Acid-Catalyzed Isomerization of 1-Acyl- and 1-Thioacylaziridines. I. The Mechanism of Nucleophilic Substitution

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Abstract: *cis*-1-(N-Phenylcarbamyl)- (Ia) and *cis*-1-(N-phenylthiocarbamyl)-2,3-dimethylaziridine (Ib) were isomerized to oxazoline and thiazoline derivatives with acids in several solvents, and the mechanism of the ring opening of the aziridine rings was investigated stereochemically. The isomerization of Ia with boron trifluoride etherate proceeded with complete retention of configuration in all the solvents tried. This retention of configuration was explained by front-side attack of the carbonyl oxygen on the ring carbon (SNi mechanism). With protonic acids, ring opening of Ia proceeded by an SN2 mechanism. In the isomerization of Ib, ring opening occurred by an SN1 or an SN2 mechanism, depending upon acid and solvent used.

Many examples of the acid-catalyzed isomerization of 1-acyl- or 1-thioacylaziridines to 2-substituted oxazolines[2] or thiazolines[2a,e,3] have been reported. These isomerizations are considered to be nucleophilic substitution reactions on the saturated carbon atom. Three types of mechanism have been proposed according to the structure of the aziridine derivatives and the nature of the acid, though no stereochemical or kinetic study has been done: (1) an addition–elimination mechanism initiated by the addition of acid to the three-membered ring and terminated by the substitution of the attached residue by the carbonyl oxygen or the thiocarbonyl sulfur, (2) a carbonium ion mechanism, and (3) a direct attack mechanism which postulates a direct intramolecular attack of the carbonyl oxygen or the thiocarbonyl sulfur on the ring carbon. Heine and his coworkers have stated that the isomerization of 1-*p*-ethoxybenzoylaziridine to 2-*p*-ethoxyphenyl-2-oxazoline by the action of aluminum chloride in *n*-heptane may proceed either by a carbonium ion or by a direct attack mechanism.[2b]

We have investigated the acid-catalyzed isomerization of 1-acyl- and 1-thioacylaziridines stereochemically. Attention was focused upon the possibility that intramolecular direct attack of the carbonyl oxygen or the thiocarbonyl sulfur on the ring carbon might occur. If so, retention of the configuration on the attacked carbon should result, because in such a case, the oxygen or the sulfur should approach the ring carbon from the same side as the leaving group (nitrogen). Moreover, the four-membered cyclic transition state of such a reaction should resemble that of the SNi reaction advanced by Ingold, *et al.*[4] The existence of the SNi reaction in liquid phase is now strongly suspected. In connection with this, we interpret the various

phenomena on the assumption that the polar transition state of the SNi reaction is essentially the same as a tight ion pair.

Results

The isomerization reactions of *cis*-1-(N-phenylcarbamyl)- (Ia) and *cis*-1-(N-phenylthiocarbamyl)-2,3-dimethylaziridines (Ib) were carried out in several solvents. Ia should give *cis*- (*cis*-IIa) and/or *trans*-2-anilino-4,5-dimethyl-2-oxazoline (*trans*-IIa) and Ib, the corresponding sulfur derivative, *cis*-IIb and/or *trans*-IIb. Stereochemically, the isomerization of I to *cis*-II

cis-IIa, Y = O
cis-IIb, Y = S

Ia, Y = O
Ib, Y = S

trans-IIa, Y = O
trans-IIb, Y = S
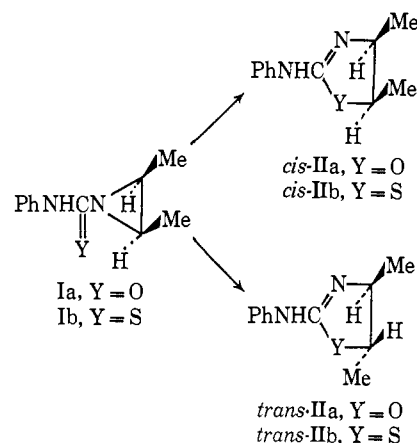
would indicate retention of configuration on the attacked carbon atom, and that of I to *trans*-II inversion of configuration. Ia or Ib was prepared by the reaction of phenyl isocyanate or phenyl isothiocyanate with *cis*-2,3-dimethylaziridine, respectively. Each authentic sample of *cis*-IIa or *cis*-IIb was obtained by heating Ia or Ib in refluxing ethyl methyl ketone or acetone in presence of sodium iodide[5] and also by heating *threo*-1-(1′-methyl-2′-hydroxypropyl)-3-phenylurea or the corresponding sulfur analog (III) in polyphosphoric acid, respectively. An authentic sample of *trans*-IIa was prepared by the method recently developed in our laboratory:[6] treatment of III with *p*-toluenesulfonyl chloride in pyridine gave pure *trans*-IIa. In each case, *cis*- and *trans*-II had very sharp and well-defined methyl

(1) Nippon Rayon Co., Ltd., Ohyodo-ku, Ohsaka, Japan.
(2) (a) S. Gabriel and R. Stelzner, *Ber.*, **28**, 2829 (1895); (b) H. W. Heine and Z. Proctor, *J. Org. Chem.*, **23**, 1554 (1958); (c) H. W. Heine, M. E. Fetter, and E. M. Nicholson, *J. Am. Chem. Soc.*, **81**, 2202 (1959); (d) S. S. Skorokhodov, S. G. Ershova, N. V. Mikhailova, and A. A. Vansheidt, *Zh. Obshch. Khim.*, **31**, 3626 (1961); (e) H. W. Heine, *Angew. Chem.*, **74**, 772 (1962); *Angew. Chem. Intern. Ed. Engl.*, **1**, 528 (1962).
(3) (a) A. S. Deutsh and P. E. Fanta, *J. Org. Chem.*, **21**, 892 (1956); (b) M. Tisler, *Arch. Pharmaz. Ber. Dtsch. Pharmaz. Ges.*, **291**, 457 (1958); (c) Y. Iwakura and A. Nabeya, *J. Chem. Soc., Japan, Pure Chem. Sect.*, **77**, 773 (1956); (d) Y. Iwakura and A. Nabeya, *Bull. Tokyo Inst. Technol.*, **42**, 69 (1961); (e) Y. Iwakura, A. Nabeya, and T. Nishiguchi, *J. Org. Chem.*, **32**, 2362 (1967).
(4) W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1252 (1937).

