2H_5SH	1.0	0.5	quant.	$C_6H_5COCH_2C_6H_5$
2	$C_6H_5COCH_2SC_2H_5$	C_2H_5SH	1.1	2	85	$C_6H_5COCH_3$
3	$C_6H_5COCH_2SCH_3$	C_2H_5SH	1.3	2	quant.	$C_6H_5COCH_3$
4	$C_6H_5COCH_2SCH_3$	C_6H_5SH	1.6	4	—	$C_6H_5COCH_3$ and $C_6H_5COCH_2SCH_3$ (4:1)
5	α-(Ethylthio)cyclohexanone	C_2H_5SH	1.3	10	10	Cyclohexanone
6	2-Ethylthio-l-tetralone	C_2H_5SH	1.3	2.5	62	l-tetralone
7	$CH_3SCH_2CO_2C(CH_3)_3$	CH_3SH	3.0	1.5	quant.	$CH_3CO_2C(CH_3)_3$

a) Molar ratio is expressed by dividing number of moles of the thiolates by that of the substrates.

TABLE 2. REDUCTION OF α-HALO CARBONYL COMPOUNDS WITH THIOLATES

Run No.	Substrate	Thiol	Molar ratio[a]	Reaction period (hr)	Yield (%)	Products
8	$C_6H_5COCHClC_6H_5$	C_2H_5SH	1.0	0.4	—	$C_6H_5COCH_2C_6H_5$, $C_6H_5COCHClC_6H_5$, and $C_6H_5COCH(SC_2H_5)C_6H_5$ (3:1:4)
9	$C_6H_5COCHClC_6H_5$	C_2H_5SH	5.0	0.25	quant.	$C_6H_5COCH_2C_6H_5$
10	$C_6H_5COCH_2Cl$	C_2H_5SH	2.0	1.5	94	$C_6H_5COCH_3$
11	$C_6H_5COCH_2Cl$	CH_3SH	2.1	1.5	84	$C_6H_5COCH_3$
12	$(CH_3)_3CCOCH_2Cl$ + $(CH_3)_3CCOCHCl_2$	C_2H_5SH	—	1.5	—	$(CH_3)_3CCOCH_3$
13	2-Chlorocyclohexanone	C_2H_5SH	2.2	10	29	Cyclohexanone
14	3-Bromocamphor	C_2H_5SH	2.5	1.5	62	Camphor
15	$C_6H_5CHClCO_2C_2H_5$	C_2H_5SH	2.0	1.5	90	$C_6H_5CH_2CO_2H$ (after hydrolysis)
16	$C_6H_5CHClCO_2C_2H_5$	C_2H_5SH	2.1	0.5	—	$C_6H_5CH_2CO_2C_2H_5$ and $C_6H_5CH(SC_2H_5)CO_2C_2H_5$ (2:1)
17	$ClCH_2CO_2C(CH_3)_3$	C_2H_5SH	2.0	3.5	—	$CH_3CO_2C(CH_3)_3$ and $C_2H_5SCH_2CO_2C(CH_3)_3$

a) Molar ratio is expressed by dividing number of moles of the thiolates by that of the substrates.

Indeed, treating **4** with **2** also afforded **3** in a good yield; in order to reduce **1** to **3** in a good yield, it was necessary to use two molar portions of **2** for each mole of **1**.

In order to test the generality of the reaction, various α-halo or α-alkylthio carbonyl compounds were treated with various thiolates: the results are shown in Tables 1 and 2. It may now be said that the reduction with thiolate is a fairly general reaction. A few of the interesting points to be pointed out are as follows: 1) even α,α-dihalo ketone can be reduced to the parent ketone with thiolate (run 12); 2) α-alkylthio and α-halo esters are also reduced with thiolate (runs 7 and 17); 3) benzenethiolate is a weaker reducing agent than the alkanethiolates (run 4). It seems that the solvent must be fairly polar in order to effect the reaction, since treating α-(methylthio)acetophenone with ethanethiolate in benzene gave only a trace of the reduced material.

