Conformational Isomerization of Hexahydro-1,3,5-trimethyl-1,3,5-triazine[1]

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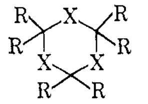
Abstract: The ^{1}H high-resolution spectrum of hexahydro-1,3,5-trimethyl-1,3,5-triazine has been observed at temperatures from −58 to +42°. The rate of conformational isomerization was determined by a complete line-shape analysis method over the temperature range −26 to +42°. From these rates the activation parameters $\Delta H^{\ddagger}_{cc}$, $\Delta G^{\ddagger}_{cc}$, and $\Delta S^{\ddagger}_{cc}$ were determined to be 15.2 ± 0.2 and 13.2 ± 0.2 kcal/mole and 7.5 eu, respectively, at the coalescence temperature of 268.1°K. It is proposed that the mechanism of conformational isomerization involves inversion of the ring in synchronism with inversion of one or two of the nitrogen atoms, followed or proceeded by a fast inversion of the other nitrogens. *s*-Trioxane and hexamethyl-1,3,5-trithiane were studied also. The isomerization rate of *s*-trioxane proved to be too fast for measurement and that of HMTT too fast for a complete study. However, spin-echo measurements of the latter gave an approximate value of 8 kcal/mole for $\Delta G^{\ddagger}_{cc}$.

Chair-to-chair isomerization has been studied in a number of heterocyclohexanes with the heteroatoms in different ring positions.[3] However, very little is known[4] about the activation parameters for the inversion of type I rings.



I, R = H, CH$_3$
X = O, S, N-R′

The symmetric disposition of the heteroatoms in these molecules makes them well suited for investigating the influence of the heteroatoms on the activation parameters for ring inversion. In particular they may prove useful in establishing effects of the C–X bonds on the barrier to inversion because, unlike the well-studied dioxanes, they contain only C–X bonds in the backbone.

Spin-echo methods as well as line-shape analysis of high-resolution nmr spectra have proved to be useful[5] for the study of chemical exchange processes such as the conformational isomerization of I. However, although we examined three compounds of type I (Ia, R = H, X = O; Ib, R = CH$_3$, X = S; and Ic, R = H, X = NCH$_3$), this paper deals mainly with a high-resolution, temperature-dependence study of Ic, hexahydro-1,3,5-trimethyl-1,3,5-triazine (HTMT). The isomerization of *s*-trioxane (Ia) proved to be too fast for study by means of either high-resolution[6] or spin-echo methods. And although the isomerization is slower in hexamethyl-1,3,5-trithiane (Ib), it is still so fast that only semiquantitative results could be obtained from a spin-echo study. In the case of Ic (HTMT) only part of the protons participate in the exchange so spin-echo measurements were not attempted.

There is evidence[7] that the free energy of activation, $\Delta G^{\ddagger}_{cc}$, for isomerization of six-membered rings containing one or two nitrogen atoms is somewhat higher than for the corresponding hydrocarbons. Thus, activation parameters for the inversion of HTMT bear on the question of the manner in which the nitrogen atoms influence the ring-inversion process. A special point of interest in the study of HTMT is that, in addition to the chair-to-chair ring inversion, the nitrogen atoms may also undergo inversion, and we consider the relationships between the two inversion processes.

Experimental Section

Materials. *s*-Trioxane (Ia) was purchased from Matheson Co., Joliet, Ill., and crystallized twice from ethyl alcohol and petroleum ether. The hexamethyl-1,3,5-trithiane (Ib) was prepared by condensation of hydrogen sulfide and acetone[8] and purified by fractional distillation. Solutions for spin-echo measurements were made using CS$_2$ from Fisher Scientific Co., Fair Lawn, N. J.

The sample of HTMT was prepared by condensation of methylamine hydrochloride with formaldehyde.[9] The condensation product was purified by distillation at atmospheric pressure until its proton resonance spectrum showed no impurity peaks. Solutions were made using Genetron 21 (CHFCl$_2$) from Matheson Co., Joliet, Ill., and CDCl$_3$ from Tracerlab, Waltham, Mass.

