

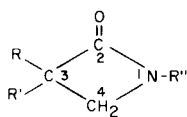
Research Laboratories, Lepetit S.p.A.

PMR Spectra and Conformation of some Four-membered Rings Containing One Nitrogen Atom. 2-Azetidinones, 2-Azetidinethiones and 1-Azetines.

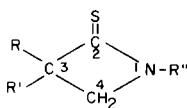
Aristide Vigevani and Gian Gualberto Gallo

By PMR studies at different temperatures a planar conformation is proposed for the 2-azetidinone, 2-azetidinethione and 1-azetine rings. The chemical shifts and the vicinal and geminal coupling constants of the ring methylene protons are reported and discussed. The application of the relationship between the J_{gem} value and the angle between the methylene group and the adjacent π -bond is considered.

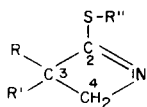
The cyclobutane ring had been accepted as planar by organic chemists since the Baeyer strain theory (1). Only recently the non-planarity of this ring has been taken into consideration and the topic is reported in a complete review (2). In fact, electron diffraction studies and spectroscopic and thermodynamic measurements on cyclobutane (3) followed by NMR investigations on cyclobutane (4-6), cyclobutanone (6-8) and cyclobutene (9-11) derivatives have favored the non-planarity of these rings (12). However, planarity has been indicated for the cyclobutanone ring by microwave spectral data (13) and for a cyclobutanone and a cyclobutene by recent accurate NMR studies (14). In the present paper we investigate the conformation of some heterocyclic four-membered rings containing one nitrogen atom by studying the PMR spectra of some 2-azetidinones (15-17) (I-IV), 2-azetidinethiones (18) (V-IX) and 1-azetines (19) (X, XI), recently synthesized.



- I, R = C₆H₅, R' = C₆H₁₁ (cyclohexyl), R'' = H
 II, R = C₆H₅, R' = n-C₄H₉, R'' = H
 III, R = C₆H₅, R' = R'' = CH₃
 IV, R = C₆H₅, R' = R'' = H

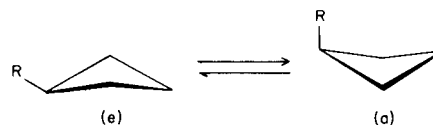


- V, R = C₂H₅, R' = C₆H₅, R'' = CH₃
 VI, R = C₂H₅, R' = C₆H₅, R'' = H
 VII, R = C₆H₁₁ (cyclohexyl), R' = H, R'' = CH₃
 VIII, R = C₆H₁₁ (cyclohexyl), R' = R'' = H
 IX, R = C₆H₅, R' = H, R'' = CH₃



- X, R = C₆H₅, R' = R'' = C₂H₅
 XI, R = C₆H₁₁ (cyclohexyl), R' = H, R'' = C₂H₅

The asymmetric carbon atom 3 ($R \neq R'$ in all the products investigated) causes the two protons in position 4 to be magnetically non-equivalent (20), thus enabling the resonance of the methylene protons to be extensively examined, including the chemical shifts, the geminal coupling constant and the vicinal coupling constants with the proton at 3. The deviation from planarity for the rings under study most likely is small, if any. In fact, the presence of the trigonal carbon and of nitrogen in the azetidinone and in the azetidinethione rings and of the carbon-nitrogen double bond in the azetine ring destabilizes the non-planar forms, because of increased angular strain, and stabilizes the planar forms, because the number of eclipsed substituents and consequently of non-bonded interactions is smaller. However, in the case of non-planarity, taking monosubstituted cyclobutane as a model (5), there will be an equilibrium between equatorial (e) and axial (a) conformations and this equilibrium is expected to be shifted towards (e).



