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Hydrogen-Deuterium Exchange Reaction *via* β-Sulfinyl Carbanion. Neighboring Sulfur Participation in Carbanion Formation

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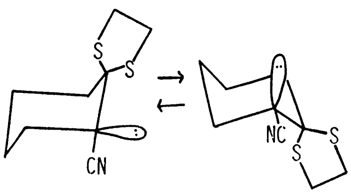
Synopsis. The rate of base-catalyzed H-D exchange reaction of substituted cyclopropanes and cyclohexanes containing sulfur atom at the β-position of reaction center was investigated. Neighboring sulfur participation in stabilization of the carbanion was suggested in the case of ethyl *trans*-2-(phenylthio)cyclopropanecarboxylate.

Participation of neighboring sulfur, and sulfur located at a remote site has widely been known in reactions where carbenium ion takes part as an intermediate.1) However, no similar participation has been reported for carbanions having sulfur-containing substituents at the β or more remote positions.2) This is quite a contrast with the fact that the considerable experimental evidence has accumulated which indicates that carbanions are stabilized by the adjacent sulfur atom.3)

We tried to reveal the effect of the participation of sulfur atom located at the β-position to carbanion. The reactions studied were base-catalyzed hydrogen-deuterium exchange of alicyclic compounds.



[A] [B]

Fig. 1. [A] Both of the sulfur atoms can participate in the carbanion lobe. [B] One of the sulfur atoms can participate in the carbanion lobe.

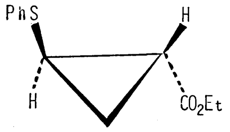
Table 1. Second-order rate constants and parameters of activation for the H-D exchange reaction of cyclohexane carbonitriles

Substrate	$10^6 k^{a),b)}$ (M^{-1} s^{-1})	Rel. *k*	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ a) (e.u.)
1	5.35	1.97	19.3±0.5	−27.0±2
2	2.72	1	21.9±0.5	−24.0±2

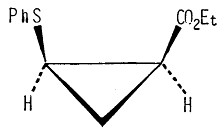
a) At 72 °C. b) [pyridine]=9.90×10^{-1} M.

The initial investigation was carried out with 1,1-ethylenedithio-2-cyanocyclohexane (**1**). In our study with cyclohexyl derivatives, though the ring inversion may be operative in **1**, at least one of the sulfur atoms should be able to interact with the carbanion lobe (Fig. 1). In Table 1, second-order rate constants and parameters of activation on pyridine-catalyzed deuterium exchange reaction of **1** are shown with those of cyclohexanecarbonitrile (**2**). Thus, in ethanol-*d*, **1** underwent the H-D exchange reaction about twice as fast as **2**, and **1** showed smaller enthalpy of activation than that of **2**. But it is too imprudent to discuss the presence of neighboring sulfur participation, since the separation of the potential effect of participation and inductive effect, both played by dithiacyclopentyl group, cannot be performed with certainty.

In the next trial, to make a clear distinction between these two effects, stereoisomers of cyclopropyl compounds were selected for the model compounds. Compounds used were ethyl *trans*-2-(phenylthio)cyclopropanecarboxylate (*trans*-**3**) and ethyl *cis*-2-(phenylthio)cyclopropanecarboxylate (*cis*-**3**), with ethyl *trans*-2-phenylcyclopropanecarboxylate (**4**) as the reference compound.



(*trans*-**3**)



(*cis*-**3**)

Cyclopropyl derivatives should be suitable for our study, since they have acidic hydrogens, and in many cases the rate of the racemization of carbanion is much smaller than that of deuterium exchange owing to the strain of cyclopropane ring.4) In fact no isomerization between *trans*-**3** and *cis*-**3** was observed during the deuterium exchange in the present study. Second-order rate constants and relative rate ratios of these compounds are listed in Table 2. More pronounced electron-withdrawing ability of phenylthio group than that of phenyl group makes *trans*-**3** and *cis*-**3** more reactive than **4**.5) *Trans*-**3** exchanges faster than *cis*-**3**, thus in *trans*-ester the operation of neighboring sulfur participation may be suggested.

Table 2. Second-order rate constants for the H-D exchange reaction of cyclopropane carboxylate esters

Substrate	$10^6 k^{a),b)}$ (M^{-1} s^{-1})	Rel. *k*
trans-**3**	45.7	18.4
cis-**3**	20.0	8.0
4	2.49	1.0

a) At 70 °C. b) [pyridine]=2.48×10^{-1} M.

Table 3. Parameters of activation for the H-D exchange of *trans*-**3** and *cis*-**3**

Substrate	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ a) (e.u.)
trans-**3**	16.0±0.5	−34.0±2
cis-**3**	19.7±0.5	−27.7±2

a) At 70 °C.

