Conformational Equilibrium of *trans*-1,2-Dimethyl-3-isopropylaziridine[1a-c]

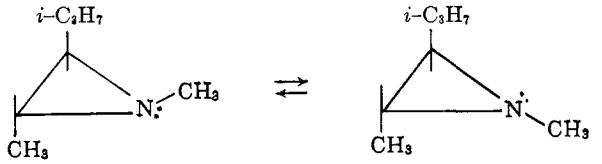
Albert T. Bottini, Robert Lee VanEtten,[1d] and Alan J. Davidson

Contribution from the Chemistry Department, University of California, Davis, California 95616. *Received October 8, 1964*

The equilibrium constant for the conformers (**1a** *and* **1b**) *of trans-1,2-dimethyl-3-isopropylaziridine has been determined at several temperatures by means of n.m.r. spectroscopy. For* **1a** → **1b** *in chloroform at 25°* ΔF *(by extrapolation)* $= -0.77$ *kcal.,* $\Delta H = -0.24 \pm 0.05$ *kcal., and* $\Delta S = +1.8 \pm 0.2$ *e.u.*

There is a relative paucity of data concerning conformational equilibria in systems other than those containing six-membered carbocyclic rings. We report here our study of the conformational equilibrium of *trans*-1,2-dimethyl-3-isopropylaziridine (**1**).

Because of the ability of trivalent nitrogen to undergo rapid inversion,[2] a *trans*-1,2,3-trisubstituted aziridine such as **1** exists as a rapidly interconverting mixture of conformers, *i.e.*, **1a** and **1b**. As previous work[3,4] has revealed that nitrogen inversion in N-substituted 2,2- and *trans*-2,3-dimethylaziridines occurs sufficiently slowly near room temperature to cause the appearance in the n.m.r. spectra of these compounds of two distinct bands due to the C-methyl hydrogens that are *cis* and *trans* to the nitrogen substituent, we considered it reasonable to expect that the conformational equilibrium of a *trans*-1,2,3-trisubstituted aziridine such as **1** would be amenable to study by means of n.m.r. spectroscopy. Consequently, we prepared **1** and examined its temperature-dependent n.m.r. spectrum.



1a **1b**

trans-4-Methyl-2-pentene (>99 mole %) with N-bromosuccinimide and water gave a mixture of bromohydrins that was converted with aqueous potassium hydroxide to *trans*-2-methyl-3-isopropyloxirane. The oxirane and aqueous methylamine gave an amino alcohol, which was converted to its sulfonate ester with sulfuric acid, and the sulfonate ester with aqueous sodium hydroxide was converted to **1**. Not unexpectedly,[5] the reactions involving formation of new bonds at carbon were highly stereospecific, and contamination of **1** by its *cis* isomer was less than 1%.

Shown in Figure 1 are n.m.r. spectra taken at −10, 44, and 80° of a 25% solution of **1** in chloroform-*d*. At and below 30°, there are two bands in the N-methyl region (*ca.* 2.4 p.p.m.) separated by 3.6 c.p.s. at 60 Mc. If one allows that ΔF and ΔH for the **1a**–**1b** interconversion have the same sign and that the steric requirements of an isopropyl group, a methyl group, and an unshared electron pair on nitrogen decrease in that order, conformer **1b** can be assumed to be more stable than **1a**. Therefore, the weaker (low-frequency) band is assigned to the N-methyl protons of the less stable conformer **1a**; the larger band is assigned to the N-methyl protons of the more stable conformer **1b**.[6] At and above 40° in chloroform, the average lifetime of each conformer is small relative to the reciprocal of the chemical shift, and the N-methyl bands coalesce at about 40° to a single, time-averaged band.

As the intensities of the N-methyl bands are proportional to the concentrations of the conformers, the equilibrium constant, **1b**/**1a**, is equal to the ratio of intensities of the N-methyl bands. The equilibrium constant was determined for **1** in chloroform at several temperatures from −55.5 to 9.0°, and this data is summarized in Table I.

Table I. Equilibrium Composition for **1a** ⇄ **1b** in Chloroform at −55.5 to 9.0°

T, °C.[a]	**1b**/**1a**[b]	*T*, °C.[c]	**1b**/**1a**[b]
−55.5	4.30	−10.5	3.89
−45.0	4.10	− 0.5	3.85
−36.5	4.03	9.0	3.69
−24.0	3.90		

[a] ±1°. [b] Mean deviations of at least six determinations ranged from 1 to 3%; maximum deviations ranged from 2 to 4%. [c] ±0.5°.

