

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, URBANA, ILLINOIS]

Nuclear Magnetic Resonance Studies of Diazirines. An Application to Conformational Analysis in Six-Membered Carbocyclic Rings¹

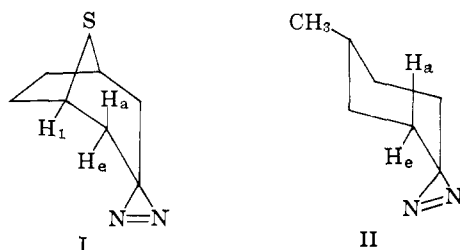
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The nuclear magnetic resonance spectra of 8-thiabicyclo[3.2.1]octane-3-spiro-3'-diazirine (I) and 1,2-diaza-6-methylspiro[2.5]-1-octene (II) are of interest because of the large chemical shift differences between the axial and equatorial protons of the methylene groups adjacent to the spiro carbon atoms. These differences (1.57 and 1.40 p.p.m., respectively, in CCl_4) largely reflect the shielding of the equatorial protons resulting from the magnetic anisotropy of the diazirine ring. This large chemical shift difference in I was exploited, through the use of double irradiation techniques, to determine that the geminal and vicinal spin-spin coupling constants are opposite in sign ($J_{a,e} = -15.2$, $J_{1,a} = +2.6$, and $J_{1,e} = +4.2$ c.p.s.). The temperature dependence of the large chemical shift difference between the comparable protons in diazirine II was used to determine accurate values for ΔS (0.42 ± 0.14 e.u.) and ΔH (-1.91 ± 0.04 kcal./mole) for the conformational equilibrium between the two chair conformers of this compound. We suggest the generality of the method for accurate measurements of conformational equilibria in six-membered rings and the determination of A -values for various substituents.

Analysis of Nuclear Magnetic Resonance Spectra.—

Unusual interest is attached to the n.m.r. spectra of compounds I and II as a result of the large chemical shift differences between H_a and H_e , the axial and equatorial protons adjacent to the diazirine ring.

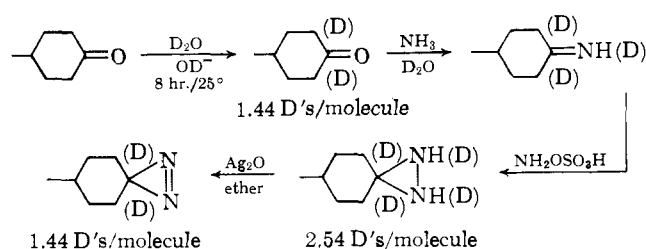


The spectrum of 1,2-diaza-6-methylspiro[5.2]-1-octene (II) is characterized by a broad, high-field doublet near τ^4 9.4 corresponding to two protons which are coupled to their geminal neighbors by an apparent coupling constant of about 12 c.p.s. The apparent chemical shift difference between these geminal protons (1.32 p.p.m. at -50°) was measured by spin-decoupling techniques which involved the irradiation of the low-field protons and measuring the frequency of irradiation necessary to effect the collapse of the high-field doublet.

The assignment of the high-field multiplet to protons H_e , made on the basis of a consideration of expected magnetic anisotropy effects,⁵⁻⁷ receives confirmation from the spectra of partially deuterated compounds.

The high-field double multiplet in II becomes a single broad multiplet (Fig. 1) upon the incorporation of 1.44 atoms of deuterium per molecule into the α -positions. Peak area measurements on the n.m.r. spectrum showed the upfield multiplet to contain 0.33 ± 0.06 deuterium atoms per molecule. Since the compound contained a total of 1.44 atoms of deuterium per molecule, 1.11 ± 0.06 atoms of deuterium must have been incorporated into those α -protons which absorb at lower field.

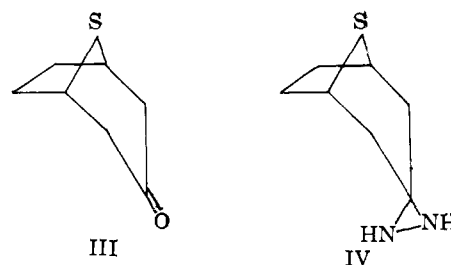
The synthesis of the partially deuterated II proceeded from the parent ketone as shown. Since the axial



hydrogens are expected⁸ to exchange more rapidly than the equatorial ones on stereoelectronic grounds, it is expected that the position which has a greater excess of deuterium is axial, *trans* to the predominantly equatorial methyl group in II. Since the downfield α -hydrogen signal in II gives evidence for more deuterium than that of the upfield α -hydrogens, it is concluded it corresponds to H_a and the upfield signal to H_e . The changes in peak shape observed on deuteration are consistent with this assignment (Fig. 1).

The spectrum of diazirine I is shown in Fig. 2. The absorption at τ 6.4 (two protons) is assigned to the bridgehead protons (H_1), the multiplet near 7.8 (six protons) to a superposition of signals from the ethylene bridge protons and H_a , and the multiplet near 9.3 to H_e . These assignments were made on the basis of chemical shift analogies in model compounds,^{9,10} including the precursor ketone III and diaziridine IV, and the analogous compounds in the series leading to II. Spin-decoupling experiments confirm these assignments. The chemical shift difference between H_a (τ 7.75) and H_e (τ 9.32) is exceptionally large—1.57 p.p.m.