All solutions were degassed *in vacuo*. They were 30% v/v solutions, except that for HTMT at 248°K a substantial increase in viscosity was observed and 20% v/v solutions were used below this temperature.

Apparatus and Procedures. The high-resolution spectra were recorded on a Varian Associates Model A-60 nmr spectrometer equipped with a V-6057 variable-temperature accessory. Temperatures were determined using a copper–constantan thermocouple inserted in a dummy sample tube. Temperature readings were taken before and after each measurement. The samples were allowed at least 10 min to attain thermal equilibrium before spectra were recorded. The spectra were calibrated by the usual side-band techniques using a Hewlett-Packard Model 200 CD audio oscillator and a Model 521C frequency counter. The spin-echo apparatus

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[2] NATO Fellow on leave of absence from the Istituto di Chimica Generale e Inorganica, Naples, Italy.

[3] (a) F. A. Bovey, E. W. Anderson, F. P. Hood, and R. L. Kornegay, *J. Chem. Phys.*, **40**, 3099 (1964); (b) J. B. Lambert and R. G. Keske, *J. Am. Chem. Soc.*, **88**, 620 (1966); (c) R. K. Harris and R. A. Spragg, *Chem. Commun.*, 314 (1966); (d) F. G. Riddell and J. M. Lehn, *ibid.*, 375 (1966); (e) R. F. Farmer and J. Hamer, *ibid.*, 866 (1966).

[4] In ref 3d and e, which appeared while this work was being completed, values are reported for $\Delta G^{\ddagger}_{cc}$ of hexahydro-1,3,5-trimethyl-1,3,5-triazine, which are in good agreement with our results.

[5] A. Allerhand, H. S. Gutowsky, J. Joans, and R. Meinzer, *J. Am. Chem. Soc.*, **88**, 3185 (1966).

[6] J. E. Anderson and J. C. D. Brand, *Trans. Faraday Soc.*, **62**, 39 (1966).

[7] L. W. Reeves and K. O. Strømme, *J. Chem. Phys.*, **34**, 1711 (1961); see also ref 3b and c, and references cited therein.

[8] H. Böhme, H. Pfeifer, and E. Schneider, *Ber.*, **75b**, 900 (1942).

[9] J. Grayremo, *J. Chem. Soc.*, **125**, 2283 (1924).

and procedures were those described previously;[10] a proton resonance frequency of 26.85 MHz was employed.

Results and Discussion

Hexamethyl-1,3,5-trithiane. For this compound it was not possible to reach a low enough temperature, in the liquid state, to freeze out the exchange and measure the chemical shift between the methyl group protons in the exchanging axial and equatorial sites. Spin-echo measurements of the apparent transverse relaxation rate $R_2 = 1/T_2$ gave values which increased only slightly (~20%) with increasing separation of the radiofrequency pulses in the Carr–Purcell train over the accessible ranges of temperature and pulse spacing.[10] Nonetheless, the total transverse relaxation rate of ~3.3 sec^{-1} at low temperatures (−100°) and large pulse separation is dominated by the chemical exchange and can be used to determine the exchange rate if the axial–equatorial chemical shift $\Delta\nu_{ae}$ is known.

A reasonable estimate of $\Delta\nu_{ae}$ between the axial and equatorial methyl group protons is obtained by assuming it to be the same as that observed in the α isomer of 2,4,6-trimethyl-1,3,5-trithiane.[11] This gives a value of approximately 9 Hz for $\Delta\nu_{ae}$ at our observation frequency of 26.85 MHz. By combining this value for the chemical shift with the value of $R_2 = 3.3$ sec^{-1} at −100°, we estimate[10] the exchange rate $k = (1/2\tau)$ to be 150 sec^{-1}. This leads to a value of about 8 kcal/mole for $\Delta G^{\ddagger}_{cc}$ at −100°. This result is somewhat lower than the $\Delta G^{\ddagger}_{cc}$ values in the neighborhood of 10 kcal/mole found for cyclohexane and several of its derivatives[3a] and for some 1,3-dioxanes.[6]

