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CONFORMATIONAL ISOMERIZATION IN HEXAHYDRO-*S*-TRIAZINES AND HEXAHYDROPYRIMIDINES

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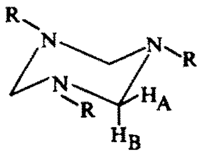
Abstract—The thermodynamic activation parameters have been determined for a series of hexahydro-*s*-triazines, 1,3-dimethylhexahydropyrimidine and its methyl iodide salt using NMR to determine the rate constants for chair-to-chair isomerization. Values of E_a, ν_a, $\Delta F^\ddagger$, $\Delta H^\ddagger$, and $\Delta S^\ddagger$ are reported. Both steric and electronic effects are investigated and their influences on the activation parameters and reaction paths discussed.

WITHIN the past five years there have been many reports of conformational isomerization in cyclic systems studied kinetically by NMR.[1] There are, however, restrictions on suitable systems for study. The experimental conditions require that the isomerization activation energy lie in the 7–20 kcal/mole range. The NMR spectrum itself should be relatively simple for accuracy in the results. Theoretical treatments for two-site exchange of uncoupled and coupled nuclei have been developed, and the experimental restrictions on these treatments defined.[2]

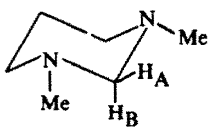
Both substituted cyclohexanes and heterocyclic compounds have received much attention. The 1,2-dioxanes and -dithianes,[3a, b] 1,3-dioxanes,[4a] -dithianes,[4b] and -oxathianes[3b] have been studied. In the 6-membered nitrogen heterocycles piperazines,[5a, b] tetrahydropyridiazines,[6] hexahydro-*s*-triazines,[7a, b] and hexahydropyrimidines[7a] have been reported. The nitrogen systems are unique since the substituent on N may be varied and its effect on the thermodynamic activation parameters measured. The hexahydro-*s*-triazines are well-suited for such a study since the ring methylene protons display an AB-type NMR spectrum. The compounds are readily synthesized from a primary amine and formaldehyde to form the aldimine which trimerizes. The study of conformational isomerization in this series also is of interest as heretofore no 6-membered ring containing three N atoms has received thorough investigation.

The spectra of 1,3-dimethylhexahydropyrimidine and its monomethyl iodide salt were also studied to ascertain the effect of quaternization of N on the thermodynamic activation parameters.

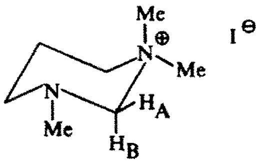
Compounds Ia–d were chosen for study as both steric and electronic effects of the N substituents could be measured. At room temperature the NMR spectra of the methylene protons were singlets for Ia–d. At lower temperatures (~ −60°) the spectra of Ia–c were well-resolved quartets, but the methylene protons of Id were a slightly broadened singlet. The signals for the substituents on N did not appear to change with temperature which indicates that the N inversion is very rapid at these temperatures. The temperature dependency of the spectra of Ia–c is attributed to intramolecular exchange of the axial and equatorial hydrogens on a ring undergoing



I



IIa



IIb

Ia, R = Me
b, R = Et
c, R = Pr
d, R = Ph

chair-to-chair conformational isomerization. The spectral properties of Ia–c and IIa–b are listed in Table 1.

TABLE 1. NMR SPECTRA* OF SUBSTITUTED HEXAHYDRO-*s*-TRIAZINES AND HEXAHYDROPYRIMIDINES

Compound	$\delta\nu_{AB}$, Hz ppm	J, Hz	T, °K	Observed Range, °K†
Ia	52·8 (0·88)	10·2	229	229–293
Ib	63·8 (1·05)	10·1	217	217–294
Ic	54·5 (0·91)	10·1	213	213–271
IIa	77·7 (1·30)	8·8	201	201–273
IIb	34·8 (0·58	9·2	213	213–288

* All compounds in $CDCl_3$ solution.

† The NMR spectra displayed temperature dependence over the observed range.

Of interest is the magnitude of the chemical shift $\delta\nu_{AB}$ for these compounds. Lambert and Keske[8] have compared the chemical shifts of the α-methylene protons in N-methylpiperidine C 0·942 ppm) and its HCl-salt (0·518 ppm) with cyclohexane (0·462 ppm) and concluded that an axial lone pair on N increases $\delta\nu_{AB}$ more than an equatorial lone pair. The chemical shifts of Ia–c and IIa indicate that the lone pairs in these compounds show conformational preference for the axial position as would be expected from 1,3,5 steric repulsion of alkyl groups axially oriented. Models indicate severe repulsions would exist for axially substituted N in both types of compounds. The effect of quaternization is seen in IIb to decrease $\delta\nu_{AB}$ to a value close to that of cyclohexane and N-methylpiperidinium hydrochloride although the methylene group is still vicinal to an axially oriented lone pair. Such a decrease in $\delta\nu_{AB}$ is surprising in view of the influence exerted by an axial lone pair in previously studied systems. With the Me group of the tertiary N restricted to an equatorial position the principle[9] postulated for the enhancement of chemical shift (interaction of an axial lone pair with the *anti*-coplanar $\sigma^*(C–H_{axial})$ orbital)) should operate more efficiently resulting in a larger $\delta\nu_{AB}$ than that observed. Such an observation provokes speculation as to the validity of applying this principle as a tool for conformational analysis.