The principal assumption made in relating the spectrum of I to that of the model compound II is



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(4) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).(5) S. G. Cohen and R. Zand, *J. Am. Chem. Soc.*, **84**, 586 (1962).(6) W. H. Graham, *ibid.*, **84**, 1063 (1962).(7) H. M. McConnell, *J. Chem. Phys.*, **27**, 226 (1957).(8) E. J. Corey and R. A. Sreen, *J. Am. Chem. Soc.*, **78**, 6269 (1956).(9) J. C. Martin and P. D. Bartlett, *ibid.*, **79**, 2533 (1957).

(10) Data taken from "N.M.R. Spectra Catalog" compiled by N. S. Bhacca, I. F. Johnson, and J. N. Shoolery of the Instrument Division of Varian Associates, Palo Alto, Calif., 1962.

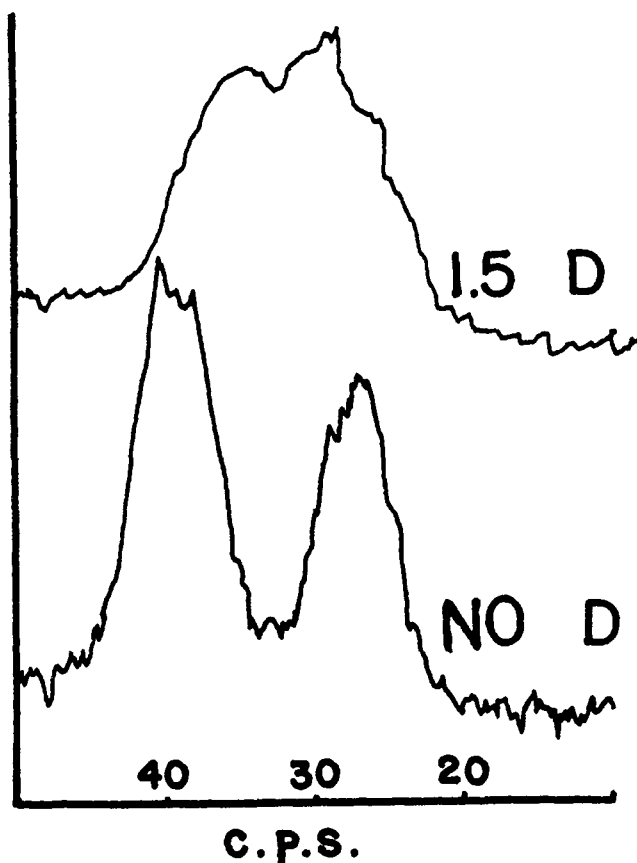


Fig. 1.— H_a n.m.r. spectrum of isotopically normal and of partially deuterated II (c.p.s. from TMS at 60 Mc.).

that the six-membered ring of I is in the chair conformation,¹¹ an assumption which may be defended on the basis of reasonable chemical analogies.¹²

This assignment for H_a and H_e receives some support from other considerations. From an inspection of Büchi models the H_1 -C-C- H_e dihedral angle is estimated to be about 55° and the H_1 -C-C- H_a angle, 65° . The values of $J_{1,a}$ (2.6 c.p.s.) and $J_{1,e}$ (4.2 c.p.s.), though larger than those predicted¹³ by the Karplus equations (1.2 and 2.5 c.p.s., respectively), are in the correct order for this assignment and the assumed geometry.

The pronounced magnetic shielding observed for H_e reflects an anisotropic magnetic susceptibility associated with the diazirine ring which parallels that observed for cyclopropyl rings.^{14,15} The ring current in the plane of the three-membered ring which is

(11) Temperature studies indicate that I probably has a strong conformational preference, presumably in the boat-chair equilibrium. Upon raising the temperature from ca. 25° to ca. 80° , the upfield quartet (H_e) shifted only about 0.7 c.p.s. downfield, with a similar upfield shift of the downfield quartet (H_a). The shift is of an order of magnitude predicted for an energy difference between upper and lower states of about 3 kcal./mole. These chemical shift changes are small, however, and may have their genesis in effects other than those associated with conformational changes in the molecule.

(12) (a) H. S. Aaron and C. P. Rader, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, p. 42Q; (b) M. R. Bell and S. Archer, *J. Am. Chem. Soc.*, **82**, 151 (1960); (c) E. A. Allan, F. Premuzic, and I. W. Reeves, *Can. J. Chem.*, **41**, 204 (1963); I. W. Reeves and K. O. Stromme, *ibid.*, **38**, 1241 (1960); A. J. Berlin and F. R. Jensen, *Chem. Ind. (London)*, 998 (1960); (d) N. J. Leonard, *Record Chem. Progr. (Kresge-Hooker Sci. Lib.)*, **17**, 243 (1956).

(13) (a) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); (b) *J. Am. Chem. Soc.*, **85**, 2870 (1963).

(14) K. B. Wiberg and B. J. Nist, *ibid.*, **83**, 1226 (1961).

(15) D. J. Patel, M. E. H. Howden, and J. D. Roberts, *ibid.*, **85**, 3218 (1963).