(5) H. W. Heine, D. C. King, and L. A. Portland, *J. Org. Chem.*, **31**, 2662 (1966).
(6) K. Kurita and Y. Iwakura, unpublished result. The authentic sample of *trans*-IIa was offered by Kurita.

Table I. Chemical Shifts and Coupling Constants of II[a]

Compd	Methyl hydrogens[b]		Methine hydrogens[c]		J[d]
cis-IIa	8.90	8.73	6.06	5.31	6.0
trans-IIa	8.76	8.61	6.43	5.83	6.0
cis-IIb	8.93	8.77	6.41	6.09	6.5
trans-IIb	8.87	8.70	6.72	6.52	6.0

[a] The nmr spectra were taken in chloroform solution with tetramethylsilane as the internal standard at 100 MHz. Resonance locations are given as τ values. [b] Two doublets. [c] Two quintets. [d] Coupling constants (cps) of methyl and methine hydrogens were equal.

trifluoroacetic acids, and 2,6- and 2,4-dinitrophenols gave ring-opened addition products. Each reaction product seemed to be composed of a single material as judged by its nmr spectrum. The product from Ia and p-nitrobenzoic acid was identical with the authentic sample obtained by the reaction of threo-1-(1'-methyl-2'-hydroxypropyl)-3-phenylurea with p-nitrobenzoyl chloride in melting point and nmr spectrum, and the mixture melting point was not dipressed. V gradually changed to cis-IIa on heating in benzene.

Table II. Acid-Catalyzed Isomerization of Ia

Acid	K_a of Acid	Solvent	Yield of IIa	Distribution of IIa, % cis-IIa	Distribution of IIa, % trans-IIa
p-Toluenesulfonic	0.10	Benzene	84	100	0
		THF	70	100	0
		DME	64	100	0
		DMF	52	100	0
		Nitromethane	76	100	0
2,4,6-Trinitrobenzenesulfonic		THF	50	100	0
Picric	0.42	Benzene	74	100	0
		THF	82	100	0
		DME	72	100	0
		DMF	58	100	0
		Nitromethane	64	100	0
Boron trifluoride etherate		Benzene	42	100	0
		THF	72	100	0
		DME	50	100	0
		DMF	67	100	0
		Nitromethane	78	100	0
		Liquid SO₂[a]	65	100	0
		Liquid SO₂[b]	50	100	0
Boron trifluoride		Benzene	40	100	0

[a] The solution of Ia was slowly added to that of boron trifluoride etherate at room temperature, and then the mixture was kept at 50°. [b] The ampoule containing Ia was broken in liquid SO₂ solution of boron trifluoride etherate kept at 50°.
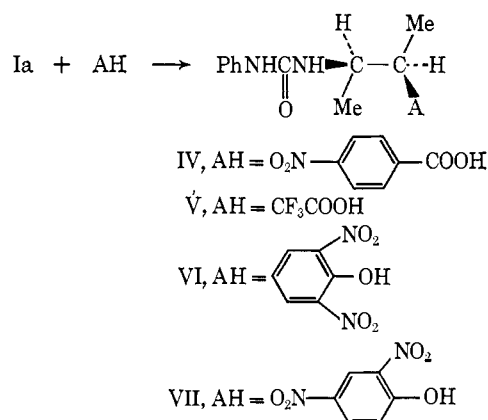
or methine peaks at different τ values in nmr spectra (100 MHz), which enabled the analysis of cis and trans mixture (see Table I).
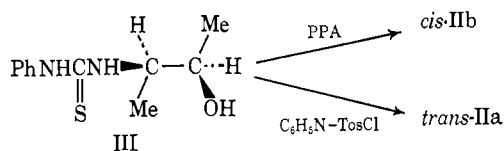
The isomerization reactions in benzene, tetrahydrofuran (THF), or 1,2-dimethoxyethane (DME) were performed by heating of Ia or Ib with excess acids in each solvent under reflux for 1 hr. When N,N-dimethylformamide (DMF) or nitromethane was used as the solvent, the reaction temperature was kept at 80°. The reaction in liquid sulfur dioxide was carried out at 50 and 25°. The reaction mixture was extracted with 2 N sulfuric acid, and the acidic solution was basified with sodium hydroxide solution to give II. Such a procedure yields almost pure II without loss of the isomer. Results obtained by the nmr analysis of the sample are summarized in Tables II and III. Some isomerization reactions were carried out several times, and the results were found to be reproducible.

The yields of IIa obtained by the reaction of Ia with p-toluenesulfonic acid in benzene after refluxing for 5 min, 30 min, 1 hr, and 5 hr were 64, 86, 88, and 93%, respectively. Reaction of Ia with p-nitrobenzoic and

Changes in the yields of cis- and trans-IIb by the reaction of Ib with trifluoroacetic acid in benzene vs. the reaction time are shown in Table IV. Ib gave only a polymer by the reaction with boron trifluoride etherate in benzene, even with high dilution techniques. In the isomerization of Ib, a polymeric substance was obtained in many cases, and generally the more polymer formed, the lower was the yield of IIb.

cis-IIa and cis-IIb were recovered quantitatively by refluxing with some protonic acids and boron trifluoride etherate in benzene for 1 hr.