It is now necessary, for studying the mechanism of the reaction further, to know the fate of the sulfur compounds: it was found that dimethyl disulfide was formed when **1** was treated with **2**. Although the treatment of **4** with sodium ethanethiolate afforded dimethyl disulfide and diethyl disulfide in addition to ethyl methyl disulfide, the formations of the symmetric disulfides could be attributed to the scrambling of the ethyl methyl disulfide because of the presence of ethanethiolate anion:[1,3]

$$RSSR' + RS^- \longrightarrow RSSR + R'S^-$$

$$RSSR' + R'S^- \longrightarrow R'SSR' + RS^-$$

Other combinations of thioethers and thiolates which could give asymmetric disulfides also afforded symmetric sulfides.

The formation of disulfides might be interpreted as indicating that the reaction proceeded *via* a radical intermediate. However, the idea is rather inconsistent with the solvent effects and the fact that the conditions

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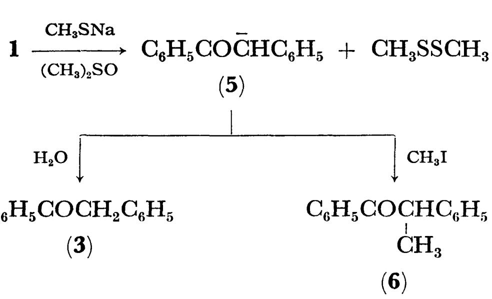
3) S. Oae and H. Tanaka, *Yukigosei Kagaku Kyokaishi*, **27**, 793 (1969).

are strongly ionic. Another fact may be added as a proof against the radical intermediate; the reduction with benzenethiolate is slow compared with that with ethanethiolate. Trapping the intermediate was thus attempted in order to ascertain the nature of this reaction.

1 was treated with sodium methanethiolate in dimethyl sulfoxide to form a deep red-orange solution. The solution was quenched with water to give **3**, whereas quenching with methyl iodide gave α-methyldeoxybenzoin (**6**). Thus, the reaction clearly proceeds *via* an ionic intermediate; otherwise it is difficult to explain the products. It is most probable to assume the intermediacy of the deprotonated anion of deoxybenzoin (**5**). Then, in ethanol and other protic solvents, **5** picks up a proton to form **3**, whereas it survives in dimethyl sulfoxide until quenched.



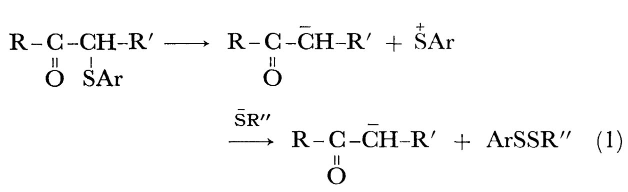
$$\mathbf{1} \xrightarrow[(CH_3)_2SO]{CH_3SNa} C_6H_5CO\bar{C}HC_6H_5 + CH_3SSCH_3$$

(**5**)

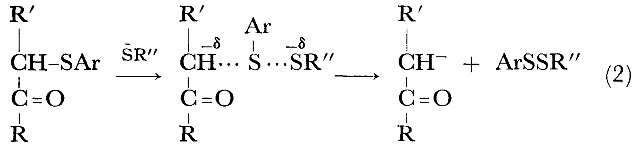
H_2O: $C_6H_5COCH_2C_6H_5$ (**3**); CH_3I: $C_6H_5COCH(CH_3)C_6H_5$ (**6**)

In view of the above discussion, thiolate must attack the sulfur atom of the thioethers as a nucleophile. That is, this reaction involves a nucleophilic attack at the sulfur atom of the thioether. If this mechanism is assumed, it is easy to explain the slow reaction with benzenethiolate, since benzenethiolate is a more stable anion than ethanethiolate[4] and may thus be a poorer nucleophile.

Two possibilities may be considered as the reaction mechanism: S_N1- and S_N2-type reactions at the sulfur atom of the thioether. These mechanisms may be expressed by Eqs. (1) and (2) respectively:



$$R\text{-}\underset{\substack{\|\\ O}}{C}\text{-}\underset{\substack{|\\ SAr}}{CH}\text{-}R' \longrightarrow R\text{-}\underset{\substack{\|\\ O}}{C}\text{-}\bar{C}H\text{-}R' + \overset{+}{S}Ar \xrightarrow{\bar{S}R''} R\text{-}\underset{\substack{\|\\ O}}{C}\text{-}\bar{C}H\text{-}R' + ArSSR'' \quad (1)$$



$$\begin{matrix} R' \\ | \\ CH\text{-}SAr \\ | \\ C{=}O \\ | \\ R \end{matrix} \xrightarrow{\bar{S}R''} \begin{matrix} R' \quad Ar \\ |_{-\delta} \quad | \quad _{-\delta} \\ CH\cdots S\cdots SR'' \\ | \\ C{=}O \\ | \\ R \end{matrix} \longrightarrow \begin{matrix} R' \\ | \\ CH^- \\ | \\ C{=}O \\ | \\ R \end{matrix} + ArSSR'' \quad (2)$$