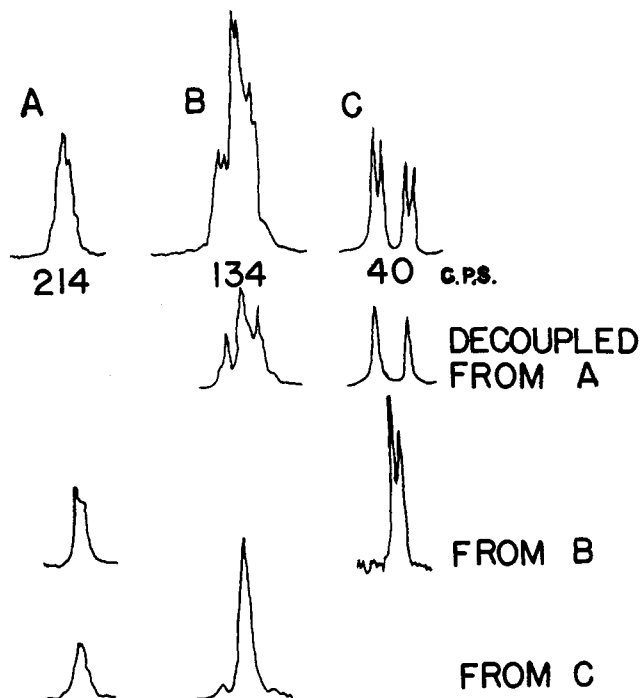


Fig. 2.—Spectrum of I with chemical shifts (expressed in c.p.s. from TMS at 60 mc.) for H_1 (A), H_a and the ethylene bridge (B), and H_e (C).

postulated to explain chemical shift observations in cyclopropane derivatives seems to have its counterpart in the diazirines.^{6,16} The increased shielding of H_e observed on oxidation of IV to I is also in keeping with the expected effect of a nitrogen-nitrogen double bond, assuming an anisotropy similar to that in a carbon-carbon double bond.¹⁷⁻¹⁹ The region of space in which shielding fields are induced is perpendicular to the plane of the double bond.

Protons H_e and H_a of I approximate the AM portion of an AMX three-spin system. Values which we derived for the parameters describing this portion of the spectrum are listed in Table I.

Signs of Coupling Constants in Diazirine I.—For a system which may be approximated by an AMX representation, Evans²⁰ has demonstrated how relative signs of coupling constants can be obtained using double irradiation techniques. The protons H_a , H_e , and H_1 in the bicyclic diazirine I meet this requirement. The further coupling of the H_1 protons to the protons of the ethylene bridge does not interfere with the application of the method. All other coupling constants to the AMX system are relatively very small. The schematic representation of Fig. 3 may be used to describe the experiments which were performed.

It is possible, for example, to cause the collapse of lines 1 and 2 without collapsing the 3,4-doublet by irradiating with a second frequency different from that of the 1,2-doublet by 183.8 c.p.s., a value which is seen, from the first entry in Table II, to suggest that

(16) J. P. Freeman, *J. Org. Chem.*, **28**, 2508 (1963).

(17) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959.

(18) (a) W. A. Ayer, C. E. McDonald, and J. B. Stothers, *Can. J. Chem.*, **41**, 1113 (1963); (b) R. R. Fraser, *ibid.*, **40**, 78 (1962); (c) G. Slomp, F. A. MacKellar, and I. A. Paquette, *J. Am. Chem. Soc.*, **83**, 4472 (1961).

(19) For increased shielding by C=O see: (a) O. I. Chapman, H. G. Smith, and R. W. King, *ibid.*, **85**, 806 (1963); L. Crombie and J. W. Town, *Proc. Chem. Soc.*, 299 (1961).

(20) D. F. Evans, *Mol. Phys.*, **5**, 183 (1962);

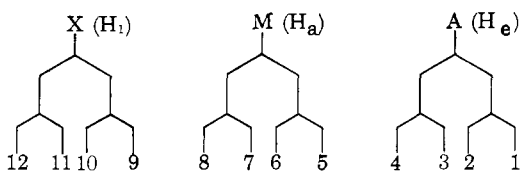


Fig. 3.—Schematic for H_1 , H_a , and H_e portion of spectrum of diazirine I.

$J_{a,e}$ and $J_{1,a}$ are opposite in sign. All of the experiments described in Table II support the relative signs ascribed to the J -values in Table I. The absolute sign of the geminal coupling constant $J_{a,e}$ was taken as negative in keeping with the results of experiments^{21,22} comparing directly the signs of C^{13} -H and

TABLE I
SPECTRAL PARAMETERS^a FOR DIAZIRINE I

Proton	Chem. shift, ^b c.p.s.	Coupling constants, c.p.s.	
H_e	40.2 ± 0.2	$J_{1,a}$	2.6 ± 0.2
H_a	$134.4 \pm .2$	$J_{1,e}$	$4.2 \pm .2$
H_1	$214.2 \pm .2$	$J_{a,e}$	$-15.2 \pm .2$
	Chem. shift difference calcd. from spectrum, c.p.s.	Chem. shift difference obsd. by spin decoupling, c.p.s.	
Protons			
H_a-H_e	94.2 ± 0.4	93.7 ± 0.5	
H_1-H_e	$174.0 \pm .4$	174.4 ± 0.5	
H_1-H_a	$79.8 \pm .4$	78.3 ± 1.0	

^a Calculated by fitting the observed spectrum using an iterative procedure and the program for the IBM 7090 computer described by J. D. Swalen and C. A. Reilly, *J. Chem. Phys.*, **37**, 21 (1962). ^b Chemical shifts are downfield from TMS in c.p.s., at 60 Mc.