Hexahydro-1,3,5-trimethyl-1,3,5-triazine (HTMT). The methylene part of the proton high-resolution spectrum of this compound observed at low temperature (−60°) is an AB quartet centered at τ 3.146 ± 0.005 ppm. All four peaks are rather broad, even at very low temperatures where the exchange broadening must be negligible. This residual broadening is attributed to unresolved coupling with the α-^{14}N nuclei and with protons in the other methylene groups. The two downfield lines are somewhat broader than the upfield pair, as in the case of 1,3-dioxane.[6] The difference is probably due to the so-called W stereochemical arrangement[12] of two equatorial protons and serves as a basis for assigning the downfield doublet to the equatorial protons.

The apparent geminal coupling constant J_{AB} and the axial–equatorial chemical shift $\Delta\nu_{ae}$, at 60 MHz, were measured for several temperatures between 245 and 215°K in a 20% v/v solution with $CHFCl_2$. As the temperature is lowered, the values increase monotonically from 10.0 to 10.2 Hz and from 53.15 to 53.8 Hz, respectively, with probable errors of ±0.1 Hz. The center of gravity of the methylene quartet and of the coalesced line is independent of temperature. The large chemical shift $\Delta\nu_{ae}$ is probably due to an all-equatorial conformation of the three methyl groups.[3b] However, solvent effects of the type suggested by Harris and Spragg[3c] cannot be excluded.

At all temperatures employed in the experiments, the N-methyl portion of the proton spectrum consists of a single peak centered at τ 2.237 ± 0.005 ppm, which becomes slightly broadened at lower temperatures. In principle, such broadening might be due to exchange of the methyl groups between axial and equatorial positions. However, if this were so, the relative populations of the axial and equatorial positions would change sufficiently with temperature to give an observable temperature dependence to the N-methyl proton shift, counter to the fact that the chemical shift is independent of temperature within experimental error. So, most likely the apparent broadening results from unresolved long-range coupling with the exchanging methylene protons. When the exchange is fast, the fine structure has a binomial type intensity distribution; but when it is slow, unequal coupling to the axial and equatorial protons could give a "flatter" intensity distribution and a less sharply peaked "line."

Exchange Rates and Activation Parameters for HTMT. The determination of the conformational exchange rate was based on the temperature dependence of the methylene part of the spectrum. In calculations of the rates, the three methylene groups were treated as a single coupled AB system. This ignores coupling with the ^{14}N two bonds away and neglects long-range coupling among the methylene groups themselves. It has been shown,[5] however, that the influence of such couplings is important only for very large or very small values of the exchange rates. It was not possible to actually measure the values of these couplings and no attempt was made to account for their influence in the calculation. However, the very small and very large exchange rates were not used in deriving the activation parameters.

The errors connected with the use of single parameter methods in the derivation of exchange rates can be quite large.[5] Accordingly a complete line-shape analysis method was used. It is similar to that described previously,[13] the main difference being in the type of computer program employed to compare theoretical and experimental absorption intensities. For the present work, the program was modified so that approximate errors could be established for the rates determined. This was accomplished by means of a least-squares treatment of the digitized experimental spectrum. A weighting factor was assigned to each of the coordinates of the digitized absorption intensities. This factor takes into account the errors connected with the digitization of the spectra, the noise level, and, at least partially, the various kinds of instrumental distortions and broadening. The iterative procedure used to obtain a satisfactory convergence was the one suggested by Strand, Kohl, and Bonham.[14]

The rates and their standard deviation as determined from the line-shape analysis are given in Table I, along with the corresponding $\Delta G^{\ddagger}_{cc}$'s calculated by means of the Eyring formulation. The rates determined outside the temperature range −26 to +42° were not included in the least-squares treatment of the Arrhenius equation which gave the plot of Figure 1 and the activation parameters summarized in Table II. It is seen that the

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[10] A. Allerhand and H. S. Gutowsky, *J. Chem. Phys.*, **41**, 2115 (1964); **42**, 1587 (1965).