By plotting ln (**1b**/**1a**) against the reciprocal of the absolute temperature and fitting the points by the least-squares method to a straight line, the slope ($= -\Delta H/R$) and the intercept ($= \Delta S/R$) were obtained. The least-squares line was extrapolated to 25° to obtain $\Delta F_{298}°$. Free energy, enthalpy, and entropy changes for **1a** → **1b** are given in Table II.

(1) (a) Structure–Activity Relationships of Ethylenmines. III. Presented in part at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964. (b) Previous paper in the series: A. T. Bottini and V. Dev, *J. Med. Pharm. Chem.*, **5**, 925 (1962). (c) This research was supported by Grant CA-05528 from the National Cancer Institute of the Public Health Service. (d) Public Health Service Predoctoral Fellow, 1963–1964.

(2) R. L. Shriner, R. Adams, and C. S. Marvel in "Organic Chemistry, An Advanced Treatise," Vol. 1, H. Gilman, Ed., 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 402–413.

(3) A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, **80**, 5203 (1958).

(4) A. Loewenstein, J. F. Neumer, and J. D. Roberts, *ibid.*, **82**, 3599 (1960).

(5) *Cf.* R. A. Raphael, *J. Chem. Soc.*, 401 (1952), and R. Ghirardelli and H. J. Lucas, *J. Am. Chem. Soc.*, **79**, 734 (1957), and references cited therein.

(6) In the n.m.r. spectrum of *trans*-1,2-dimethyl-3-ethylaziridine, the weaker N-methyl resonance also appears at lower field. Because of the small chemical shift between the N-methyl resonances of *trans*-1,2-dimethyl-3-ethylaziridine, accurate determinations of its conformational equilibrium (~1.8 at −10° in chloroform) at various temperatures must await the availability of 100-Mc. n.m.r. in these laboratories.

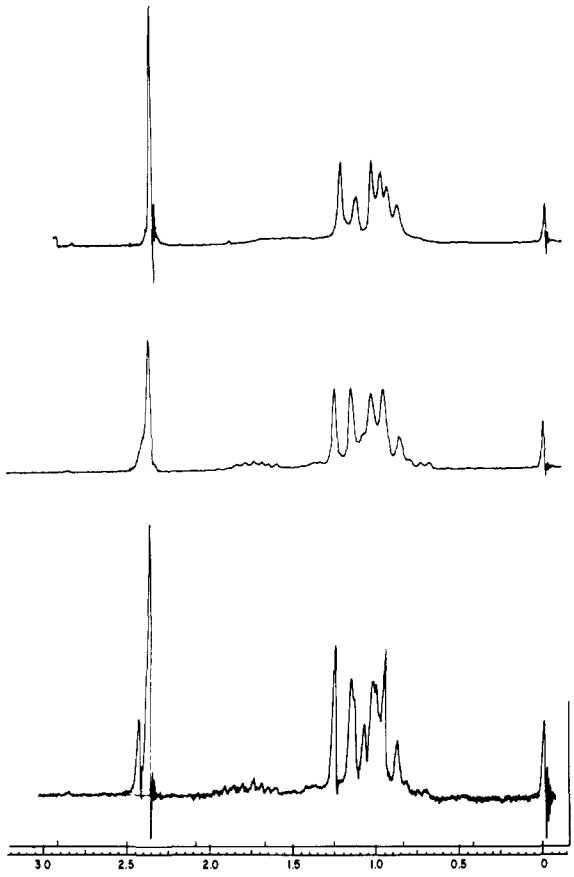


Figure 1. N.m.r. spectra of *trans*-1,2-dimethyl-3-isopropylaziridine (**1**) as a 25% solution in chloroform-*d* at 80° (top), 44° (center), and −10° (bottom) taken at 60 Mc. Resonance frequencies are in p.p.m. downfield from tetramethylsilane at 0 p.p.m.

Two features of the thermodynamic data are noteworthy. First, ΔF and ΔH, as assumed, do have the same sign. Second, $T\Delta S$ is greater than $-\Delta H$ in the entire temperature range studied. We consider it likely that a substantial part of the entropy change can be equated with the greater rotational freedom of the isopropyl group in **1b**.

Table II. Thermodynamic Quantities for **1a** ⇄ **1b** in Chloroform at −10.5 and 25°

T, °C.	ΔF, kcal./mole	ΔH, kcal./mole	ΔS, e.u.
−10.5	−0.71 ± 0.01[a]	−0.24 ± 0.05[b,c]	+1.8[d]
25	−0.77[b]		+1.8 ± 0.2[b,c]

[a] Experimental value with mean deviation. [b] Calculated using the equation obtained by the least-squares method. [c] Error is for 95% confidence limits as determined by machine computation. [d] Calculated from $\Delta F = \Delta H - T\Delta S$.