TABLE II
DETERMINATION OF RELATIVE SIGNS OF COUPLING CONSTANTS^a

Coupling constants	Relative sign	—Collapsed lines/frequencies ^b —			
		1 and 2	3 and 4	9 and 11 and 5 and 6	7 and 8 10 and 12
$J_{a,e}:J_{1,a}$	Same, calcd.	180.3	160.9		
	Opposite, calcd.	182.9	163.5		
	(Found)	183.8	165.5		
$J_{a,e}:J_{1,e}$	Same, calcd.	85.3	74.3	85.3	74.3
	Opposite, calcd.	89.5	70.1	70.1	89.5
	(Found)	89.5	67.0	70.0	82.5
				5 and 7	6 and 8
$J_{1,a}:J_{1,e}$	Same, calcd.	95.0	93.4	95.8	93.4
	Opposite, calcd.	97.6	90.8	90.8	97.6
	(Found)	94.0	92.5	95.0	92.0

^a Chemical shift differences and coupling constants from Table I were used to calculate the frequencies at which the doublets are expected to collapse. ^b Frequency values, in c.p.s., represent differences, at 60 Mc., between the center of gravity of the doublet undergoing collapse and the frequency of irradiation in the decoupling experiment. Lines are designated with reference to the numbering in Fig. 3.

geminal H-H coupling constants. Since the sign of the C^{13} -H coupling constant is known with some certainty,²³ the assignment of a negative value to the geminal H-H coupling constant is relatively secure. The difference in signs of the geminal and vicinal coupling constants has now been established for a number of different molecular geometries.²⁴

(21) P. C. Lauterbur and R. J. Kurland, *J. Am. Chem. Soc.*, **84**, 3405 (1962).

(22) F. A. L. Anet, *ibid.*, **84**, 3767 (1962), and references therein.

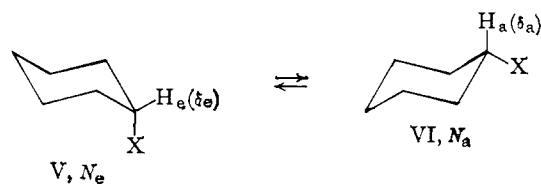
(23) M. Karplus, *ibid.*, **84**, 2458 (1962); see also A. D. Buckingham and K. McLauchlan, *Proc. Chem. Soc.*, 144 (1963).

(24) (a) R. R. Fraser, R. U. Lemieux, and J. D. Stevens, *J. Am. Chem.*

The Use of Diazirines in Conformational Analysis.

The free-energy difference between an axially and an equatorially substituted cyclohexane ring is a quantity of fundamental importance in conformational analysis. This quantity is usually designated by the symbol A ²⁵ and considered to be a characteristic property of the substituent. It is defined by eq. 1 as it applies to the equilibrium between V and VI, where N_a and N_e represent the mole fractions of the species.

The most widely used methods for the determination of conformation by n.m.r. spectroscopy take advantage of the fact that axial and equatorial protons on cyclohexane rings have different chemical shifts. For a monosubstituted cyclohexane the tertiary proton may occupy two distinct positions—axial, VI, or equatorial, V,—each of which has its own particular associated chemical shift, δ_a or δ_e , respectively. At normal temperatures an average line position is



$$A = -\Delta F = RT \ln N_a/N_e \quad (1)$$

observed, δ_{obsd} . If δ_e and δ_a are known, the equilibrium constant (K), and the free-energy difference between V and VI (cf. eq. 2 and 3) can be calculated.²⁶ (We have throughout the treatment used subscripts to refer to the position of hydrogen; thus N_e refers to the mole fraction of molecules with equatorial hydrogen at C_1 .)

$$\delta_{\text{obsd}} = N_a \delta_a - N_e \delta_e \quad (2)$$

$$K = \frac{N_a}{N_e} = \frac{\delta_e - \delta_{\text{obsd}}}{\delta_{\text{obsd}} - \delta_a} \quad (3)$$

It is easily seen that if the equilibrium constant is 5 or more, δ_{obsd} becomes quite close to δ_a for the usual case where the value of $(\delta_a - \delta_e)$ is of the order of 20 c.p.s. or less. Since K is expressed as the ratio of two differences in eq. 3, it becomes quite sensitive to experimental error as one of the differences becomes small. To circumvent this difficulty, Eliel²⁷ has extended the method by using disubstituted cyclohexanes with one axial and one equatorial substituent. The difference between individual A -values is obtained. If one of them is known with sufficient accuracy, the other may be calculated. Any newly calculated A -value, however, has all the uncertainty of the "known" value plus any uncertainty in the measured difference. Also, as Eliel has pointed out,^{27b} the additivity postulate is an assumption which may not always hold.

Soc., **83**, 3901 (1961); (b) F. Kaplan and J. D. Roberts, *ibid.*, **83**, 4666 (1961); (c) F. A. L. Anet, *ibid.*, **84**, 1053 (1962); (d) K. A. McLauchlan and D. H. Whiffen, *Proc. Chem. Soc.*, 144 (1962); (e) C. A. Reilly and J. D. Swalen, *J. Chem. Phys.*, **36**, 1522 (1961); (f) H. S. Gutowsky and C. Juan, *ibid.*, **37**, 120 (1962); (g) R. Freeman, K. A. McLauchlan, J. I. Musher, and K. G. R. Pachler, *Mol. Phys.*, **5**, 321 (1962); (h) R. R. Fraser, *Can. J. Chem.*, **40**, 1483 (1962); (i) K. B. Wiberg and B. J. Nist, *J. Am. Chem. Soc.*, **85**, 2788 (1963); (j) H. Finegold, *Proc. Chem. Soc.*, 213 (1962).

(25) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).

(26) (a) E. L. Eliel, *Chem. Ind. (London)*, 568 (1959); (b) E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, 97 (1962); (c) E. L. Eliel and B. P. Thill, *Chem. Ind. (London)*, 88 (1963).

(27) (a) E. L. Eliel, E. W. Della, T. H. Williams, *Tetrahedron Letters*, 831 (1963); (b) E. L. Eliel, *J. Chem. Educ.*, **37**, 126 (1960).