Discussion

As mentioned in the introductory section, three types of mechanisms have been advanced for the iso-

Table III. Acid-Catalyzed Isomerization of Ib

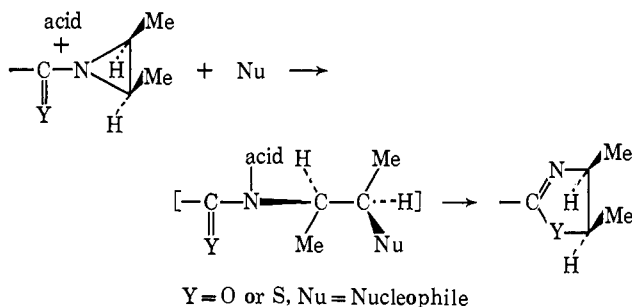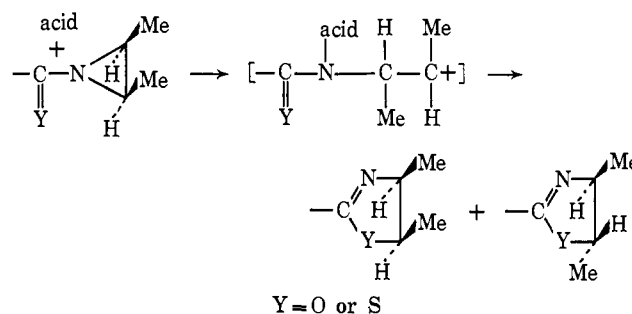| Acid	K_a of acid	Solvent	Yield of IIb	Distribution of IIb, % cis-IIb	trans-IIb
p-Toluenesulfonic		Benzene	80	100	0
		THF	68	100	0
		DME	75	100	0
		DMF	78	100	0
		Nitromethane	72	100	0
2,4,6-Trinitrobenzenesulfonic		THF	70	100	0
Picric		Benzene	75	50	50
		THF[a]	72	100	0
		DME	68	89	11
		DMF	83	100	0
		Nitromethane	52	50	50
2,6-Dinitrophenol	5.9×10^{-6}	Benzene	15	50	50
		THF	35	66	34
2,4-Dinitrophenol	9.8×10^{-5}	Benzene	20	74	26
		THF	16	61	39
		DME	19	75	25
		DMF	42	100	0
		Nitromethane	54	74	26
Trifluoroacetic	0.59	Benzene	32	82	18
		THF	32	81	19
		DME	65	83	17
		DMF	40	100	0
		Nitromethane	40	76	24
Trichloroacetic	0.23	Benzene	19	77	23

[a] The experiment was repeated.

Table IV. Isomerization of Ib Catalyzed with Trifluoroacetic Acid in Benzene

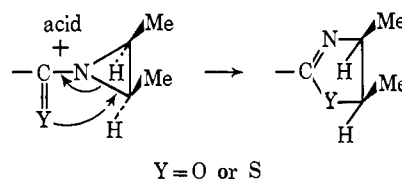| Reaction time, hr	Total yield of IIb, %	Distribution of IIb, % cis-IIb	trans-IIb	Yield of IIb, % cis-IIb	trans-IIb
0.5	22	75	25	17	5
1	32	82	18	26	6
5	38	88	12	33	5
10	40	90	10	36	4

merization of 1-acyl- or 1-thioacylaziridines. However, we prefer to classify the isomerization mechanisms into the following three from the viewpoint of the stereochemistry of the ring-opening reaction of the three-membered ring: (1) carbonium ion formation (SN1), (2) double inversion (SN2), and (3) front-side attack mechanism (SNi). In acid-catalyzed isomerization reactions, it would be reasonable to assume that complex formation between the acid and the aziridine compound will take place at the first stage.[7]

If a carbonium ion is formed by the ring-opening of the formed complex, complete racemization should result unless tight ion-pair formation or the participation of the solvent occurs. When the conjugate base of the acid or some other nucleophile, e.g., the nucleophilic solvent or another molecule of the aziridine compound as will be mentioned later, is added to the three-membered ring with complete inversion, complete retention of configuration is expected after the isomerization is completed (double inversion). If the carbonyl oxygen or the thiocarbonyl sulfur attacks the

Y = O or S

Y = O or S, Nu = Nucleophile

ring carbon directly, complete retention of configuration should result owing to the particular stereochemical circumstances of the three-membered ring (front-side attack).

Y = O or S

(7) A referee of this paper pointed out the possibility that the intermediate "ion" from Ib has enol form (thiol form), PhNHC(SH)=NCH-MeC+HMe, rather than keto form (thione form) and that in the enol form, the life of the ion is long enough to allow rotation and loss of specificity. S-Protonation seems to occur in Ib, while N-protonation in Ia. Though we concluded in the previous paper[8] that (thio) ureas have keto form, the intermediate from S-protonated Ib might have the enol form for awhile. The position of the acid in the complex will be discussed in detail in the next paper.