The absolute value of J is seen to decrease in going from Ia to IIa. Such a change can be indicative of an increase in ring strain due to change in valence bond angles and could account for the differences in $\delta\nu_{AB}$ in these compounds. Quaternization in other systems has been shown to increase the absolute value of J.[10]

The values for E_a, $\Delta F^{\ddagger}$, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, T_c (the temperature at which the quartet coalesces to a singlet), and k_c (the rate constant at T_c) are given in Table 2. Free energy and entropy activation parameters are reported for chair-to-chair (subscript *cc*) and chair-to-boat (subscript *cb*) interconversions. It is assumed that an intermediate similar to the boat or twist boat form as in cyclohexane exists in the isomerization process.[11]

In discussing the triazines it is noted that the trimethyl compound Ia possesses higher activation parameters than those of cyclohexane.[11] It is not surprising that these values lie close to the cyclohexane values or that the values are larger.[*] Because of the symmetry of the N positions in the molecule, the valence angle strain contribution is held to a minimum. Steric interactions between the groups on N must be considered since ring inversion is slow compared to the isomerization on N. These 1,3,5-interactions should play an important role in determining the energy and reaction pathway for the izomerization. If the steric interaction and valence angle strain are minimal, then the main contribution to the activation energy would be the increase in torsional strain ("bond opposition"). Torsional strain is known to be higher about C–N bonds than about C–C bonds if the N is di-substituted.[12] The step-wise decrease in E_a, $\Delta F^{\ddagger}$, and $\Delta H^{\ddagger}$ might be attributed to increases in the energy of the ground state due to the steric demands of the alkyl groups during the N inversion process. The Ph substituted compound Id could possess the highest energetic ground state or $\delta\nu_{AB}$ could be of such a low value that T_c lay below our experimental limits.[†] A resonance interaction of the benzene ring with the N lone pair should affect the valence angles of the ring bond framework and increases the ring strain resulting in a higher ground state or the anisotropy of the benzene rings could reduce the magnetic non-equivalence of the axial and equatorial positions.

The hexahydropyrimidines display parameters lower than those of Ia. This is to be expected as isomerization should be more easily effected with the removal of a N-methyl group reducing some torsional energy requirements. From observations on the coupling constants, the increase in ring strain relative to Ia should also contribute to reducing the activation energy. Quaternization raises the free energy of activation considerably reflecting the change of N hybridization.

The values for the entropies of activation enable one to postulate a conformation for the barrier form. If one assumes a chair ground state (C_{3v}) for the hexahydro-*s*-triazines and considers that reaction path degeneracies are the main contributions to the activation entropy, then the experimental values may be compared with those calculated from $\Delta S^{\ddagger} = R \ln n$ where n represents the number of distinct paths for reaching the transition state. This number may be determined from the considerations of Schlag[14] on symmetry and reaction rates.[‡] For a chair ground state and assuming

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[*] Although the E_a values have been reported for N-methyl piperidine and N,N′-dimethylpiperazine, it is not valid to predict a value for Ia as different solvents were used for each compound. An interesting study would be an investigation of trends in activation energies with heteroatom substitution using the same solvent.

[†] A decrease in $\delta\nu_{AB}$ could greatly reduce T_c. For example, acetone diperoxide posseses $\delta\nu = 26{\cdot}5$ Hz and $T_c = 303$°K, but duplodithioacetone on lowering to 115°K shows no resolution of M_2 signals which is indicative of a small $\delta\nu$ between the methyl signals.

[‡] It was kindly pointed out to us by Dr. R. K. Harris that our calculation of $\Delta S^{\ddagger}_{cb}$ for Ia which appears in Ref. 7*b* is wrong because of a misinterpretation of statistical weight factors in the Harris equation for $\Delta S^{\ddagger}$. Calculated values for $\Delta S^{\ddagger}$ elsewhere in the literature using this equation may require recalculation.