The accuracy of these methods depends upon obtaining reliable values for δ_e , δ_a , and δ_{obsd} . Difficulty in doing this has been encountered because the resonance signals are often broad^{21c,26b}, and $(\delta_e - \delta_a)$ small.²⁵ The reference of footnote *e*, Table IV, describes a method involving deuteration at neighboring carbons to remove the spin-spin splitting responsible for the broadening of the peaks of interest. The use of any of these n.m.r. methods required that the peak for the tertiary hydrogen be sufficiently separate from the rest of the spectrum to be readily observable. This requirement is usually met when X is an electro-negative substituent, but not when X, for example, is an alkyl substituent.

The diazirine group can be used as a conformational probe. It serves not only to shift appropriate protons into accessible portions of the spectrum, but it also serves to increase $(\delta_e - \delta_a)$. As a direct result, much more accurate data can be obtained and more bulky groups producing greater equilibrium imbalance can be investigated directly, without the observed chemical shift difference approaching too nearly that in the more stable of the rapidly equilibrating conformers. It should be noted that in this system the equatorial protons absorb at higher field than the axial protons, in contrast to the usual order.²⁶⁻²⁸ The magnetic anisotropy of the diazirine ring, which is responsible for this inversion in order, was discussed earlier in this paper.

To demonstrate such an application, spectra of diazirine II were studied in measurements of the chemical shift differences between the two α -protons at several different temperatures. Spin-decoupling techniques²⁹ were used to make these measurements. Irradiation in the region of the spectrum near the H_a multiplet, which is buried in a mass of other peaks, results in maximum H_a - H_e decoupling, as reflected in the coalescing of the easily observable high-field twin peaks, at a frequency which is easily measured. This approach to the problem, involving a direct measurement of the quantity $(\delta_a - \delta_e)$ instead of separate measurements of the two δ -values, provides a further increase in the accuracy of measurements used in this method over that enjoyed by other methods using n.m.r. to determine conformational equilibrium constants. Reproducibility of measured values of $(\delta_e - \delta_a)$ was consistently within ± 0.2 c.p.s.

Measurements were made at five temperatures ranging from -49.4 to $+75.4^\circ$. Within this range the equilibrium is rapid and the observed chemical shift differences are weighted averages; *cf.* eq. 2. In the derivation of the expression for K the δ refers to the observed chemical shift for the proton shown in bold-face type (eq. 4 and 6). The quantities Δ and Δ' in eq. 6 and 7 are the chemical shift differences between axial and equatorial α -protons in VIII and VII, respectively. It is reasonable to assume that Δ and Δ' are quite similar and that their ratio is therefore close to one.³⁰ Small deviations from this approxi-

(28) L. W. Reeves and K. O. Stromme, *Trans. Faraday Soc.*, **57**, 390 (1961).

(29) R. F. Freeman, *Mol. Phys.*, **4**, 385 (1961).

(30) An empirical approach using apparent average shielding values for alkyl substituents may be used to show that $(\Delta' - \Delta)$ is small. The shift parameters of Eliel, Gianni, Williams, and Stothers²¹ successfully correlate the observed chemical shifts for 36 substituted cyclohexanols, generally to within 1 c.p.s. The introduction of an axial-3-methyl substituent into

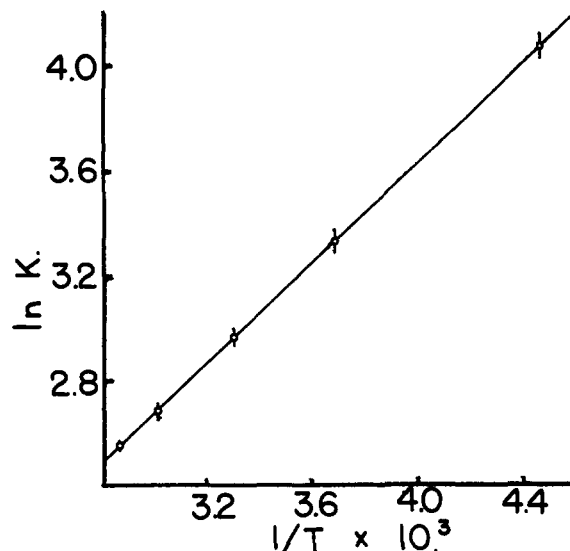
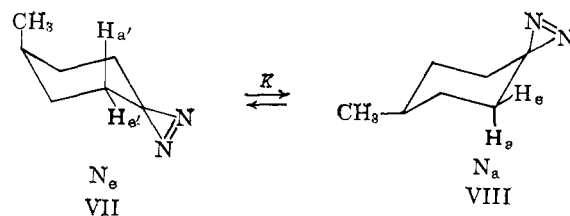


Fig. 4.—Temperature dependence of the equilibrium constant for the VII-VIII interconversion (calculated from eq. 7 with $\Delta = 84.2$ c.p.s.).

mation will cause no significant change in the derived quantities, since the numerator, which contains the Δ'/Δ quantity, is the sum of two relatively large numbers divided by a smaller number in the denominator.



$$\delta_{\text{obsd}, ea'} = N_a \delta_a + N_e \delta_{e'} \quad (4)$$

$$\delta_{\text{obsd}, ea'} = N_a \delta_e + N_e \delta_{a'} \quad (5)$$

Upon subtraction

$$(\delta_{ae'} - \delta_{ea'})_{\text{obsd}} \equiv \Delta_{\text{obsd}} = N_a \Delta - N_e \Delta' \quad (6)$$

where $\Delta = (\delta_a - \delta_e)$ and $\Delta' = (\delta_{a'} - \delta_{e'})$.