Before discussion of the results with Ib, it must first be mentioned that in the isomerization of Ib, polymerization occurs at the same time. It becomes significant when the acid is not very strong, that such a polymer from Ib can give rise to the thiazoline on
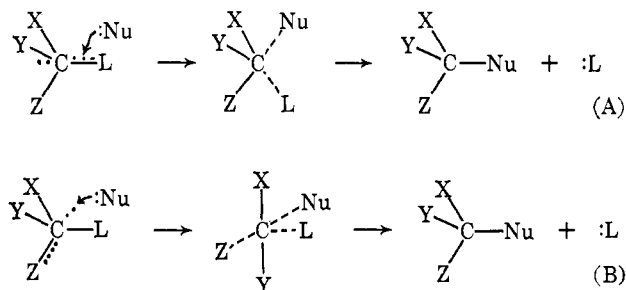
heating with acids. As reported in a previous paper,[8] polymers obtained by the base-catalyzed or thermal polymerization of 1-thioacylaziridines have imino thioether structures in the polymer chain. Some of such polymers give thiazolines on heating with acids,

$$X-\underset{\underset{S}{\|}}{C}-N{\triangleleft} \longrightarrow -(CH_2CH_2N=\underset{\underset{X}{|}}{C}-S)_n \xrightarrow{acid} X-C\overset{N}{\underset{S}{\diagdown}}$$

X = Ar, PhNH−

e.g., the polymer obtained from 1-(N-phenylthiocarbamyl)aziridine gave 2-anilino-2-thiazoline in 85% yield on heating with picric acid in refluxing THF for 3 hr. From its infrared spectrum, the polymer obtained in the isomerization of Ib is also considered to have an isothiourea linkage in addition to the thiourea structure. From Table IV it is seen that in the reaction of Ib with

trifluoroacetic acid, where an appreciable amount of polymer was obtained after 1 hr reaction, the yield of *cis*-IIb increased as the reaction time was extended, while that of the *trans* isomer remained unchanged. This would suggest that *cis*-IIb could also have been formed from Ib through the polymer.

It is seen from Table III that almost complete racemization on the attacked carbon atom took place in the isomerization of Ib with picric acid, in a weakly nucleophilic solvent such as benzene DME, or nitromethane.[7] The fact that racemization has taken place in the isomerization of Ib with picric acid precludes the possibility of front-side attack in the case of Ib with any other protonic acid of comparable acidity, because an SNi reaction, like an SN1, should be independent of the conjugate base of the acid, as long as the acid strength is not greatly changed.

In the isomerization of Ib with *p*-toluene- and 2,4,6-trinitrobenzenesulfonic acids, complete retention of configuration was observed. This is explicable by the double-inversion mechanism mentioned above. In these cases, polymer formation was not appreciable. When DMF was used as the solvent, the configuration was retained with all acids tried, presumably because DMF acted as a nucleophile. When THF was used, the isomerization of Ib was complicated.

The isomerization of Ia to IIa proceeded always with 100% retention of configuration. When protonic

(8) Y. Iwakura, A. Nabeya, and T. Nishiguchi, *J. Polymer Sci.*, *Part A-1*, 6, 2591 (1968).

acids were used, the isomerization must have proceeded by the double inversion mechanism. Ia gave the ring-opened addition products with *p*-nitrobenzoic and trifluoroacetic acids or 2,4- and 2,6-dinitrophenols. The products were all considered to have the *threo* configuration from the nmr spectra, and the addition product with trifluoroacetic acid (V) gave pure *cis*-IIa on heating in benzene for 10 hr.

Isomerization of Ia with boron trifluoride or boron trifluoride etherate attracts our attention, because, in spite of the absence or the very poor nucleophilicity of the conjugate base of these catalysts, the configuration was completely retained in all the solvents tried. If Ia itself could act as a nucleophile, there still exist the possibility that the isomerization might have proceeded by the double inversion mechanism.[9] However, this seems quite unlikely since Ia should be complexed with boron trifluoride completely so that the nucleophilicity of Ia would be much reduced, and even when the reaction was carried out under high dilution, 100% retention was observed.

Two possible mechanisms must be considered for the retention of configuration in the isomerization of Ia with boron trifluoride or boron trifluoride etherate: front-side attack mechanism and solvent-separated ion-pair formation. The latter should be influenced by the nature of the solvent. In the reaction of Ia with boron trifluoride etherate, the change in the solvent nature had no influence upon the stereochemical feature of the isomerization: benzene which has little solvating power either for a cation or to an anion, DME, THF, and DMF which are apt to solvate cations, and nitromethane and liquid sulfur dioxide which are anion solvating solvents all gave 100% retention of configuration. Therefore, the reaction of Ia with boron trifluoride etherate is not considered to have proceeded by a solvent-separated ion-pair mechanism.[10]

Several reactions have been reported which were considered to occur through nucleophilic substitution *via* front-side attack on a saturated carbon resulting in retention of configuration.[4,12] However, most of them were later proved to proceed *via* an ion-pair or a radical pair rather than by a one-step SNi mechanism; kinetic studies for thermal decomposition of chlorosulfites[12] and chloroformates[13] in liquid phase have shown that the reactions are better interpreted by a

(9) *threo*-1-(1'-Methyl-2'-chloropropyl)-3-phenylurea or *threo*-1-(1'-methyl-2'-hydroxypropyl)-3-phenylurea was quantitatively recovered unchanged by heating with excess boron trifluoride etherate in benzene. The former experiment precludes the possibility that fluoride ion is formed from boron trifluoride etherate and catalyzes the isomerization of Ia as a nucleophile to give *cis*-IIa by a double-inversion mechanism, because fluoride ion is a poorer leaving group than chloride ion. The latter experiment also would preclude the existence of the double-inversion mechanism in the isomerization of Ia with boron trifluoride etherate which was contaminated with moisture.

(10) Moreover, considering the isomerization of Ib where almost complete racemization took place in some cases, we prefer to presume that, if carbonium ion is really formed, racemization must occur in the case of Ia, too. The isomerization *via* proton abstraction is also not conceivable. If the carbonyl oxygen abstracts the ring or the methyl hydrogen, an unsaturated urea should be formed[11] and cyclization of the unsaturated urea in acids should cause racemization to give a mixture of *cis*- and *trans*-IIa. See (a) P. E. Fanta and E. N. Walsh, *J. Org. Chem.*, 31, 59 (1966); (b) P. E. Fanta and A. S. Deutsh, *ibid.*, 23, 72 (1958).