TABLE 2. THERMODYNAMIC ACTIVATION PARAMETERS FOR CONFORMATIONAL ISOMERIZATION

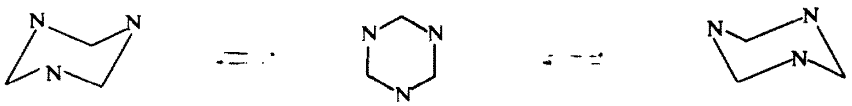
Compound[a]	Ia	Ib	Ic	IIa	IIb	Cyclohexane[d]-d_{11}
T_c, K	269·5 ± 0·5[b]	256·8 ± 0·5	242·0 ± 0·5	242·8 ± 0·5	254·0 ± 0·5	211·8
E_a, kcal/mole	14·6 + 0·2	13·3 ± 0·1	12·1 ± 0·1	11·4 ± 0·1	11·9 ± 0·1	
γ_0, sec^{-1}	8·5 × 10^{13}	2·8 × 10^{13}	1·0 × 10^{13}	3·0 × 10^{12}	1·4 × 10^{12}	
$\Delta F^{\ddagger}_{cc}$, kcal/mole	12·8 ± 0·1	12·1 ± 0·1	11·4 ± 0·1	11·6 ± 0·1	12·5 ± 0·1	
$\Delta F^{\ddagger}_{cb}$, kcal/mole[c]	12·5 ± 0·1	11·8 ± 0·1	11·1 ± 0·1	11·3 ± 0·1	12·2 ± 0·1	10·22
$\Delta S^{\ddagger}_{cc}$, e. u.	3·7 ± 0·7	1·3 ± 0·5	−0·6 ± 1·0	−4·3 ± 0·6	−5·8 ± 0·6	
$\Delta S^{\ddagger}_{cb}$, e.u.	5·1 ± 0·7	2·7 ± 0·5	0·8 ± 1·0	−2·9 ± 0·6	−4·4 ± 0·6	2·8 ± 0·5
$\Delta H^{\ddagger}$, kcal mole	14·1 ± 0·2	12·8 ± 0·1	11·6 ± 0·1	10·9 ± 0·1	11·4 ± 0·1	10·8 ± 0·1
k_c, sec^{-1}	125	140	131	176	87	64

[a] Compounds Ia–c, IIa 15% in $CDCl_3$ with 4% TMS (w/v) in sealed tube under N; IIb 5% in $CDCl_3$ with 10% CH_2Cl_2 added as reference.

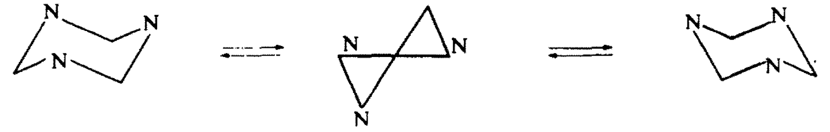
[b] All errors are reported as statistical probable errors except those for C_6HD_{11} which are subjectively estimated.

[c] These values are in agreement with those in Ref. 7*a*; $\Delta F^{\ddagger}$ and $\Delta S^{\ddagger}$ values evaluated at coalescence temp.

[d] In CS_2, values taken from Ref. 11.



a planar transition state ($\mathbf{D}_{3h}$), $\Delta S^\ddagger = \mathrm{R} \ln \frac{1}{2}$ or $-1{\cdot}4$ eu. Using a "cyclohexene-like" or half-chair transition state $\Delta S^\ddagger = \mathrm{R} \ln 12$ or $4{\cdot}9$ eu. This value is very close to the experimental $\Delta S^\ddagger$ for Ia and Ib. The validity of using differences in symmetry of ground and transition state forms as a basis for interpretation of conformational isomerization mechanisms has been the subject of current controversy. The calculated entropy which accounts for reaction path degeneracies should be valid if differences in vibrational and rotational entropies of the ground and transition states are small. Anet and Bourn[11] have presented reasonable evidence that symmetry arguments are valid in cyclohexane isomerization and that rotational and vibrational contributions are minimal. It is likely that these arguments apply to hexahydro-*s*-triazine isomerization, and that a half-chair describes the transition state.



For IIa the chair form possesses only a plane of symmetry ($\mathbf{C}_s \equiv \mathbf{C}_{1h}$). A planar transition state ($\mathbf{D}_{1h}$) requires $\Delta S^\ddagger = \mathrm{R} \ln \frac{1}{2}$ or $-1{\cdot}4$ eu while a half chair state (no elements of symmetry) requires $\Delta S^\ddagger = \mathrm{R} \ln 4 = 2{\cdot}8$ eu. Clearly, other contributions to $\Delta S^\ddagger$ must be operative for the hexahydropyrimidines. For the experimental and calculated values of IIa to agree would require inclusion of $\Delta S^\ddagger$ of $-1{\cdot}5$ eu (for a planar transition state) or $-5{\cdot}7$ eu (for a half-chair transition state) as vibrational and rotational contributions.

