

Seven-membered Heterocyclic Rings

II. A Proton Magnetic Resonance Study of Slow Inversion in 4H-1,2-Diazepines*

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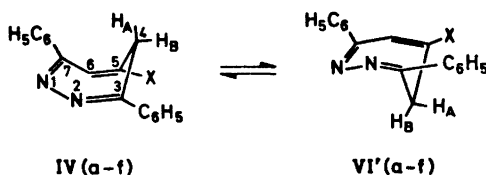
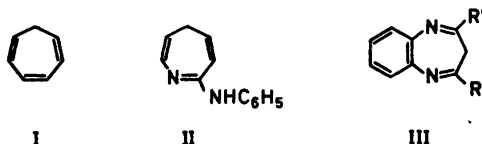
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The ^1H NMR spectra of a series of substituted 4H-1,2-diazepines (IVa-h) have been investigated. The compounds were found to exist in a non-planar configuration. Further, theoretical line shapes for exchange of two coupled protons have been calculated and the energy barriers (E_a , ΔG^\ddagger , ΔH^\ddagger , and ΔS^\ddagger) for inversion derived from a comparison of the theoretical spectra with the experimental ones. Substituents in the aryl group in the 5-position of the diazepines (IVa-f) have almost no effect on the energy barriers, whereas substitution in the 6-position of the seven-membered ring (IVg and IVh) increases the energy barriers by at least 5 kcal/mol.

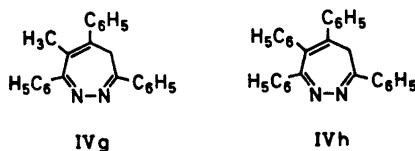
It has previously been shown, by proton magnetic resonance (^1H NMR) spectroscopy, that cycloheptatrienes (I),^{2,3} 3H-azepines (II),⁴ 3H-benz-[b][1,4]diazepines (III),⁴ and 4H-1,2-diazepines (IV)^{1,5} exist in non-planar boat forms. It was found^{1,3,4} that the free energies of activation for inversion at the coalescence temperature (ΔG_c^\ddagger) (e.g. $\text{IV} \rightleftharpoons \text{IV}'$ for 4H-1,2-diazepines) increased in the following way: $\text{I} < \text{II} < \text{III} < \text{IV}$ (Tables 1 and 2). The present paper describes a further examination of IV by ^1H NMR spectroscopy. The energy barriers in bromobenzene (Table 1) for interconversion ($\text{IV} \rightleftharpoons \text{IV}'$) between the two identical, equally stable boat conformations of a series of 3,5,7-triaryl-4H-1,2-diazepines (IVa-f) have been derived from rate constants obtained by a line shape analysis. Furthermore, lower limits of ΔG_c^\ddagger for 3,5,6,7-tetrasubstituted 4H-1,2-diazepines (IV g, h) have been estimated.

The magnetically non-equivalent methylene protons (H_A and H_B , IVa-f) form the AB part of an ABX system (H_X is the proton on C(6)). The long-range coupling constants, $^4J_{AX}$ and $^4J_{BX}$, are small (ca. 2 Hz) compared to the chemical shift differences, and the system is treated as an AB pattern in the line shape calculation. The theoretical line shapes were calculated using

* For Paper I in this series, see Ref. 1.



X		C ₆ H ₅		<i>p</i> CH ₃ C ₆ H ₄		<i>p</i> CH ₃ OC ₆ H ₄		<i>p</i> ClC ₆ H ₄		<i>p</i> NO ₂ C ₆ H ₄		<i>m</i> NO ₂ C ₆ H ₄
IV		a		b		c		d		e		f



the density matrix treatment of spin exchange evolved by Kaplan⁶ and Alexander.⁷ The actual equation used in the calculations was that derived by Heidberg *et al.*⁸

EXPERIMENTAL

The 4H-1,2-diazepines IVa-f were prepared according to the method described in the previous paper.¹ The 3-methyl-2,4,6-triphenylpyrylium and 2,3,4,6-tetraphenylpyrylium perchlorates were prepared according to a previously described method,¹² and the diazepines IVg and h were prepared from the pyrylium perchlorates as described in Ref. 1 (satisfactory analyses were obtained).