(11) H. W. Heine and M. S. Kaplan, *ibid.*, 32, 3069 (1967).

(12) E. L. Eliel, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, pp 79–83 and 479.

(13) K. B. Wiberger and T. M. Shryne, *J. Am. Chem. Soc.*, 77, 2774 (1955).

Figure. 1. A sketch of front-side attack mechanism: dotted lines show antibonding orbitals and broken lines do half-bonds.
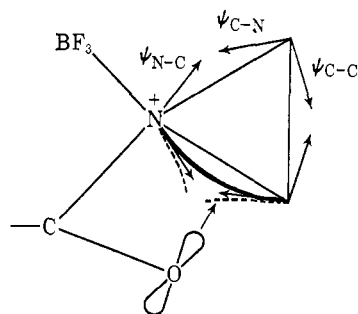

Figure 2. The sketch of the front-side attack in the acid-catalyzed isomerization of an 1-acylaziridine. A bold line shows a bonding orbital and dotted lines antibonding orbitals.

solvent-participated ion-pair mechanism.[12] It was further demonstrated that the stereochemistry of the reactions was very much influenced by the solvent. Some 1,2 rearrangements such as the Stevens,[14] Wittig,[14] and Meisenheimer[15] are assumed to proceed through either ion[16] or radical pair.[17] The only example known to proceed purely by a front-side attack mechanism is the thermal decomposition of chloroformates to alkyl chlorides at *ca.* 250° in gas phase, where the configuration is completely retained, the activation entropy is small (*ca.* −20 eu), no rearranged product is detected, and no participation of solvent is considered.[18] All these data strongly suggest that the reaction might proceed by an SNi mechanism, and up to now, no disproof has been proposed. It is noteworthy that in this reaction the introduction of alkyl groups into α position accelerates the reaction rate, namely, the reaction has SN1 character rather than SN2 in the substituent effect.

Up to the present, it has not been possible to decide whether the isomerization of Ia with boron trifluoride etherate proceeds by a direct front-side attack mechanism or *via* a tight ion-pair formation. Although highly polar transition states and tight ion pairs are generally classified separately, they are almost indistinguishable in many cases. We believe that there is no clear-cut distinction between the front-side attack mechanism and the tight ion-pair mechanism: the polar transition state of a front-side attack is essentially of the same nature as a tight ion pair. Such an idea may be supported by Jaffé and Doak's calculation that even the carbon–potassium bond which is considered to be highly ionic has a significant amount of covalent bond character.[19] The fact that the isomerization reaction of 1-acylaziridines catalyzed with boron trifluoride etherate has a highly polar transition state will be shown in our next paper. The SN1-like nature of the thermal decomposition of chloroformates in the gas phase has also suggested a highly polar nature for the transition state. Closely related to our result is the

thermal isomerization of *cis*-1-*p*-nitrobenzoyl-2,3-diphenylaziridine to the *cis*-oxazoline derivative recently reported by Heine and Kaplan.[11]

On the localized molecular orbital theory, two processes are assumable for the front-side attack mentioned above: the lone-pair electrons of a nucleophile (the carbonyl oxygen) enter into (A) the antibonding orbital of the C–L bond from the same side of the leaving group (L) or into (B) the antibonding orbital of a bond other than the C–L (*e.g.*, C–Z) from the back side of L as shown in Figure 1. Three-membered ring compounds often show particular physical[12,20] and chemical[21] behaviors which are not observed in other strain-free cyclic compounds, and the fact is attributed to the unique electronic structure of these compounds.[22] By applying the maximum overlap method, Certain, *et al.*,[23] have shown that the energy of an aziridine ring becomes minimum when the wave functions ψ_{C-N}, ψ_{N-C}, and ψ_{C-C} are bent 19° 33′, 24° 4′, and 21° 55′ from the C–N, N–C, and C–C bonds, respectively. In such bent bonds, bonding and antibonding orbitals may be bent to a little different direction from each other. Therefore, if the reaction takes place by process A, the electrostatic repulsion between the bonding electrons of the C–N bond and the lone-pair electrons of the oxygen is considered to be less compared with the case where such a strain does not exist. Such a consideration leads us to conclude that the front-side attack is not unlikely in an aziridine derivative because of the unique electronic structure (Figure 2).

Experimental Section[24]

cis-1-(N-Phenylcarbamyl)-2,3-dimethylaziridine (Ia). *cis*-2,3-Dimethylaziridine was synthesized from *threo*-3-amino-2-butanol according to the direction of Lucas, *et al.*,[25] bp 82–83° (lit.[25] bp 82.5–82.9°).

Ia was prepared from equimolar *cis*-2,3-dimethylaziridine and phenyl isocyanate in ether and recrystallized from benzene and *n*-hexane, mp 100–101°; ir (Nujol mull) 3380 (NH) and 1657 cm^{-1} (C=O); nmr (CHCl$_3$) τ 8.84 (doublet, CH$_3$, J = 6.0 cps) and 7.43 (multiplet, CH).

(14) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., Inc., New York, N. Y., 1959, pp 640–641.

(15) A. C. Cope and P. H. Towle, *J. Am. Chem. Soc.*, 71, 3423 (1949).

(16) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, pp 223–233.