We have determined the conformation of the ring by studying the temperature effect on the PMR spectra. In fact, for non-planar compounds the chemical shift difference between the non-equivalent protons will vary with temperature as the equilibrium $(e) \rightleftharpoons (a)$ shifts. Lower temperatures will favor conformer (e), while higher temperatures will cause an approach to equal population of both conformations. On the contrary, absence of such an effect will indicate planarity. The PMR spectra of compounds IV, IX and XI, as representative for the three

TABLE I

Chemical shifts (τ) and vicinal and geminal coupling constants (c/s) of the ring methylene protons

Compound	Solvents (a)	τ H in 4 (ppm)	$\Delta\tau$	J_{gem} (c/s)	J_{vic} (c/s)	
					<i>trans</i>	<i>cis</i>
I	C ₆ D ₆	7.02 7.00	0.02	5.7	—	—
II	CDCl ₃	6.58 6.49	0.09	5.7	—	—
III	CDCl ₃	6.68 6.52	0.16	5.2	—	—
IV	CDCl ₃	6.75 6.36	0.39	5.6	2.7	5.3
V	CCl ₄	6.15 6.03	0.12	6.9	—	—
VI	CCl ₄	6.05 5.93	0.12	7.0	—	—
VII	CCl ₄	6.42 6.20	0.22	7.2	2.0	4.3
VIII	CDCl ₃	6.36 6.13	0.23	7.2	2.0	4.5
IX	C ₆ D ₆	6.98 6.76	0.22	6.9	2.1	4.8
X	CCl ₄	6.15 6.12	0.03	9.9	—	—
XI	CCl ₄	6.54 6.29	0.25	10.0	2.0	4.0

(a) The spectra of I and IX were recorded in perdeuteriobenzene because in this solvent $\Delta\tau$ was better measured. However, no differences were observed of $\Delta\tau$ in deuteriochloroform and perdeuteriobenzene.

classes under investigation, were run in hexadeuteriodimethyl sulphoxide solution at +30° and at +130° and in tetradeuteriomethanol at +30° and at -40°. The absence of any significant change of chemical shift difference between the methylene protons in the above temperature range is conclusive evidence for the planarity of the studied rings. No lower temperatures could be studied because of solubility limitations. However the -40° temperature reached should be sufficient for observing the change of conformer populations, if occurring (5,14).

All the methylene proton resonances are reported in Table I. The vicinal coupling constant values for all the compounds with a hydrogen at 3 fall in two narrow distinct ranges, 2.0-2.7c/s for the higher field doublets and 4.0-5.3c/s for the lower field doublets. The assign-

ment of the range 4.0-5.3c/s to the J_{vic}^{cis} and of the range 2.0-2.7c/s to the J_{vic}^{trans} is based on the comparison with data recently reported for some β -lactams (21-23). As, for equal electronegativity of substituents, equal bond length and equal HCC'H' bond angles (24), the dihedral angle between the planes HCC' and CC'H' is the only factor affecting the $J_{vic}^{HH'}$ values, the fact that the $J_{vic}^{H_3H_4}$ values are the same for all the compounds studied is a further proof that these compounds have the same ring conformation. From the evidence of the ring planarity, the *cis* protons will define a dihedral angle of about 0° and the *trans* protons an angle of about 120°. The Karplus equation gives a J_{vic}^{cis} value (about 8c/s) greater than the observed ones (4.0-5.3c/s) and a J_{vic}^{trans} value (about 2c/s) which fits the observed range (2.0-2.7c/s). It is evident

that the original Karplus equation can not be applied to these strained rings, as also found for the cyclobutene ring (10). But the relative magnitude of the vicinal coupling constants is in agreement with the predictions of the relationship.

As far as the chemical shifts are concerned, the $\Delta\tau$ values for the methylene hydrogens are proportional to the difference in size of the substituents in 3. The data reported for the 2-azetidinones (I-IV), which have at position 3 a phenyl group and a substituent of decreasing size clearly illustrated this trend. This could depend mainly on intramolecular dispersion forces (25a); the proximity of a bulky substituent to a hydrogen causes steric congestion and, consequently, deshielding. In our case, for compound I the phenyl and the cyclohexyl groups have a similar deshielding effect and the $\Delta\tau$ of the protons at 4 is very small. For compound IV, the different effect of the phenyl group and of the hydrogen atom causes a high $\Delta\tau$ value. The compounds II and III show intermediate $\Delta\tau$ values.