The n.m.r. spectrum of **1** as the neat liquid and as a 20% solution in methanol was also examined, but at fewer temperatures. The conformational equilibrium constant was consistently greater in both the neat liquid (4.33 ± 0.06 at −10° and 4.47 ± 0.08 at −34°) and in methanol (4.05 ± 0.13 and −2° and 4.39 ± 0.14 at −52°) as compared with chloroform; however, no profound change in ΔH was apparent.

Interestingly, coalescence of the N-methyl bands occurs at below 30° in the spectra of neat **1** and **1** as a 20% solution in benzene or toluene. This indicates that interaction of **1** with chloroform, presumably by weak hydrogen bonding, effectively slows the rate of nitrogen inversion.[3,4]

Experimental

Boiling points are uncorrected. Microanalyses were performed by Mr. V. H. Tashinian, Berkeley, Calif. Infrared spectra were obtained using a Beckman IR-4 spectrophotometer. Gas–liquid partition chromatograms were obtained using either a Loe Model 1 Chromat-O-Flex or a Wilkens Model A-700.

trans-2-Methyl-3-isopropyloxirane. Water (1200 ml.) and 176 g. (2.09 moles) of *trans*-4-methyl-2-pentene (Phillips pure grade, >99 mole %) were stirred vigorously in a 2-l., three-necked, round-bottom flask. N-Bromosuccinimide (372 g., 2.09 moles) was added in small portions in 5 hr. at such a rate that the temperature remained below 45°, and the mixture that resulted was stirred overnight. During the course of the reaction, the upper alkene phase disappeared, and a heavy, dark-colored phase formed. This lower phase (375 g.) was separated and added slowly to a vigorously stirred solution prepared from 320 g. (5.7 moles) of potassium hydroxide and 900 ml. of water. A yellow organic layer, which was lighter than the aqueous solution, separated during the reaction. The reaction mixture was saturated with sodium chloride, and the organic layer was separated, dried, and distilled through a 17 × 500 mm. column packed with glass helices. The *trans*-2-methyl-3-isopropyloxirane had b.p. 96–97°, $n^{27}D$ 1.3876, and it weighed 150 g. (72%).

Anal. Calcd. for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 71.92; H, 12.13.

Reaction of Methylamine with trans-2-Methyl-3-isopropyloxirane. A heterogeneous mixture prepared from 30 g. (0.30 mole) of *trans*-2-methyl-3-isopropyloxirane and 155 g. (2.0 moles) of 40% aqueous methylamine was held at room temperature and shaken occasionally during a period of 18 days. After 11 days, the mixture became homogeneous. Sodium hydroxide (20 g.) was added to the cold reaction mixture, and the strongly alkaline mixture that resulted was saturated with sodium chloride and extracted three times with 100-ml. portions of ether. The ether solutions were combined, dried, and distilled to yield 24.6 g. (62%) of amino alcohol with b.p. 174–176°, $n^{25}D$ 1.4442.

Anal. Calcd. for $C_7H_{17}NO$: C, 64.07; H, 13.06; N, 10.68. Found: C, 64.04; H, 13.06; N, 10.38.

trans-1,2-Dimethyl-3-isopropylaziridine (**1**). The amino alcohol (108 g., 0.824 mole) prepared from methylamine and *trans*-2-methyl-3-isopropyloxirane was titrated to the methyl red end point with *ca.* 6 *N* sulfuric acid, and an equal volume of sulfuric acid was added. The mixture that resulted was concentrated in a rotary film evaporator by heating on a steam bath at aspirator pressure for 1 day and in an oil bath at 140–160° for 10 hr. The residue was added in portions to a solution prepared from 160 g. of sodium hydroxide and 500 ml. of water. The organic phase that formed was separated, dried with sodium hydroxide, and distilled. *trans*-1,2-Dimethyl-3-isopropylaziridine (66 g., 71%) had b.p. 112–113°, $n^{25}D$ 1.4071.

Anal. Calcd. for $C_7H_{15}N$: C, 74.27; H, 13.36; N, 12.38. Found: C, 73.99; H, 13.60; N, 12.61.

cis-1,2-Dimethyl-3-isopropylaziridine. Using the procedures described for conversion of *trans*-4-methyl-2-pentene to **1**, *cis*-4-methyl-2-pentene (Phillips pure grade, >99 mole %) was converted to *cis*-1,2-dimethyl-3-isopropylaziridine, b.p. 102–103°, $n^{25}D$ 1.4016.

Anal. Calcd. for $C_7H_{15}N$: C, 74.27; H, 13.36; N, 12.38. Found: C, 74.12; H, 13.38; N, 12.55.