The 60 MHz ¹H NMR spectra were recorded using 5–10 % solutions in bromobenzene on a Varian A 60 A spectrometer equipped with a Varian variable temperature controller (V 6040) and a Varian 1024 time averaging computer. At each temperature, the spectra for the line shape analyses were recorded with 60–100 spectra accumulations. The spectrometer was operated with high response, slow sweep rate and the rf. level kept well below saturation in order to avoid distortions of the line shapes. The use of the spectra accumulation technique may give broadened lines if the field/frequency ratio drifts during a scan. The temperature was determined by measuring the chemical shift difference between the signals from CH₂ and OH protons of an ethylene glycol sample. This method for temperature determination gives uncertain values, but E_a is only dependent on the relative temperature measurements which were found to be correct within $\pm 1^\circ$ by repeated recordings of the spectrum of ethylene glycol over an extended period of time. Furthermore, the temperature dependence of ΔG^\ddagger is small, since ΔS^\ddagger is numerically small.

The 100 MHz spectra were recorded on a Jeol JMN-4H-100 spectrometer and the temperature was determined by measuring the chemical shift difference between the signals from the 2-CH₂ and OH protons of a 1,3-propanediol sample.

The chemical shift differences $\Delta_{AB} = \nu_A - \nu_B$ and the coupling constants J_{AB} , without exchange (Table 1), were determined as the mean values of several recordings

Table 1. Thermodynamic parameters

Compound	Δ_{AB}^b (Hz)	J_{AB}^c (Hz)	T_2^d (sec)	E_a (kcal/mol)	$\log A$ (sec ⁻¹)
IVa	109.02 ± 0.2	12.3 ± 0.2	0.106 ^g	19.63 ± 0.47	14.12 ± 0.28
IVa ^h	179.6 ± 0.2	12.25 ± 0.2	0.100 ^g	20.80 ± 0.71	14.53 ± 0.42
IVb	108.34 ± 0.2	11.9 ± 0.2	0.08 ^h	20.46 ± 0.84	14.54 ± 0.50
IVc	109.34 ± 0.2	12.0 ± 0.2	0.106 ^g	20.08 ± 0.73	14.33 ± 0.43
IVd	103.30 ± 0.2	12.0 ± 0.2	0.103 ^g	20.84 ± 0.55	14.77 ± 0.33
IVe	98.0 ± 0.2	12.6 ± 0.2	0.096 ^g	20.09 ± 0.91	14.26 ± 0.54
IVf	100.51 ± 0.2	12.2 ± 0.2	0.103 ^g	20.80 ± 0.93	14.75 ± 0.55
IVg ^f	67.6 ± 0.2	12.3 ± 0.2	—	—	—
IVh ^f	78.59 ± 0.2	11.94 ± 0.2	—	—	—

^a Derived from the temperature dependence of ¹H NMR spectra recorded with field sweep at 60 MHz in bromobenzene, except for compound IVa, which are recorded at both 60 and 100 MHz.

^b The chemical shift difference, without exchange, between the non-equivalent methylene protons. The methylene protons form the AB part of an ABX pattern. The signals from H_X and the aromatic protons are covered by the signals from the solvent. The chemical shifts of H_A and H_B are derived from an AB analysis.

^c The coupling constant, without exchange.

^d $T_2 = 1/\pi W$ (W (in Hz) = line width without exchange).

at 10°. The temperature was varied between -20° and +20°, in 10° intervals, to establish the dependence of Δ_{AB} and J_{AB} on temperature. No systematic change was found, and the line shape calculations were performed assuming Δ_{AB} and J_{AB} to be temperature independent. The 60 MHz spectra of IVa - f used for the line shape analyses were recorded in the temperature range 60 - 130°, at intervals of 10°, using the time averaging computer technique. The dependence of the spectrum of IVa on the temperature was also investigated at 100 MHz in the range 60 - 150°.