Substituting $1 - N_a$ for N_e in eq. 6 we get

$$N_a = (\Delta' + \Delta_{\text{obsd}})/(\Delta + \Delta') \quad (7)$$

and similarly

$$N_e = (\Delta - \Delta_{\text{obsd}})/(\Delta + \Delta') \quad (8)$$

$$K = N_a/N_e = \frac{\Delta' + \Delta_{\text{obsd}}}{\Delta - \Delta_{\text{obsd}}} = \frac{\Delta'/\Delta + \Delta_{\text{obsd}}/\Delta}{1 - \Delta_{\text{obsd}}/\Delta} \approx \frac{1 + \Delta_{\text{obsd}}/\Delta}{1 - \Delta_{\text{obsd}}/\Delta} \quad (9)$$

the cyclohexanol ring results in a chemical shift change (at 60 Mc.) of -10.5 c.p.s. for an axial 1-proton or -5.0 c.p.s. for an equatorial 1-proton. Changes resulting from the introduction of an equatorial 3-methyl substituent result in shifts of -1.5 c.p.s. for an axial 1-proton or $+0.5$ c.p.s. for the equatorial epimer. From these values one can calculate a difference of 3.5 ± 2 c.p.s. between Δ' and Δ . Since Δ is about 82 c.p.s., Δ' would be about 85.5 c.p.s. The anisotropies associated with the diazirine ring are so large that the differences associated with the methyl group are negligible. The change in ΔF introduced by equating Δ' to Δ , at room temperature, would be of the order of 10 cal./mole, a negligible error.

(31) E. L. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Letters*, 741 (1962).

Since the quantity Δ is the ($H_a - H_e$) chemical shift difference for VII in the absence of rapid interconversion, it could presumably be obtained directly from spectra taken at sufficiently low temperature. Solubility and probe limitations made it impractical for us to obtain spectra below -50° , too high a temperature to accomplish the "freezing out" of the rapid equilibrium between VII and VIII. In order to determine Δ indirectly, the linear correlation of $\ln K$ vs. $1/T$ was undertaken using trial values of Δ . A computer program was utilized to minimize the standard deviation for this correlation as a function of these trial values of Δ . In this treatment values of $\ln K$ were provided statistical weights to reflect their probable error, calculated assuming errors in measurements of Δ_{obsd} to be ± 0.2 c.p.s. (These measurements could be duplicated at room temperature to within ± 0.13 c.p.s.) Variation of the trial values of Δ in increments of 0.1 c.p.s. showed the minimum standard deviation at $\Delta = 84.2$ c.p.s., the value used to calculate the results listed in Table III. From these values we calculate: $\Delta F_{30^\circ} = -1.78 \pm 0.06$ kcal./mole, $\Delta H = -1.91 \pm 0.04$ kcal./mole, and $\Delta S = -0.42 \pm 0.14$ e.u.

TABLE III
TEMPERATURE DEPENDENCE OF THE ($H_a - H_e$) CHEMICAL SHIFT DIFFERENCE FOR COMPOUND VII and VIII

$T, ^\circ\text{C.}$	$\Delta_{\text{obsd}} (\pm 0.2),$ c.p.s.	K^a	Weight ^b
-49.9 ± 0.5	81.4	59.1	1.00
$-1.9 \pm .9$	78.4	28.0	2.08
$31.1 \pm .2$	75.9	19.3	2.56
$58.6 \pm .3$	73.2	14.3	3.85
$75.4 \pm .9$	72.0	12.9	4.52

^a Calculated using eq. 7 with $\Delta = 84.2$ c.p.s. ^b Statistical weights for points were calculated assuming ± 0.2 c.p.s. error in values of Δ_{obsd} .

While the value for ΔS (-0.42 e.u.) differs from zero by an amount which is probably outside experimental error, the difference is so small that it may well be used in justification of the assumption usually made that $\Delta S = 0$. An assessment of the significance of the small deviation from zero must await further results.

The assumed linear relationship between $\ln K$ and $1/T$ is equivalent to assuming a temperature-independent ΔH for the interconversion of VII and VIII.³²

$$(\delta\Delta H/\delta T)_p = \Delta C_p = 0 \quad (10)$$

The A -values found in this work, together with those obtained from independent sources, are listed in Table IV. The agreement is very good considering the wide variety of methods and conditions used.

The values for ΔH and ΔS , which are made available in this method through the accurate determinations of equilibrium constants over a wide temperature range, are compared in Table V with literature values for comparable interconversions of equatorial methyl- and axial methylcyclohexane derivatives.

In order to determine the possible importance of a temperature-dependent solvent effect on Δ_{obsd} we

(32) This assumption is supported by a consideration of the probable heat capacity differences in VII and VIII. That these might reasonably be expected to be small differences is seen from C_p data for the model compounds *cis*- and *trans*-1,4-dimethylcyclohexane. Over our temperature range the C_p difference is about 0.4 cal./deg.-mole for these model compounds. Such a ΔC_p would occasion a change in ΔH of only 0.05 kcal./mole, a change so small that our assumption of a linear correlation would seem justified.