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(18) (a) A. R. Choppin, H. A. Frediani, and G. F. Kirby, Jr., *J. Am. Chem. Soc.*, 61, 3176 (1939); (b) A. R. Choppin and G. F. Kirby, Jr., *ibid.*, 62, 1952 (1940); (c) A. R. Choppin and E. L. Compere, *ibid.*, 70, 3797 (1948); (d) E. S. Lewis and W. C. Herndon, *ibid.*, 83, 1955 (1961); (e) E. S. Lewis, W. C.Herndon, and D. C. Duffey, *ibid.*, 83, 1959 (1961); (f) E. S. Lewis and W. C. Herndon, *ibid.*, 83, 1961 (1961).

(19) H. H. Jaffé and G. O. Doak, *J. Chem. Phys.*, 21, 196 (1953).

(20) C. A. Coulson and T. H. Goodwin, *J. Chem. Soc.*, 2851 (1962).

(21) T. Yonezawa, K. Shimizu, and H. Kato, *Bull. Chem. Soc. Japan*, 40, 456 (1967).

(22) (a) W. A. Bernett, *J. Chem. Educ.*, 44, 17 (1967); (b) A. D. Walsh, *Trans. Faraday Soc.*, 45, 179 (1949).

(23) P. R. Certain, V. S. Watts, and J. H. Goldstein, *Theoret. Chim. Acta*, 2, 324 (1964).

(24) Melting points and boiling points are uncorrected. Nmr spectra were measured in specified solvents with tetramethylsilane as the internal standard at 100 MHz.

(25) F. H. Dickey, W. Fickett, and H. J. Lucas, *J. Am. Chem. Soc.*, 74, 944 (1952).

Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.51; H, 7.20; N, 14.53.

cis-1-(N-Phenylthiocarbamyl)-2,3-dimethylaziridine (Ib) was prepared from equimolar *cis*-2,3-dimethylaziridine and phenyl isothiocyanate in ether and recrystallized from ether, mp 96–97°; ir (Nujol mull) 3180 cm⁻¹ (NH).

Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58. Found: C, 64.06; H, 6.74; N, 13.48.

cis-2-Anilino-4,5-dimethyl-2-oxazoline (*cis*-IIa). Method A. Compound Ia was refluxed with sodium iodide[26] in ethyl methyl ketone for 5 hr. The solvent was evaporated and the residue was dissolved in benzene. The organic layer was extracted with 2 N sulfuric acid. The aqueous solution was made alkaline with sodium hydroxide, and extracted with benzene. Evaporation of benzene gave *cis*-IIa. It was recrystallized from benzene and *n*-hexane and melted at 118–119°; ir (KBr pellet) 3070 (NH, broad and weak) and 1689 cm⁻¹ (C=N).

Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.58; H, 7.30; N, 14.78.

Method B. *threo*-1-(1'-Methyl-2'-hydroxypropyl)-3-phenylurea was heated in polyphosphoric acid at 120° for 3 hr. The reaction mixture was poured into water. The aqueous solution was made alkaline with sodium hydroxide and extracted with benzene. From the benzene solution almost pure *cis*-IIa was obtained.

trans-2-Anilino-4,5-dimethyl-2-oxazoline (*trans*-IIa) was offered by Kurita.[6] It melted at 115–116°; ir (KBr pellet) 3060 (NH, broad and weak) and 1690 cm⁻¹ (C=N).

Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.73; H, 7.33; N, 14.70.

cis-2-Anilino-4,5-dimethyl-2-thiazoline (*cis*-IIb) was obtained by refluxing Ib with sodium iodide in acetone[26] for 8 hr and also by the cyclization of III in polyphosphoric acid.[6] The procedure was mentioned in the preparation of *cis*-IIa, mp 116–118°; ir (KBr pellet) 3090 (NH, broad and weak) and 1636 cm⁻¹ (C=N).

Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.86; N, 13.58. Found: C, 64.20; H, 6.76; N, 13.43.

Isomerization of Ia and Ib with *p*-Toluenesulfonic Acid and Some Other Acids. a. Into a solution of 1.9 g (0.011 mol) of *p*-toluenesulfonic acid in 20 ml of benzene, a solution of 1.9 g (0.01 mol) of Ia in 20 ml of benzene was added dropwise over a period of 5 min with refluxing and stirring, and refluxing was continued for 1 hr. The reaction mixture was extracted with 2 N sulfuric acid several times. The aqueous solution was made alkaline with sodium hydroxide and extracted with benzene. Evaporation of benzene gave 1.6 g (84%) of *cis*-IIa. *cis*-IIa was dissolved in chloroform (in 10% concentration) and submitted to the nmr analysis.

Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.67; H, 7.54; N, 14.69.

b. The isomerization of Ia with boron trifluoride etherate and that of Ib with *p*-toluenesulfonic, trifluoroacetic, or trichloroacetic acid in benzene were carried out in a similar manner as described above.

c. When THF or DME was used as a solvent, the isomerization reactions of Ia and Ib were carried out under reflux for 1 hr. The reactions in DMF or nitromethane were done at 80° for 1 hr. When THF, DME, DMF, and nitromethane were used as solvents in the isomerization reactions of Ia with *p*-toluenesulfonic acid or boron trifluoride etherate and those of Ib with *p*-toluenesulfonic or trifluoroacetic acid, the solvent was evaporated under reduced pressure from the reaction mixture, and then the residue was dissolved in benzene. The organic solution was treated in the same manner as described in a.

d. When high dilution techniques were adopted in the reactions of Ia and Ib with boron trifluoride etherate, 500 ml of benzene was used. After the reactions were over, the solvent was reduced to 50 ml by evaporation.