In the density matrix theory for spin exchange, T_2 is introduced to give the spectra without exchange (and very fast exchange) a finite line width, and is given by $T_2 = 1/\pi W$ (where W , in Hz, is the full line width, without exchange, at half maximum intensity). The two AB doublets, without exchange, are broadened by long range coupling with H_X, and they gave slightly different T_2 values due to a small difference between J_{AX} and J_{BX} . The T_2 values used in the line shape calculations were determined from either the high, or the low, field doublets and, accordingly, only the same part of the spectra were used in the comparison between experimental and calculated spectra below coalescence. It was assumed that the main reasons for the temperature dependence of W were changes in viscosity and homogeneity, which have the same effect on all lines in the spectrum. For this reason, W was corrected by the term ΔW_{ref} . (the change with temperature in the line width of the signal from TMS) at temperatures where the AB doublets were exchange broadened.

Determination of the rate constants and thermodynamic parameters. Equation (4) of Heidberg *et al.*⁸ was programmed for an IBM 7094 computer. The intensity of absorption as a function of the frequency was calculated for different values of the mean lifetime τ and

for inversion in 4H-1,2-diazepines.^g

T_c (°K)	ΔG_c^\ddagger (kcal/mol)	ΔH_c^\ddagger (kcal/mol)	ΔS_c^\ddagger (e.u.)	$\Delta G^\ddagger_{343^\circ\text{K}}$ (kcal/mol)	$\Delta H^\ddagger_{343^\circ\text{K}}$ (kcal/mol)	$\Delta S^\ddagger_{343^\circ\text{K}}$ (e.u.)
365.9 ± 1.6	17.55 ± 0.08	18.91 ± 0.47	3.7 ± 1.5	17.64	18.95	3.82
381.2 ± 3.0	17.97 ± 0.15	20.05 ± 0.72	5.45 ± 2.32	18.18	20.12	5.66
368.3 ± 2.8	17.68 ± 0.14	19.73 ± 0.85	5.56 ± 2.74	17.83	19.79	5.70
367.9 ± 2.5	17.65 ± 0.13	19.35 ± 0.74	4.60 ± 2.39	17.77	19.40	4.74
367.4 ± 1.8	17.68 ± 0.09	20.11 ± 0.56	6.62 ± 1.8	17.84	20.16	6.75
368.8 ± 3.1	17.78 ± 0.15	19.36 ± 0.92	4.30 ± 2.97	17.89	19.41	4.44
366.8 ± 3.0	17.66 ± 0.15	20.08 ± 0.93	6.56 ± 3.0	17.83	20.12	6.69
> 453	> 22.3	—	—	—	—	—
> 463	> 22.7	—	—	—	—	—

^e From ¹H NMR spectra recorded with field sweep at 100 MHz in bromobenzene-*d*₅.^f A line shape analysis could not be performed for compounds IVg and IVh because of too high coalescence temperatures and instability at high temperatures. The coalescence temperatures are assumed to be at least 10° higher than the values given in the Table, and the lower limits of ΔG_c^\ddagger are calculated, by the method used in Ref. 1, from spectra recorded at 60 MHz in nitrobenzene-*d*₅.^g T_2 values are calculated from the line width (*W*) of the high field AB doublet.^h T_2 values are calculated from the line width (*W*) of the low field AB doublet.

Table 2. Energy barriers for inversion of seven-membered ring systems.

Compound	Solvent	T_c (°C)	ΔG_c^\ddagger (kcal/mol)	Ref.
I	CF ₂ Cl ₂	-143	6.1	3
II	Pyridine- <i>d</i> ₅ / CH ₂ Cl ₂ (1:1)	-55 ± 10	10.2 ± 2	4
III	a: R = R' = C ₆ H ₅	0 ± 10	12.6 ± 6.5	4
	b: R = CH ₃ ; R' = C ₆ H ₅	-12 ± 7	12.2 ± 0.4	
	c: R = R' = CH ₃	-26 ± 8	11.7 ± 0.4	
	d: R = R' = C ₆ H ₅ CH = CH	-20 ± 10	11.7 ± 0.5	

compared with the experimental spectra in order to obtain the τ -values as a function of temperature (Fig. 1).The Arrhenius activation energy E_a for the interconversions IV \rightleftharpoons IV' (a-f) was obtained by the method of least squares, by fitting the rate constant (1/ τ) at a series of temperatures to the Arrhenius equation.