TABLE IV
VALUES OF A FOR THE METHYL GROUP

Solvent	$T, ^\circ\text{C.}$	$A, \text{kcal./mole}$	Method
CDCl_3	30	1.78 ± 0.06	N.m.r. (this work)
H_2SO_4	25	$1.54 (1.75)^c$	Epimerization of 1,4-dimethylcyclohexane ^a
CCl_4	30	1.74 ± 0.06	N.m.r. ^e
2-D-2-propanol	30	$1.60 \pm .06$	N.m.r. ^e
CS_2	30	$1.97 \pm .06$	Infrared ^f
H_2O	100	1.54	Hydroxyacid-lactone equilibrium ^g
Ether	35	1.5 ± 0.1	Epimerization ^h
Gas phase	25	$1.90 \pm .4$	Calorimetric ⁱ
Gas phase	25	$1.80 \pm .3$	Thermodynamic ^j
...		$1.97 \pm .3$	Epimerization of 1,4-dimethylcyclohexane ^k

^a Calculated by R. D. Stolow, *J. Am. Chem. Soc.*, **81**, 5806 (1959), using data from ref. b. ^b A. K. Roebuck and B. L. Evering, *ibid.*, **75**, 1631 (1953). ^c Calculated using data of ref. b and entropy data of ref. d. ^d H. M. Huffman, S. S. Todd, and G. D. Oliver, *J. Am. Chem. Soc.*, **71**, 584 (1949). ^e A. H. Lewin and S. Winstein, *ibid.*, **84**, 2464 (1962). ^f F. R. Jensen and L. H. Gale, *J. Org. Chem.*, **25**, 2075 (1960). ^g D. S. Noyce and L. J. Dolby, *ibid.*, **26**, 3619 (1961). ^h E. L. Eliel and M. N. Rerick, *J. Am. Chem. Soc.*, **82**, 1367 (1960); see also E. L. Eliel and T. J. Brett, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, p. 19Q. ⁱ E. J. Prosen, W. H. Johnson, and F. D. Rossini, *J. Res. Natl. Bur. Std.*, **39**, 173 (1947). Value is the ΔH of isomerization for 1,4-dimethylcyclohexanes. ^j C. W. Beckett, K. S. Pitzer, and R. Spitzer, *J. Am. Chem. Soc.*, **69**, 2488 (1947). ^k N. L. Allinger and S. E. Hu, *J. Org. Chem.*, **27**, 3417 (1962). A more accurate value privately communicated by Prof. Allinger is 1.86 ± 0.08 kcal./mole at 256° .

TABLE V
VALUES OF ΔH AND ΔS

Solvent	$-\Delta H, \text{kcal./mole.}$	$-\Delta S, \text{e.u.}$	Method
CDCl_3	1.91 ± 0.03	0.4 ± 0.1	N.m.r. ^a
$\text{CH}_3\text{C}_6\text{H}_{11}$	$1.90 \pm .25$	2.22 ± 0.22	Ultrasonic ^b
Gas phase	$1.90 \pm .4$...	Calorimetric ^c

^a This work. ^b M. E. Pedinoff, *J. Chem. Phys.*, **36**, 777 (1962). ^c E. J. Prosen, W. H. Johnson, and F. D. Rossini, *J. Res. Natl. Bur. Std.*, **39**, 173 (1947).

measured the apparent Δ directly from spectra in various solvents at room temperature. In carbon tetrachloride, chloroform-*d*, dimethylformamide, carbon disulfide, deuterioacetone, and benzene, Δ_{obsd} was 73 ± 3 c.p.s. Since for these solvents any solvent effect on Δ_{obsd} is negligibly small relative to Δ_{obsd} it is reasonable to expect the temperature dependence of the effect to be small also.

Summary

The close agreement between the A -values for the methyl group determined by the method of this paper and values obtained by other methods suggests that the distortion of the six-membered ring in the spirodiazirines used in this work is relatively minor and energy differences between axial and equatorial conformers similar to that of the corresponding cyclohexanes. This suggests the general usefulness of the method in conformational analysis. A possible limitation to the generality of the method exists for highly electronegative substituents where dipole-dipole interactions with the diazine group moment (~ 1.5 D.)³³ may introduce important energy terms in the apparent A -value.

(33) L. Pierce and V. Dabyns, *J. Am. Chem. Soc.*, **84**, 2651 (1962); see J. C. Martin and J. J. Uebel, *ibid.*, **86**, 2936 (1964), for a discussion of this effect.

Experimental³⁴

8-Thiabicyclo[3.2.1]-3-octanone (III) was prepared by the method outlined by Horak.³⁵ From tropinone methiodide (36.6 g., 0.13 mole) the ketone was produced in 63% yield (11.6 g.), m.p. 150–153°. Recrystallization of the material from hexane gave 10.9 g. in three crops, m.p. 159–160°, lit.³⁵ 155°.

8-Thiabicyclo[3.2.1]octane-3-spiro-3'-diaziridine (IV).—The diaziridine was prepared by a method similar to that used for an analogous compound by Schmitz and Ohme.³⁶ In a typical preparation, a solution of ketone III (2.84 g., 0.02 mole) in 10 ml. of methanol was dissolved in anhydrous ammonia (30–40 ml.) and the resulting solution was stirred with a magnetic stirrer, under reflux, for 0.5 hr. Hydroxylamine-O-sulfonic acid³⁷ (5.65 g., 93% pure) was added slowly over a period of 1 hr. at –78°. The cooling bath was removed, and stirring resumed. After 14 hr. the ammonia was allowed to evaporate. The residue was triturated with methylene chloride, the filtrate dried over potassium carbonate, and the methylene chloride removed. The residue was recrystallized from methylene chloride-ether to give 1.04 g. (33%) of a white solid, m.p. 161.5–164°. Further recrystallization from methylene chloride-ether gave m.p. 169–171°.

Anal. Calcd. for C₇H₁₂N₂S: C, 53.79; H, 7.75; N, 17.52. Found: C, 53.99; H, 7.97; N, 17.40.