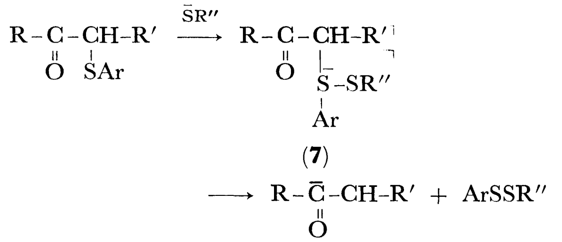
However, the possibility of the S_N1-type reaction can be ruled out for the following reason: if it were an S_N1-type reaction, there would be no reason for the alkoxide ion to fail to cause a similar reaction, but it actually is the case as will be demonstrated in the following paper.[5]

Information about the transition state of the reaction can be obtained by measuring the substituent effects on the rates of the reaction. The pseudo-first-order rates of the reaction of α-(phenylthio)acetophenone and α-(*p*-bromophenylthio)acetophenone with sodium benzenethiolate were thus obtained using an excess of thiophenol and a reasonable amount of sodium in order to keep the concentration of the thiolate constant, while the second-order rates were calculated by using the concentration of the thiolate ion. The results are listed in Table 3. The rates are slightly diminished when the substituent is electron-withdrawing. Thus, the results may be taken as favoring the S_N2-type transition state rather than the S_N1-type, since, if it were an S_N1-type reaction, the decrease in ratio would be much larger.

TABLE 3. RATES OF REACTION OF α-(ARYLTHIO)-ACETOPHENONE ($ArSCH_2COC_6H_5$) WITH SODIUM BENZENETHIOLATE IN ETHANOL (65°C)

Ar	$k_1 \times 10^2$ hr^{-1}	$k_2 \times 10^5$ $l\cdot$mol$^{-1}\cdot$hr^{-1}
C_6H_5	2.65	1.15
p-BrC_6H_4	1.4	0.7

Another alternative may be postulated as a rate-determining step: the electron pair is donated by the anion to the sulfur *d*-orbital to form **7**:



$$R\text{-}\underset{\substack{\|\\ O}}{C}\text{-}\underset{\substack{|\\ SAr}}{CH}\text{-}R' \xrightarrow{\bar{S}R''} \left[R\text{-}\underset{\substack{\|\\ O}}{C}\text{-}\underset{\substack{|\\ \bar{S}\text{-}SR''\\ |\\ Ar}}{CH}\text{-}R'\right] (\mathbf{7}) \longrightarrow R\text{-}\underset{\substack{\|\\ O}}{C}\text{-}\bar{C}H\text{-}R' + ArSSR''$$

This possibility can, however, be ruled out also: if it were the case, the electron-withdrawing substituent would enhance the reaction rate.

It may be argued that reduction may not be directly caused by the thiolate anion, but by the hydride shift from either alkoxide or the thiolate anion, as many reductions are known to occur by the action of alkoxide through the hydride shift. However, this possibility can be discarded for two reasons. First, as will be discussed in the following paper,[5] ethoxide is not capable of reducing the α-alkylthio ketone. The second reason is that benzenethiolate can reduce α-alkyl(or aryl)-thio ketone in ethanol. In the latter reaction, the reducing agent must be the benzenethiolate ion, which has no α-hydrogen, since ethoxide, which may exist because of an equilibrium and also as a reaction product, has no power to reduce the alkylthio ketone.

Having established the nucleophilic nature of the reaction, the next problem is to clarify the role of the carbonyl group. The role of the carbonyl group may be considered to be two-fold. First, it acts as an anion-stabilizing substituent because of its intrinsic mesomeric and inductive nature **8**. Second, the attacking base may add to the carbonyl group first, and then within the adduct **9** a nucleophilic reaction may take place, as is indicated by the arrows:

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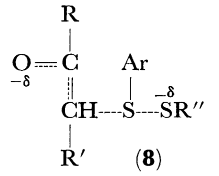
4) p*Ka* values of benzenethiol and ethanethiol are 12.0 and 8.3, respectively. M. Ōki, "San to Enki (Acids and Bases)," Baifūkan, Tokyo (1967), p. 66.