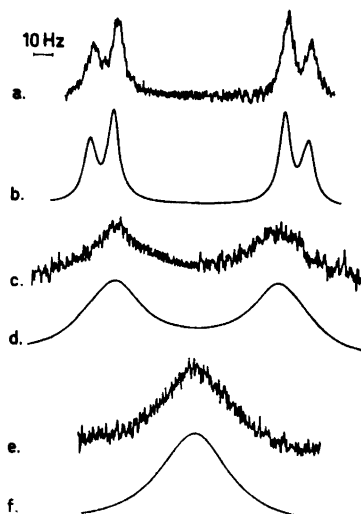


Fig. 1. Calculated and experimental spectra of 5-(*m*-nitro-phenyl)-3,5-diphenyl-4H-1,2-diazepine (IVf). a, c, e: experimental spectra at 60°, 80°, and 100°C, respectively. b, d, f; Calculated for $\tau = 0.071$, 0.011, and 0.0022 sec., respectively.

$$\ln(1/\tau) = \ln A - E_a/RT.$$

The free energies of activation, ΔG_T^\ddagger , were calculated from the Eyring equation (assuming unity for the transmission coefficient)

$$\Delta G_T^\ddagger = RT \ln(Tk\tau/h)$$

ΔH_T^\ddagger and ΔS_T^\ddagger are then given by

$$\Delta H_T^\ddagger = E_a - RT$$

$$\Delta S_T^\ddagger = (\Delta H_T^\ddagger - \Delta G_T^\ddagger)/T$$

Thermodynamic parameters for IV (a–f) were calculated for $T = T_c$ (coalescence temperature) and $T = 343^\circ\text{K}$ (τ_c was found from the computed line shapes and T_c from the Arrhenius equation). The limits were computed by conventional statistical methods,⁹ using 90% confidence limits for E_a and $\log A$. The thermodynamic parameters for IV (a–f) were calculated on an IBM 7094 computer.

T_c could not be reached for compounds IVg and h, and lower limits for ΔG_c^\ddagger were estimated by the method used in Ref. 1.

RESULTS AND DISCUSSION

The thermodynamic parameters for 3,5,7-triaryl-4H-1,2-diazepines (IVa–f), and lower limits of ΔG_c^\ddagger for 3,5,6,7-tetrasubstituted 4H-1,2-diazepines (IVg, h), are given in Table 1. A plot of $\log(1/\tau)$ versus $10^3/2.3026 RT$ for IVa is shown in Fig. 2. The limits for the energy barriers given in Table 1 include only standard deviations from the least squares treatment. The true errors are greater because the reliability of the τ -values is influenced by uncertainties in the determination of the parameters (Δ_{AB} , J_{AB} , T_2) used in the line shape calculations. The observation that Δ_{AB} and J_{AB} are temperature independent at low temperatures (-20° to $+20^\circ$) does not exclude the possibility of these parameters being temperature dependent in the range

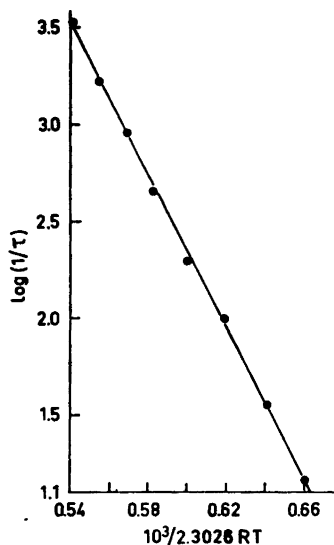


Fig. 2. A graph of $\log(1/\tau)$ versus $10^3/2.3026RT$ for 3,5,7-triphenyl-4H-1,2-diazepine (IVa)