8-Thiabicyclo[3.2.1]octane-3-spiro-3'-diazirine (I).—In a typical preparation 20 ml. of 1.0 M sodium hydroxide was added to 20 ml. of 1.0 M silver nitrate with stirring. The mixture was cooled to about 10° before the diaziridine (0.78 g., 0.005 mole) was added. The mixture was shaken vigorously for 3–4 min., filtered, and the aqueous solution extracted with ether. The silver oxide was also triturated with ether and the combined extracts were washed with 5 M sulfuric acid. After drying over potassium carbonate, the ether was distilled under vacuum, leaving a clear oil which solidified to give 0.61 g. of material (79%), m.p. 101–104°.

Anal. Calcd. for C₇H₁₀N₂S: C, 54.50; H, 6.55. Found: C, 54.38; H, 6.62.

1,2-Diaza-6-methylspiro[2.5]octane was prepared by a method analogous to that of Schmitz, Ohme, and Schmidt.³⁸ 4-Methylcyclohexanone (11.2 g., 0.10 mole) was stirred for 45 min. in concentrated ammonium hydroxide, then the suspension was cooled to 0–5°. Hydroxylamine-O-sulfonic acid³⁷ (14.0 g., ca. 90% pure) was added portionwise over an hour and a half. After stirring for an additional 0.5 hr. the mixture was cooled to –20°. The precipitate was filtered, dissolved in ether, and dried over potassium carbonate. Cooling gave 4.65 g. (37%) of product, m.p. 75–78°. Further recrystallization from ether gave material, m.p. 81–82°.

(34) We wish to acknowledge the assistance of J. Nemeth, O. Norton, and R. Johnson in obtaining microanalyses and n.m.r. and infrared spectra. Spectra are reproduced in the Ph.D. Thesis of J. J. U., University Microfilms, Ann Arbor, Mich.

(35) V. Horak, *Chem. Abstr.*, **54**, P8855d (1960); also see: V. Horak, J. Zavada, and A. Piskala, *Chem. Ind.* (London), 1113 (1958).

(36) E. Schmitz and R. Ohme, *Chem. Ber.*, **94**, 2166 (1961).

(37) V. F. Sommer, O. F. Schulz, and M. Nassau, *Z. anorg. allgem. Chem.*, **147**, 142 (1925).

(38) E. Schmitz, R. Ohme, and R. D. Schmidt, *Chem. Ber.*, **95**, 2714 (1962).

Anal. Calcd. for C₇H₁₄N₂: C, 66.62; H, 11.18. Found: C, 66.83; H, 11.03.

1,2-Diaza-6-methylspiro[5.2]-1-octene (II).—The oxidation of the isohydrazone of 4-methylcyclohexanone (5.04 g., 0.04 mole) was carried out as in the preparation of pentamethylene diazirine³⁶ with freshly prepared silver oxide (29.0 g., 0.125 mole) in 175 ml. of ether. The product (4.53 g.) was flash distilled at 75 mm. and a pot temperature of 80° to give 1.86 g. (37%) of nearly pure material (containing traces of olefin; n.m.r.).

Anal. Calcd. for C₇H₁₂N₂: C, 67.69; H, 9.74. Found: C, 68.34; H, 9.82.

4,6-Deuterio-1,2-diaza-6-methyl[2.5]-1-octene.—4-Methylcyclohexanone (15.0 g., 0.134 mole) was mixed with 10.0 g. of D₂O (greater than 99% enriched) containing a catalytic amount of deuterioxide, and stirred for 10 hr. at room temperature. The ketone was then extracted from the mixture with ether and dried over Na₂SO₄ to give 14.4 g. of ketone, which was divided into two portions of 4.9 and 9.4 g. The former portion was distilled once, b.p. 92–93° at 50 mm., and analyzed for deuterium.

Anal. Calcd. for C₇H₁₀,D_{1.6}O: C, 73.89; H (D), 10.59. Found: C, 73.42; H (D), 10.64; excess deuterium (by combustion), 12.05 ± 0.2%; excess deuterium (by n.m.r.), 12.3 ± 0.2%.

The latter portion of the ketone (9.4 g., 0.084 mole) was stirred at room temperature for 1 hr. with 35 ml. of D₂O saturated with ammonia, then treated as above to give diaziridine (37%) containing 18.1 ± 0.2% (by n.m.r.) excess deuterium. The diazirine II was prepared as before.

Anal. Calcd. for C₇H₁₀,D_{1.6}N₂: C, 66.88; H, 9.62. Found: C, 67.16; H, 9.83; excess deuterium, 12.05 ± 0.2%.

Nuclear Magnetic Resonance.—The 60-Mc. spectra were taken on a Varian A-60 instrument. Line positions were determined on the A-60 spectrometer by the "side-band" technique. In each case a side band of the internal reference, tetramethylsilane, was generated in the vicinity of the lines under investigation, and that region swept at a sweep-width of 50 c.p.s. A Hewlett-Packard 300 audio-frequency oscillator in conjunction with a Hewlett-Packard-521C counter was used. Decoupling experiments were made on a modified Varian DP-60 spectrometer equipped with a V-K3506 Super Stabilizer. The instrument was modified as described by Varian Associates³⁹ in order to use the V-3521 integrator for the decoupling experiments.

The exact positions of maximum decoupling were obtained by plotting the frequency of the audio-frequency signal used to generate the decoupling side band *vs.* the peak height after the procedure of Freeman.²⁹ The temperature of the probe was measured before and after a run by use of a copper-constantan thermocouple in a dummy sample tube. The averages of the temperatures before and after a run were recorded.

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(39) "Varian Technical Bulletin," Vol. III, No. 3, 1471, available from Varian Associates, Palo Alto, Calif.