[11] E. Campaigne, N. F. Chamberlain, and B. E. Edwards, *J. Org. Chem.*, **27**, 135 (1962).

[12] A. Rassat, C. W. Jefford, J. M. Lehn, and B. Waegell, *Tetrahedron Letters*, 233 (1964).

[13] J. Jonas, A. Allerhand, and H. S. Gutowsky, *J. Chem. Phys.*, **42**, 3396 (1965).

[14] T. G. Strand, D. A. Kohl, and R. A. Bonham, *ibid.*, **39**, 1307 (1963).

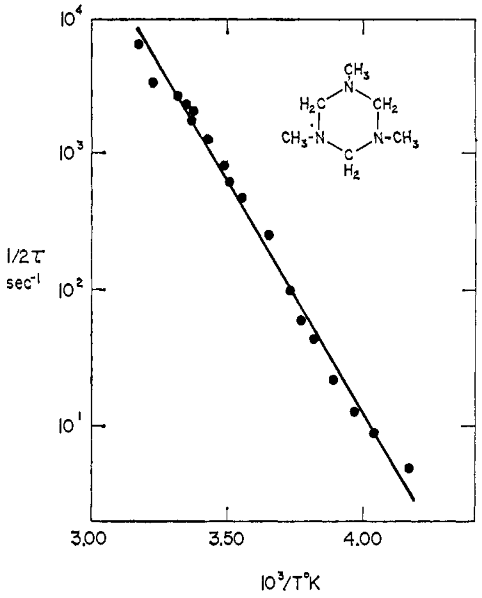


Figure 1. An Arrhenius plot of the conformational isomerization rate of HTMT as obtained from an nmr complete line-shape analysis.

standard deviations of the individual rates are about ±5%, and the errors in the activation parameters are modest, being ±0.2 kcal/mole. Nonetheless, the value for $\Delta S^{\ddagger}_{cc}$ is 7.5 eu/mole, which is sufficiently large that one questions its accuracy.

Table I. Temperature Dependence of the Conformational Isomerization Rate of HTMT, Including the Corresponding Free Energies of Activation, Determined by Nmr Complete Line-Shape Analysis

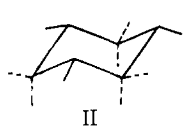
Temp, °K	$^1/_2\tau$, 10^3 sec^{-1}	$\Delta G^{\ddagger}_{cc}$, kcal/mole	Temp, °K	$^1/_2\tau$, 10^2 sec^{-1}	$\Delta G^{\ddagger}_{cc}$, kcal/mole
315.2	6.64 ± 0.34	13.0	281.6	4.84 ± 0.18	13.0
308.7	3.45 ± 0.15	13.1	273.6	2.55 ± 0.11	12.9
301.2	2.72 ± 0.11	12.9	268.1	1.00 ± 0.05	12.3
298.6	2.34 ± 0.11	12.9	265.5	0.61 ± 0.04	13.3
296.7	1.80 ± 0.09	12.9	262.0	0.44 ± 0.02	13.3
296.2	2.10 ± 0.09	12.8	256.5	0.22 ± 0.01	13.4
292.1	1.31 ± 0.07	12.9		10^1 sec^{-1}	
	10^2 sec^{-1}		252.3	1.30 ± 0.05	13.4
287.0	8.35 ± 0.32	12.9	247.7	0.90 ± 0.07	13.3
285.3	6.30 ± 0.31	12.9	240.1	0.50 ± 0.05	13.4

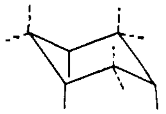
Table II. Activation Parameters[a] Determined From the Temperature Dependence of the Conformational Isomerization Rate of HTMT

T_c, °K	E_a, kcal/mole	A, sec^{-1}	$\Delta H^{\ddagger}_{cc}$, kcal/mole	$\Delta G^{\ddagger}_{cc}$, kcal/mole	$\Delta S^{\ddagger}_{cc}$, eu/mole
268.1	15.7 ± 0.2	7×10^{14}	15.2 ± 0.2	13.2 ± 0.2	7.5

[a] The quantity T_c is the temperature at which the methylene proton resonance coalesces to a single line; A and E_a are the Arrhenius frequency factor and activation energy.