5) M. Ōki and W. Funakoshi, This Bulletin, **44**, 832 (1971).

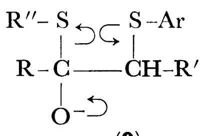
TABLE 4. REACTIONS OF SOME α-SUBSTITUTED KETONES WITH THIOLATES IN ETHANOL

Substrate	Thiol	Molar ratio[a)]	Reaction period (hr)	Yield of parent ketone (%)
$C_6H_5CH(SCN)C_6H_5$	C_2H_5SH	6.0	2	quantitative
$C_6H_5COCH_2SCN$	C_2H_5SH	2.5	7	45
$C_6H_5COCH_2Cl$	H_2S	20	5	10
$C_6H_5COCH_2SCOCH_3$	C_2H_5SH	8.0	1	84

a) Molar ratio was calculated on the basis of sodium used for making thiolates. Thiols were used always in excess relative to sodium.



(8)

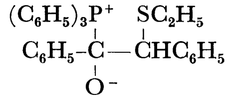


(9)

The data are rather contradictory and confusing. Triphenylmethyl chloride, ethyl triphenylmethyl thioether, phenyl trichloromethyl thioether, and *p*-benzoylbenzyl ethyl thioether gave no sign of reduction when treated with thiolate either in ethanol or in dimethyl sulfoxide-ethanol, although triphenylmethyl, trichloromethyl, and *p*-benzoylbenzyl groups are supposed to stabilize the anion to a considerable extent. These results suggest that the presence of the anion-stabilizing substituent is not good enough to cause the reaction, thus favoring the intermediate **9**. Failure of methyl *p*-tolyl sulfone to be formed from phenylthiomethyl *p*-tolyl sulfone may be added as another proof for the intermediacy of **9**, since bromomethyl *p*-tolyl sulfone is reported to be reduced by a thiolate to methyl *p*-tolyl sulfone.[6)] However, it may be argued that this is not direct proof of the importance of the carbonyl group in the reduction with thiolate, because deprotonation may compete with the nucleophilic attack at the sulfur atom.

$$p\text{-}CH_3C_6H_4SO_2CH_2Br \xrightarrow{\bar{S}C_6H_5} p\text{-}CH_3C_6H_4SO_2CH_3$$

On the other hand, there is a fact which cannot be explained by the intermediate **9**: α-(ethylthio)deoxybenzoin is smoothly reduced with triphenylphosphine. The details of the reaction will be discussed in the next paper.[5)] If the adduct **10**, which itself will be of high energy because of the charge separation and the steric effect, is formed, it has to be assumed that the positively-charged phosphorus behaves as a nucleophile: this is, though, highly unlikely.



$$C_6H_5\text{-}\overset{(C_6H_5)_3P^+}{\underset{O^-}{C}}\text{—}\overset{SC_2H_5}{C}HC_6H_5$$

(**10**)

The mechanism of the reaction could be different according to the structure of the substrate and the attacking base. This point must be explored further.

Finally, we wish to point out that the reaction of α-carbonyl sulfide with thiolate is not limited to α-carbonyl thioethers; some other sulfur compounds are also cleaved at the C–S bond to produce the parent carbonyl compounds. Some of the results are shown in Table 4. It will be seen that thiocyano and acetylthio ketones are smoothly reduced to the parent ketones.[7)] The isolation of acetophenone in a low yield on the treatment of α-chloroacetophenone with sodium hydrogen sulfide may be attributed to the presence of an equilibrium of ionization such as is expressed by the following equation (negative charge on the sulfur atom should certainly reduce the possibility of the nucleophilic attack):

$$C_6H_5COCH_2SH + HS^- \rightleftharpoons C_6H_5COCH_2S^- + H_2S$$

It has been well established that disulfides are cleaved at the S–S bond by various bases, and excellent reviews have been published.[1,3)] However, thioethers are known to be fairly inert toward bases, and under forcing conditions a proton alpha to the sulfur atom is removed because of the stabilization due to the sulfur atom.[8)] The reaction discovered here occurs under rather mild conditions and is a unique one in a sense mentioned above.