The geminal coupling constant values (26) are in the ranges 5.2-5.7c/s, 6.9-7.2c/s and 9.9-10.0c/s for azetidinones, azetidinethiones and azetines, respectively. The range for azetidines is 7.4-8.0c/s, as derived from our data (7.4c/s for 3-*n*-butyl-3-phenylazetidine (29), 7.4c/s for 1-methyl-3-hydroxymethyl-3-phenylazetidine (30) and 8.0c/s for 3-hydroxymethyl-3-phenylazetidine (30). The decrease of the absolute values of J_{gem} in the order azetidines, azetidinethiones, azetidinones seems to be

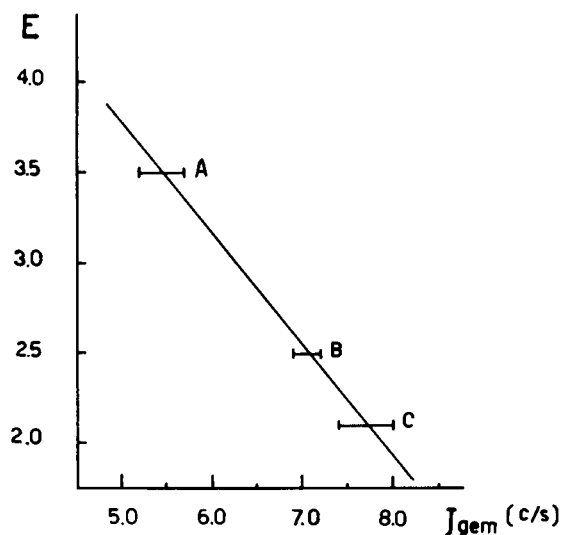


Figure 1. Relationship between the absolute value of the geminal coupling constant of the hydrogens at 4 and the electronegativity (E) of the atoms attached to carbon 2. A = 2-azetidinones; B = 2-azetidinethiones; C = azetidines.

correlated with the increasing electron-withdrawing power of the atoms attached to carbon 2, as shown in Fig. 1. A similar correlation has been reported for cyclopropanes (31) for which, contrary to our case, J_{gem} increases in absolute value with increasing electronegativity of the substituents. A possible contribution from hyperconjugation of the CH_2 group across the ring seems to be ruled out by its distance from the $\text{C}=\text{X}(\text{X}=\text{O},\text{S})$ group (28).

The higher absolute values of J_{gem} for azetines compared to azetidines is likely due to the presence of the carbon-nitrogen double bond in the ring. This difference can be tentatively interpreted by means of the correlation between the J_{gem} value and the angle between the methylene group and the adjacent π -bond, as established for the cyclic system $-\text{CH}_2-\text{C}=\text{X}(\text{X}=\text{C},\text{O})$ by Barfield and Grant (32). In the original study (32) the J_{gem} of methane (-12.4c/s) was taken as a reference value. In our case we have chosen as a reference the value of about -7.5c/s (26) of azetidines, as the J_{gem} for the methylene group depends on the overlapping of the C-H bonds with the electron pair of the adjacent nitrogen atom (27,28). If we apply the Barfield and Grant relation to the observed difference of about -2.5c/s we obtain a value of about 11° (or 5°) for the angle between the methylene group and the adjacent π -bond. Assuming an angle of about 120° between the two methylene C-H bonds, in a planar ring the angle between the methylene group and the π -bond would have to be about 30° , corresponding to a ΔJ_{gem} value from -4.1 to -4.4c/s. The experimental ΔJ_{gem} value of -2.5c/s would seem to indicate a deviation from planarity for azetines, in disagreement with the results from spectra at different temperatures. But, as pointed out by Bhacca and Williams (25b), the Barfield and Grant relation should be applied with caution. Furthermore, the application to our case could be prevented by the fact that the original relation was established for systems $-\text{CH}_2-\text{C}=\text{X}$, different from our $-\text{CH}_2-\text{N}=\text{C}$ system.

EXPERIMENTAL

All the products were kindly supplied by Prof. E. Testa of Lepetit Research Laboratories.

The PMR data were obtained from spectra taken at 38° with a Varian A-60 (60Mc/s) spectrometer, in solution (10%) of the indicated solvents, with TMS as internal reference ($\tau = 10.00$ ppm). The coupling constant values were obtained directly from the spectra, averaging the results of at least three registrations. The chemical shift values were calculated using the formula (25c) for the deviation from the first-order treatment.

The PMR spectra were taken with a Varian HA-100 (100Mc/s) spectrometer at $+130^\circ$ and at $+30^\circ$ in hexadeuteriodimethyl sulphoxide solution (5%) and at $+30^\circ$ and -40° in tetradeuterio-methanol solution (2%), with TMS as internal reference, by courtesy of Miss Dr. A. Segre of the "Istituto di Chimica Industriale del Politecnico di Milano".

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