A measure of these contributions can be ascertained from the parameters for isomerization in IIb. Here the $\Delta S^\ddagger_{cb} = 0$ from symmetry considerations as the isomerization could only take one distinct path. From the experimental value we can attribute $-4{\cdot}4$ eu to the rotational-vibrational contribution in this system. Assuming this to approximate the rotational-vibrational contribution in IIa, the adjusted experimental value for $\Delta S^\ddagger_{cb}$ due to dissymmetry contributions is equal to $\Delta S^\ddagger_{cb}$ (IIa) $-\Delta S^\ddagger_{cb}$ (IIb) $=$ $1{\cdot}5$ eu. While this value lies below that calculated from differences in group symmetry, there is nonetheless close agreement of the experimental $\Delta S^\ddagger_{cb}$ with the calculated entropy for a half-chair transition state.

EXPERIMENTAL

A Varian A-60 NMR spectrometer equipped with a V-6057 variable-temp probe was used for these determinations. The recorder was calibrated before each experiment. The "methanol thermometer" technique was used before and after each spectrum was recorded. A sweep rate of 0·25 Hz/sec and a r.f. field of 0·05 milligauss were used in order to approximate steady-state, unsaturated conditions.

The isomerization activation energy was calculated using the Arrhenius equation

$$k = \nu_o e^{-E_a/RT}$$

where k is the isomerization rate constant for chair-to-chair interconversion, ν_0 the frequency factor, and E_a the isomerization activation energy. The rate constants were obtained from the analysis of the line spectrum for each compound over the temp ranges listed in Table 1. Experimental spectra were recorded every 5 degrees over the listed range and then compared to the computer-generated line shape obtained from the quantum mechanical expression for two coupled nuclei undergoing chemical exchange.[15] In order to carry out the comparison, the computer was presented with the experimental spectrum and a guessed value for the rate constant. After normalization theoretical spectra were generated at regular intervals about the guessed rate constant and the intensities were compared to the intensities of the experimental spectrum by the least equares method. The rate constant, k,* and the theoretical spectrum for the best fit were then printed. An Arrhenius plot of log k versus $10^3/T$ gave a straight line with a slope of $-E_a/2{\cdot}303R$.

The computer program requires input data of $\delta\nu_{AB}$, J, and the natural linewidth, W_{nat}, in the absence of exchange. According to Schmid *et al.*,[3b] the total or observed linewidth, W_{total}, is comprised of broadening contributions from exchange, W_E, from the fluctuating magnetic fields of neighboring nuclei (relaxation broadening), W_R, from long range coupling with other nuclei, W_C, and from inhomogeneity of the external magnetic field, W_I. Thus $W_{total} = W_E + W_R + W_C + W_I$. W_{nat} is also defined as W_R. Most past treatments have neglected to incorporate possible temperature variation of the natural linewidth. It has been shown that the activation energy is systematically determined to be too small if the variation in $W_{nat.}$ is not considered. The procedure used to determine the natural line-width parameter at each temperature is described in Ref. 3*b*.

The enthalpies of activation were obtained from

$$\Delta H^{\ddagger} = E_a - RT$$

The Eyring formulation of a rate process yielded the free energies of activations

$$k = \kappa(k/2h)\,BT\,e^{-\Delta F^{\ddagger}/RT}$$

or

$$\Delta F^{\ddagger} = 2{\cdot}303\,RT\,(10{\cdot}32 + \log T - \log k + \log \kappa)$$

where κ, the transmission coefficient, is equal to one for the chair-to-chair process. With κ as one it has been assumed that all molecules continue the isomerization process to completion. The chair-to-boat values were calculated using a $\kappa = \frac{1}{2}$ where it is assumed that if a metastable intermediate exists in the isomerization process, the intermediate has an equal chance of passing to either ground state conformation.

The entropy values were calculated from

$$\Delta S^{\ddagger} = (\Delta H^{\ddagger} - \Delta F^{\ddagger})/T$$

The calculations were performed by an IBM 7044 computer using modified programs kindly provided by Professor Adam Allerhand. Ten minutes of computer time were required for the analysis of each compound.

Compounds Ia–d,[16] Ib,[17] and Ic,[18] Id,[19] and IIa,[20] were prepared by established methods, possessed acceptable b.p. or m.p., and had NMR spectra in agreement with their structure.

N,N,N'-*Trimethylhexahydropyrimidinium iodide.* To an ether solution of 2·3 g Ia was added 2·8 g Me. A white ppt formed immediately. The product was filtered, washed with dry ether, dried *in vacuo*, and gave a quantitative yield, m.p. 153–154°. (Found: C, 33·02; H, 6·83. $C_6H_{17}IN_2$ requires: C, 32·80; H, 6·69%.)

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* Errors in k (and log k) cannot be accurately determined from the program but are subjectively estimated not to contribute appreciably to the deviation of the Arrhenius plot. Accurate values of k_c were determined from calculation of theoretical spectra representing coalescence using a program written by Dr. M. Saunders for the Alexander equation.

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