Conformation and Isomerization of HTMT. A wider range of conformers and conformational changes is possible for HTMT than for cyclohexane because HTMT can undergo nitrogen inversion as well as ring inversion. The most stable form of HTMT is expected to be the chair form in which all three N-methyl groups are equatorial (II), because in it the repulsive interactions involving the methyl groups would be minimized.[15] Conversely, the chair form with all three N-methyl groups axial (III) is of very much higher energy. Ring inversion without nitrogen inversion interconverts forms II and III. There is also the pair of chair forms, of structure and energy intermediate to II and III, in which one and two of the N-methyl groups are axial, and which are also interconverted by ring inversion without nitrogen inversion.[16]


II


III

However, the nmr spectra indicate that of the possible conformers none but the "equatorial chair form" II occurs to any significant extent. There are three main steps in the argument. First, the low-temperature AB spectrum of the methylene groups proves that ring inversion is slow on the nmr time scale. Secondly, the detection of only one N-methyl line and one AB spectrum requires that the three N-methyl groups be equivalent and also the three methylene groups. Such nmr equivalence can result either from the inherent symmetry of a single molecular species or from fast exchange of an appropriate nature among two or more species. A single noninverting form such as II or III would have equivalent N-methyl and methylene groups, but not the less symmetric "intermediate" chair forms nor, for that matter, any of the boat forms.[17] Also, fast inversion of the nitrogens at random among appreciable concentrations of the various chair forms, but without ring inversion, would make the three N-methyl groups equivalent and also the AB spectra of the three methylene groups.

Actually, this latter possibility seems unlikely because the equilibrium concentrations would change with temperature and, if the concentrations of conformers other than II were appreciable, one would expect the N-methyl and, methylene group proton shifts to also change. But this is counter to our third point, the fact that the shifts were found to be temperature independent. Therefore, we conclude that chair forms other than II occur to a negligible extent. Nonetheless, the experimental results do not eliminate the possibility that nitrogen inversion occurs more rapidly than ring inversion[3d,11] or that very small amounts of the chair forms with one to three axial N-methyl groups are in equilibrium with II. Indeed, the former has been proposed to account for the absence of any change in the spectrum of the N-methyl protons in N,N'-dimethylpiperazine over a wide temperature range.[7]

In any event, the temperature dependence of the high-resolution spectrum of the methylene protons corre-

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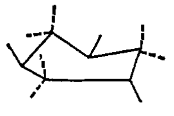
(15) J. B. Hendrickson, *J. Am. Chem. Soc.*, 83, 4537 (1961). For the chair form, we estimate an equatorial N-methyl group to be $\gtrsim 3$ kcal/mole lower in energy than an axial N-methyl.

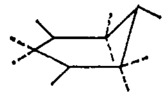
(16) The boat forms corresponding to the four chair forms are of such relatively high energy that the possibility of their presence is negligible at the temperatures in question, except perhaps as transient states in the isomerization.

(17) There is ample evidence that there would be substantial chemical shifts of methylene and of N-methyl group protons between the various conformers; see, *e.g.*, ref 3,6,7, 11, and 13.

sponds to a conformational process in which chair form II goes to the equivalent form II′ with axial and equatorial protons interchanged in each methylene group. Possible reaction paths include: (a) ring inversion synchronous with inversion of all three nitrogens;[18] (b) ring inversion followed and/or preceded by fast inversion of one, two, or three nitrogens to give a net inversion of all three nitrogens; and (c) ring inversion synchronous with inversion of one or two nitrogens, followed or preceded by fast inversion of the other two or one nitrogens. Of these, the latter is preferred.