(60°–130°) used in the calculations. Although T_2 was corrected for changes in viscosity and homogeneity, the values may also be temperature dependent due to changes in relaxation times and long-range coupling constants. The T_2 -values were determined from the line width of one of the AB doublets, and accordingly, because $J_{AX} \neq J_{BX}$, a different value should have been used above T_c . The error introduced by neglect of this is small since J_{AX} , J_{BX} , and $J_{AX} - J_{BX}$ are numerically small and because the effect of changes in T_2 on the exchange rates is inversely proportional to Δ_{AB} (which is large for the 4H-1,2-diazepines) and, furthermore, is less pronounced at fast rates.¹⁰

The equation applied in the calculation of the theoretical line shapes is not truly valid for the 4H-1,2-diazepines (IVa–f) since H_A and H_B couple with H_X , but the errors introduced are probably small because the chemical shift differences are large and the long range coupling constants small.

The good agreement between the energy barriers determined from 60 MHz and 100 MHz spectra (Table 1), the agreement between experimental and calculated line shapes (Fig. 1), and the pronounced linearity of the Arrhenius plots at all temperatures, justify the assumptions used in the calculations. It is, therefore, believed that the energy barriers given in Table 1 are reliable.

The energy barriers of the 4H-1,2-diazepines (IVa–f) show no systematic dependence on mesomeric or inductive effects of the aryl group in the 5-position, whereas the introduction of a methyl or phenyl group in the 6-position increases the inversion barrier by at least 5 kcal/mol. A similar effect of substitution on inversion barriers has been observed for 3H-benz[1,4]diazepines (III)⁴ and benzodiazepinones.¹¹ This increase in the energy barriers caused by introducing additional substituents is probably due to an increase in the energy of the transition state brought about by increasing steric interaction between the substituents in the planar transition state.

A comparison of the energy barriers for compounds I, II, III (Table 2), and IV (Table 1) seems to indicate that the barriers increase with the number of nitrogen atoms in the seven-membered ring. However, because the compounds I, II, III, and IV are differently substituted, the increase in ΔG_c^\ddagger in the order I < II < III < IV is, in view of the dependence of the inversion barriers on substitution, more probably due to an effect of the substitution pattern, rather than to the number of nitrogen atoms.

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REFERENCES

1. Buchardt, O., Pedersen, C. L., Svanholm, U., Duffield, A. M. and Balaban, A. T. *Acta Chem. Scand.* **23** (1969) 3125.
2. Conrow, K., Howden, M. E. H. and Davis, D. *J. Am. Chem. Soc.* **85** (1963) 929.
3. Anet, F. A. L. *J. Am. Chem. Soc.* **86** (1964) 458.
4. Mannschreck, A., Rissmann, G., Vögtle, F. and Wild, D. *Chem. Ber.* **100** (1967) 335.
5. Balaban, A. T. *Tetrahedron* **24** (1968) 5059.
6. Kaplan, J. I. *J. Chem. Phys.* **28** (1958) 278; **29** (1958) 462.
7. Alexander, S. *J. Chem. Phys.* **37** (1962) 967, 974.
8. Heidberg, J., Weil, J. A., Janusonis, G. A. and Anderson, J. K. *J. Chem. Phys.* **41** (1964) 1033.
9. Bennett, C. A. and Franklin, N. L. *Statistical Analysis in Chemistry and the Chemical Industry*, Wiley, New York 1954, p. 227.
10. Allerhand, A., Gutowsky, H. S., Jonas, J. and Meinzer, R. A. *J. Am. Chem. Soc.* **88** (1966) 3185.
11. Linscheid, D. and Lehn, J. - M. *Bull. Soc. Chim. France* **1967** 992.
12. van Allan, J. A. and Reynolds, G. A. *J. Org. Chem.* **33** (1968) 1104.

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