Assay of Purity of **1** *and Its cis Isomer.* Gas–liquid partition chromatograms obtained using a 1/4 in. × 10 ft. column packed with didecyl phthalate on Chromosorb W-HMDS and a 1/4 in. × 15 ft. column packed with Silicone XF-1150 on Chromosorb W-HMDS indicated that *cis*- and *trans*-1,2-dimethyl-3-isopropylaziridine were >99% pure and that the major impurity in each was the isomeric aziridine. The n.m.r. and infrared spectra of the aziridines were in accord with the assigned structures, and the absence of resonance bands in their n.m.r. spectra above 2.5 p.p.m. and absorption in their infrared spectra in the 1650 and 3300-cm.$^{-1}$ regions indicated further that contamination by unsaturated isomers or by amino alcohols was insignificant.

N.m.r. spectral measurements of the conformational equilibrium of **1** were obtained with a Varian Associates HR-60 system equipped with integrator and baseline stabilizer housed in an air-conditioned room.[7] Contents of the spinning sample tube were maintained at the desired temperature below room temperature using a variable temperature probe insert and accessories obtained from Varian Associates and following essentially the procedure described by Piette and Anderson.[8] The temperature measuring device was calibrated for actual sample temperature in a manner already described,[9] and the thermocouple used for measuring sample temperature was calibrated using solid–liquid mixtures of water (0°), carbon tetrachloride (−22.9°), chlorobenzene (−45.2°), and chloroform (−63.5°).[10]

Before attempting to measure the conformational equilibrium constant of **1**, we determined that at temperatures between −55 and 10° the widths of the N-methyl bands at half-height were the same as the widths at half-height of the individual bands of the acetaldehyde quartet when determined under the same operating conditions. We also examined the spectra of known mixtures of methyl acetate and toluene. As the widths at half-height of the methyl bands in the spectra of these known mixtures were the same as the widths at half-height of the individual bands of the acetaldehyde quartet, and as analyses of these mixtures by comparison of peak heights gave sample compositions which differed from the known compositions by less than the mean deviations (<2.5%) of the measurements, the conformational equilibrium constant (**1b**/**1a**) was taken to be identical with the ratio of peak heights of the N-methyl bands in n.m.r. spectra of **1**.

Samples were prepared by volume, flushed with a gentle stream of nitrogen, and sealed. After the temperature in the probe insert, which contained a spinning sample of acetaldehyde, had been maintained for 15 min. at the highest temperature at which measurements were to be made, the instrument resolution was optimized, and 6–10 sweeps through the acetaldehyde quartet were made in order to check the agreement of observed peak heights with theoretical intensities. The tube containing acetaldehyde was replaced with the tube containing **1**. After at least 15 min., the spectrum of the sample was determined, and from 6–12 sweeps through the N-methyl region were made. The following peak-height ratios, obtained for a 20% solution of **1** in chloroform at 9.0° by successive (alternate upfield and downfield) sweeps, are typical of data obtained: 72.0:20.1 (3.58), 72.0:19.0 (3.79), 72.3:20.1 (3.60), 72.0:19.0 (3.79), 72.3:20.0 (3.62), 72.6:19.2 (3.78), 68.3:18.8 (3.63), and 70.7:18.8 (3.76); mean = 3.69 ± 0.09. (For methanol solutions and the neat liquid, in which peak separation was 2.2–2.5 c.p.s., mean deviations were generally larger than those observed for chloroform solutions of **1**.) The temperature of the sample was decreased by 10–20°, maintained at the desired temperature for at least 15 min., and similar measurements were taken. After measurements had been taken at the lowest temperature, the tube containing **1** was replaced with the tube containing acetaldehyde. After 15–20 min., the instrument resolution was checked, and 6–10 sweeps through the acetaldehyde quartet were made to test the agreement of observed peak heights with theoretical intensities.

Redeterminations of **1b**/**1a** made several days after the data summarized in Table I were taken gave results (3.68 ± 0.07 at 9.0° and 3.94 ± 0.08 at −21°) that agreed satisfactorily.

(7) N.m.r. spectra of 1 and its *cis* isomer were also obtained using A-60 and HR-100 spectrometer systems. These spectra, which include those shown in Figure 1, were obtained at Varian Associates, Palo Alto, Calif., with the kind assistance of Mr. E. Pier.

(8) L. H. Piette and W. A. Anderson, *J. Chem. Phys.*, 30, 899 (1959).

(9) F. R. Jensen, D. S. Noyce, C. H. Sederholm, and A. J. Berlin, *J. Am. Chem. Soc.*, 84, 386 (1962).

(10) W. L. Jolly, "Synthetic Inorganic Chemistry," Prentice-Hall Co., Inc., New York, N. Y., 1960, p. 182.