Isomerization of Ia and Ib with Picric Acid and Some Other Acids. a. Into a solution of 2.5 g (0.011 mol) of picric acid in 20 ml of benzene, a solution of 1.9 g (0.01 mol) of Ia in 20 ml of benzene was added dropwise over a period of 5 min with refluxing and stirring, and the reaction mixture was refluxed for 1 hr. After evaporating benzene, the residue was dissolved in a small quantity of acetone. The acetone solution was poured into sodium hydroxide aqueous solution with stirring and the alkaline solution was extracted with benzene. After the benzene solution was treated in the same way as the reaction of Ia with *p*-toluenesulfonic acid in benzene, 1.4 g (74%) of *cis*-IIa was obtained.

b. The isomerization reactions of Ib with picric acid, 2,4- and 2,6-dinitrophenol and those of Ia and Ib with 2,4,6-trinitrobenzenesulfonic acid in benzene were carried out in a similar way as mentioned above. In the cases where solvents except for benzene were used, the solvents were evaporated from the reaction mixture. The residue was dissolved in benzene and treated in the same manner as in the case in which benzene was used as the solvent.

Isomerization of Ia with Boron Trifluoride. From a bomb, boron trifluoride was bubbled into refluxing benzene (250 ml) and then 1.0 g of Ia in 100 ml of benzene was added dropwise over a period of *ca.* 30 min with bubbling and stirring. The benzene solution was refluxed for 40 min longer and 300 ml of the solvent was evaporated. The benzene solution was treated in the same manner as described above.

Isomerization of Ia with Boron Trifluoride Etherate in Liquid Sulfur Dioxide. Liquid sulfur dioxide was dehydrated with phosphorus pentoxide and handled with an apparatus contrived by Matsuda, *et al.*[27]

a. Liquid sulfur dioxide (10 ml) was collected by distillation into a pressure-resistant glass vessel containing 1.0 g (0.005 mol) of boron trifluoride etherate. In the same way, 1.0 g (0.005 mol) of Ia was dissolved in 40 ml of the solvent. The solution of Ia was added into that of boron trifluoride etherate through stainless steel joints over a period of 1 hr at room temperature. The mixture was kept at 50° for 2 hr, and the sulfur dioxide was evaporated. The residue was dissolved in benzene and treated in the same way as described above.

b. In a pressure-resistant glass vessel, 1.4 g (0.01 mol) of boron trifluoride etherate, 85 ml of purified liquid sulfur dioxide, and a glass ampoule containing 1.0 g (0.0005 mol) of Ia were placed and kept at 50°. Then, the ampoule was broken by shaking the vessel and the mixture was kept at 50° for 3 hr.

Yield of IIa or IIb *vs.* Reaction Time. a. To a solution of *p*-toluenesulfonic acid in benzene (20 ml), a solution of Ia (2.30 g) in 25 ml of benzene was added over a period of 5 min with refluxing and stirring. Each sample (10 ml) was pipetted out from the refluxing reaction mixture at the time of 5 min, 30 min, 1 hr, and 5 hr after the addition. The samples were treated in the same way as described above.

b. A solution of Ib (5.0 g) in 25 ml of benzene was added into a solution of trifluoroacetic acid (3.0 g) in 25 ml of benzene over a period of 5 min with refluxing and stirring. Each sample was pipetted out from the refluxing reaction mixture 30 min, 1 hr, 5 hr, and 10 hr after the addition. The samples were treated in the manner similar to the isomerization of Ia with *p*-toluenesulfonic acid.

Reaction of Ia with Trifluoroacetic Acid. Into a solution of trifluoroacetic acid (0.6 g, 0.005 mol) in 10 ml of benzene, a solution of Ia (1.0 g, 0.005 mol) in 10 ml of benzene was added dropwise with refluxing and the reaction was carried out for 1 hr. The reaction mixture was left standing overnight at room temperature. The crystalline precipitate was separated by filtration, washed with 2 N sulfuric acid several times to remove oxazolines, and dried to give 1.0 g (63%) of *threo*-1-(1'-methyl-2'-trifluoroacetyloxypropyl)-3-phenylurea (V), mp 136–138°; ir (Nujol mull) 3200 (NH), 1790 (C=O), and 1638 cm⁻¹ (C=O); nmr (CHCl₃) τ 8.89 (doublet, CH₃, J = 6.0 cps), 8.70 (doublet, CH₃, J = 6.0 cps), 5.90 (complex multiplet, CH), and 4.96 (complex multiplet, CH).

Anal. Calcd for $C_{13}H_{15}N_2O_3F_3$: C, 51.32; H, 4.97; N, 9.21. Found: C, 51.25; H, 4.54; N, 9.13.

Reaction of Ia with *p*-nitrobenzoic acid was carried out in the same manner as the reaction of Ia with trifluoroacetic acid. The yield of *threo*-1-(1'-methyl-2'-*p*-nitrobenzoyloxypropyl)-3-phenylurea (IV) was 63%, mp 180–182°; ir (Nujol mull) 3340 (NH), 1730 (C=O), and 1640 cm⁻¹ (C=O); nmr (CF₃COOH) τ 8.60 (doublet, CH₃, J = 6.0 cps), 8.45 (doublet, CH₃, J = 6 cps), 5.65 (quintet, CH, J = 6 cps), 4.67 (quintet, CH, J = 6 cps), 2.65 (complex multiplet, aromatic protons) and 1.66 (complex multiplet, aromatic protons).

Anal. Calcd for $C_{18}H_{19}N_3O_5$: C, 60.50; H, 5.36; N, 11.76. Found: C, 60.68; H, 5.48; N, 11.64.

An authentic sample of IV was prepared from *threo*-1-(1'-methyl-2'-hydroxypropyl)-3-phenylurea and *p*-nitrobenzoyl chloride in THF with triethylamine. It was recrystallized from THF, mp 181–182°.