Parameters of activation were evaluated for *trans*-**3** and *cis*-**3**, and are shown in Table 3. Large negative values of entropy of activation ($\Delta S^{\ddagger}$) indicate that the rate-determining step of this reaction is the removal of the acidic proton by the base (pyridine) to form a hydrogen-bonded carbanion.[4] In *trans*-**3** the attack of pyridine is sterically more hindered than in *cis*-**3**, since both the phenylthio group and the hydrogen being attacked reside on the same side of the cyclopropane ring. Although the contribution of this steric hindrance can hardly be evaluated, such a hindrance can cause an increase in enthalpy of activation ($\Delta H^{\ddagger}$) for *trans*-**3**, partly compensating a decrease in $\Delta H^{\ddagger}$ that results from the presence of the sulfur participation.

Thus the difference in $\Delta H^{\ddagger}$ between *trans*-**3** and *cis*-**3** should be appreciated to show apparently the neighboring sulfur participation for the former compound in stabilizing the transition state and the resulting carbanion.

TABLE 4. IR AND UV ABSORPTIONS OF *trans*-**3** AND *cis*-**3**

Substrate	cm^{-1} a)	$\lambda_{\max}$ b) (MeOH) (log ε)
trans-**3**	1040	250.0 (4.1)
cis-**3**	1028	252.5 (4.1)

a) Skeletal vibration of cyclopropane ring in IR spectrum.
b) N→V transition of the three-membered ring.

Furthermore, IR and UV spectroscopic data, summarized in Table 4, suggest that *cis*-**3** is less stable than *trans*-**3** at the ground state due to the steric strain. In IR spectrum, frequencies of skeletal vibration for cyclopropane ring is lower in *cis*-**3**, which indicates the increase of molecular strain in *cis*-**3**.[6] In UV spectrum, the absorption maximum of *cis*-**3** appears at 252.5 nm (N→V transition of the three-membered ring), 2.5 nm longer than that of *trans*-**3**, reflecting the difference in the ground state strain perturbation.[7] Thus one can estimate that *cis*-**3** exists at about 1 kcal/mol higher in energy than *trans*-**3** does at the ground state.[8]

Therefore, taking into account the increase of $\Delta H^{\ddagger}$ by steric hindrance for the approach of base, and the difference in ground state energy, the stabilization should be more pronounced for *trans*-**3** than that inferred from the difference in observed $\Delta H^{\ddagger}$.[8] Consequently it is quite probable that a neighboring sulfur atom participates in stabilizing the carbanion of *trans*-**3**.

Experimental

The IR spectra were obtained using a Perkin-Elmer 521 spectrophotometer. The NMR spectra were recorded on a JEOL PS-100 spectrometer. The UV spectra were measured with a Hitachi 200-10 spectrophotometer. All compounds gave satisfactory results on spectroscopic analysis (IR, NMR), and on elemental analysis.

Materials. *1,1-Ethylenedithio-2-cyanocyclohexane (1)*: Dry HCl gas was bubbled into a benzene solution (30 ml) of 2-cyanocyclohexanone[9] (7.5 g) and 1,2-ethanedithiol (15 g) for 1 h at room temperature. After usual work-up and recrystallization from benzene, 2.0 g (13 %) of **1** was obtained; white needles, mp 61 °C.

Cyclohexanecarbonitrile (2): A benzene solution (10 ml) of cyclohexanecarboxamide (8.7 g) and thionyl chloride (17.8 g) was heated under reflux for 6 h. After cooling, the solution was poured in ice–water, and the organic layer was extracted with ether. After usual work-up, distillation of the residual oil gave 5.8 g (78 %) of **2**; bp 75 °C/18 mmHg.

Ethyl trans- *and* cis-*2-(Phenylthio)cyclopropanecarboxylate* (trans-*3*), (cis-*3*): Ethyl diazoacetate (12 g) was added dropwise to the refluxing xylene solution (50 ml) of phenyl vinyl sulfide (10 g) in 1 h. The solution was heated under reflux for additional 1 h, and then xylene was distilled off, leaving brown residual oil (18 g), which was fractionated by preparative GLC (Shimadzu GC-5A) to give *trans*-**3** and *cis*-**3**.

Ethyl trans-*2-phenylcyclopropanecarboxylate (4)*: Ethyl diazoacetate (12 g) was added dropwise to refluxing xylene solution (30 ml) of styrene (20 g) and hydroquinone (0.5 g) in 1 h. After the same procedure for *trans*-**3** and *cis*-**3**, **4** was obtained.

Kinetics. The stock solutions were prepared in volumetric flask by adding the stock base solutions (pyridine in ethanol-*d*) to a weighed amount of the substrate. With a syringe each 0.5 ml portion was transferred to glass ampoules, which were then flame sealed. The tubes were placed in a thermostat at an appropriate temperature. After predetermined time, tubes were withdrawn and were quenched in a Dry Ice–acetone bath. After removing ethanol and pyridine *in vacuo*, the remaining substrate was transferred with CCl_4 to an NMR tube. Rate constants were evaluated by comparing the intensity of the specified peak with that of standard one in their NMR spectra.

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