Experimental

Materials. The following new thioethers were identified.

α-(Methylthio)deoxybenzoin. α-Chlorodeoxybenzoin (26.5 g or 0.115 mol) was allowed to react with sodium methanethiolate in ethanol prepared from 27 g (0.56 mol) of methanethiol at −15°C. The reaction mixture was poured into water after 30 min at 0°C and extracted with ether to afford α-(methylthio)deoxybenzoin, mp 73—73.5°C, in almost quantitative yield. Found: C, 74.36; H, 5.70%. Calcd for $C_{15}H_{14}OS$: C, 74.36; H, 5.80%.

Similarly the following compounds were prepared.

α-(Ethylthio)deoxybenzoin: mp 74.1—75.5°C. Found: C, 75.29; H, 6.30%. Calcd for $C_{16}H_{16}OS$: C, 74.98; H, 6.29%.

α-(Ethylthio)cyclohexanone: bp 119—121°C/30 mmHg. Found: C, 60.70; H, 8.66%. Calcd for $C_8H_{14}OS$: C, 60.74; H, 8.92%.

[6)] F. G. Bordwell and B. B. Jarvis, *J. Org. Chem.*, **33**, 1182 (1968).

[7)] Incidentally, this makes a very interesting contrast with the reaction between some nucleophiles and methyl α-thiocyanoacetate in that the latter yields $^-SCH_2CO_2CH_3$ anion. See R. G. Hiskey, W. H. Bower, and D. N. Harpp, *J. Amer. Chem. Soc.*, **86**, 2010 (1964); R. G. Hiskey and D. N. Harpp, *ibid.*, **86**, 2014 (1964).

[8)] Hydrogen atoms of the methylene group which is placed between two sulfur atoms are easily exchanged by deuterium under the influence of the basic catalyst. See for example: S. Oae, W. Takagi, and A. Ohno, *Tetrahedron*, **20**, 427 (1964).

α,α-Bis(methylthio)acetophenone: mp 65.5—66.5°C. Found: C, 56.80; H, 5.58%. Calcd for $C_{10}H_{12}OS_2$: C, 56.60; H. 5.70%.

The Reaction of Thiolates with Sulfides and Halogen Compounds. As an example of the general procedure, the reduction of α-chlorodeoxybenzoin with methanethiolate will be described. The reduction of the sulfides proceeded smoothly with equimolar thiolate, whereas the halides needed at least 2 molar portions of thiolate to produce the parent ketone in a good yield. Sometimes an excess of thiol was used to cover the loss by vaporization.

To a solution prepared from 0.3 mol of sodium and 150 m*l* of ethanol, was added 0.4 mol of methanethiol and then 0.126 mol of α-chlorodeoxybenzoin. The solution was heated under reflux and poured into water after 30 min. The subsequent extraction of the mixture gave deoxybenzoin, mp 56—57°C, in an almost quantitative yield.

The other products were analyzed by vapor-phase chromatography.

Reaction of α-(Methylthio)deoxybenzoin with Methanethiolate in Dimethyl Sulfoxide. A solution prepared from 0.958 g (0.04 mol) of sodium and 60 m*l* of ethanol was treated with an excess of methanethiol and then evaporated. The residue was taken up in 60 m*l* of dimethyl sulfoxide and mixed with a solution of 4.808 g (0.02 mol) of α-(methylthio)deoxybenzoin in 20 m*l* of dimethyl sulfoxide. The mixed solution was heated for 45 min at 85°C to produce a deep red-orange color, Quenching the solution with water gave deoxybenzoin, whereas treating the solution with methyl iodide yielded α-methyldeoxybenzoin (NMR, δ from TMS in CCl_4 4.51 (q) and 1.50 (d)).

Determination of the Reaction Rates. A solution was prepared containing *ca* 7×10^{-2} mol of α-(arylthio)acetophenone, *ca* 5 mol of thiophenol, and *ca* 2×10^{-2} mol of sodium in 200 m*l* of ethanol. Di-*p*-methoxyphenyl ketone was added to the solution for use as an internal standard of analysis. Ten-mililiter portions of the solution were sealed in separate tubes, and the decrease in the quantity of the α-keto sulfides was determined by means of NMR.

The cost of this study has been defrayed in part by the Grant-in-Aid for Fundamental Research from the Ministry of Education, to which the author's thanks are due.