Anal. Found: C, 60.20; H, 5.15; N, 11.91.

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Admixture of the IV obtained in the reaction of Ia with *p*-nitrobenzoic acid and of the authentic sample showed no melting point depression. The nmr and the infrared spectra were also identical.

Reaction of Ia with 2,6- or 2,4-dinitrophenol was accomplished in the same way as the reaction of Ia with trifluoroacetic acid. The yield of *threo*-1-(1'-methyl-2'-*o*,*o*'-dinitrophenoxypropyl)-3-phenylurea (VI) was 65%, mp 166–168°, after recrystallization from chloroform and *n*-hexane; ir (Nujol mull) 3320 (NH) and 1650 cm⁻¹ (C=O); nmr (CF₃COOH) τ 8.55 (doublet, CH₃, J = 6.0 cps), 8.74 (doublet, CH₃, J = 6.0 cps), 5.80 (complex multiplet, CH), 5.53 (complex multiplet, CH), 2.53 (multiplet, aromatic protons) and 1.90 (doublet, aromatic protons, J = 8.0 cps).

Anal. Calcd for C₁₇H₁₈N₄O₆: C, 54.54; H, 4.85; N, 14.97. Found: C, 54.87; H, 5.01; N, 14.79.

threo-1-(1'-Methyl-2'-*o*,*p*-dinitrophenoxypropyl)-3-phenylurea (VII) was obtained in 58% yield, mp 185–187°, after recrystallization from chloroform and *n*-hexane; ir (Nujol mull) 3370 (NH) and 1690 cm⁻¹ (C=O); nmr (CF₃COOH) τ 8.60 (doublet, CH₃, J = 6.0 cps), 8.49 (doublet, CH₃, J = 6.0 cps), 5.68 (complex multiplet, CH), and 5.18 (complex multiplet, CH).

Anal. Calcd for C₁₇H₁₈N₄O₆: C, 54.54; H, 4.85; N, 14.97. Found: C, 54.80; H, 5.05; N, 14.77.

Acid-Catalyzed Isomerization of 1-Acyl- and 1-Thioacylaziridines. II.[1] The Orientation of Ring Opening

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Abstract: The isomerization of 1-(N-phenylcarbamyl)- (IIIa) and 1-(N-phenylthiocarbamyl)-2-methylaziridines (IIIb) with acids was investigated. In the isomerization of IIIa, 2-anilino-5-methyl-2-oxazoline (IVa) was obtained as the major product along with the isomeric 2-anilino-4-methyl-2-oxazoline (Va). IIIb gave a mixture of almost equal amounts of 2-anilino-5-methyl-2-thiazoline (IVb) and 2-anilino-4-methyl-2-thiazoline (Vb). The orientation of the ring opening of IIIa or IIIb seems to be nearly independent of acids and solvents. Investigation using optically active IIIa and IIIb suggests that IVa is formed by an SN2 mechanism with protonic acids and by a frontside attack mechanism when boron trifluoride etherate is used, and IVb would either be an SN2 or SN1 mechanism depending upon the acid and solvent used. These results clearly indicate that the mechanism of ring opening is not determined by the orientation. Such an SN2 mechanism is considered to be a "modified" SN2 in which substituents exhibit an SN1-like effect. An interpretation in which the difference in the orientation of the ring opening between IIIa and IIIb on the assumption that the site of the protonation would be different from IIIa to IIIb was also considered.

I n the ring opening of unsymmetrically substituted three-membered heterocyclic compounds, cleavage between the heteroatom and the less substituted carbon atom has often been termed "normal" cleavage and that between the heteroatom and the more substituted carbon atom termed "abnormal" cleavage. There are some discussions[3] concerning the relationship between orientation and the mechanism of ring opening of unsymmetrically substituted aziridines with acids, but no stereochemical study has been done on the relationship. As for kinetic studies, Clapp and coworkers[4] investigated the ring-opening reaction of 2-ethyl- and 2,2-dimethylaziridine with several acids and concluded from the kinetic parameters and the structure of the reaction products obtained that the "abnormal" cleavages proceed by an SN1 mechanism and the "normal" cleavages by an SN2 mechanism. The mechanism of the acid-catalyzed isomerization of 1-acyl- or 1-thioacylaziridines to oxazolines or thiazolines,

respectively, has also been considered relative to the orientation of the ring opening. Heine, *et al.*,[5] found that 1-aroyl-2,2-dimethyl- or 1-aroyl-2-phenylaziridine was isomerized in cold sulfuric acid to give 2-aryl-5,5-dimethyl- or 2-aryl-5-phenyl-2-oxazoline, respectively. Deutsch and Fanta[6] reported that the isomerization of 1-(N-phenylthiocarbamyl)-2,2-dimethylaziridine with hot dilute hydrochloric acid gave 2-anilino-5,5-dimethyl-2-thiazoline. These isomerization reactions were considered to proceed *via* carbonium ion formation from the orientation of the ring cleavage, *i.e.*, "abnormal" cleavage.
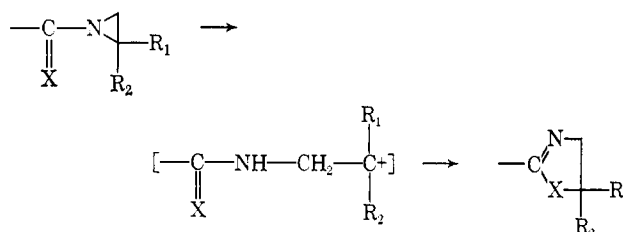
X = O: R₁ = Me; R₂ = Me or R₁ = H; R₂ = Ph
X = S: R₁ = Me; R₂ = Me

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