For the case of the cyclohexane ring inversion, Hendrickson has considered the nature of the transition state in detail.[15] The most probable transition state[19] is a cyclohexene-like[3a] form of C_2 symmetry which has four ring atoms coplanar. Another, less probable state is a "half-boat" form of C_s symmetry with five ring atoms coplanar and about 1.5 kcal/mole higher in energy than the C_2 form. In adapting these to HTMT, we note that ring strain and repulsive interactions can be reduced by having the nitrogen atom(s) in the main coplanar part of the ring assume the sp^2 configuration(s) shown in IV and V. Thus, IV and V are transition states not only for ring inversion but also for the


IV


V

simultaneous inversion of one and two nitrogens, respectively.[20] Therefore, if ring inversion of HTMT is similar to that of cyclohexane, it is accompanied by inversion of only one or two of the nitrogens. And this process must be followed or preceded by the fast inversion of the other one or two nitrogens in order that the net conformational change agree with the nmr results.

Acknowledgment. We, particularly P. A. T., wish to thank Dr. Jiri Jonas for his help in many ways.

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[18] This seems to have been suggested by Harris and Spragg in the case of morpholine and piperazine derivatives; see ref 3c.

[19] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1965.

[20] The energy of the transition state with all six ring atoms planar is probably too high for it to contribute appreciably to the exchange process; see, *e.g.*, ref 15.

7,12-Dihydropleiadenes. VI. Conformational Preferences of 7-Alkyl-7,12-dihydropleiadenes[1]

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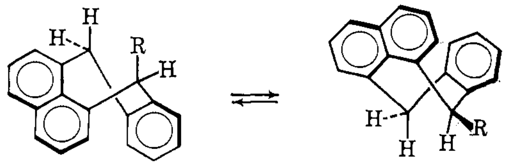
Abstract: The conformational preferences of the alkyl groups in 7-methyl-, 7-ethyl-, and 7-isopropyl-7,12-dihydropleiadenes have been shown to vary widely, from mainly equatorial for methyl to overwhelmingly axial for isopropyl. These results are derived from conformational equilibrium measurements by nmr and equilibration studies involving *cis* and *trans* isomers of 7,12-dialkyl-7,12-dihydropleiadenes and 7-alkyl-12-methoxy-7,12-dihydropleiadenes. It is proposed that the steric effect of β as well as α atoms of the 7-alkyl group play a role in determining the relative stabilities of the two possible conformations.

A 7-substituted 7,12-dihydropleiadene has available to it two readily interconvertible[4] folded conformations in which the substituent can occupy either an axial or equatorial position.[5]



axial equatorial

We have already studied the conformational equilibria of several derivatives of 7,12-dihydropleiadenes[5] (DHP). It was found that phenyl, carbomethoxy, and chlorine substituents exist overwhelmingly ($\gtrsim 98\%$) in the axial conformation and methoxy and acetoxy groups have modest axial preferences also.[5] When we extended our studies to 7-alkyl DHP's, we were somewhat surprised to find that a 7-methyl group had a strong preference for the equatorial position and furthermore that substantially different results are obtained with 7-ethyl and 7-isopropyl groups[1] (increasing axial preference). In this paper we present several approaches used to establish preferred conformations of 7-alkyl DHP's. In addition to direct conformer population measurements on these compounds (by low-temperature nmr), equilibrations of diastereomers were also carried out, *e.g.*, *cis*- $\rightleftarrows$ *trans*-7,12-dimethyl DHP's. A possible rationale for experimental results is presented.

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[1] A preliminary account of some of this research has appeared: P. T. Lansbury and A. J. Lacher, *J. Am. Chem. Soc.*, **88**, 3877 (1966).

[2] Alfred P. Sloan Foundation Fellow, 1963–1967.

[3] Du Pont Predoctoral Teaching Fellow, 1966–1967.

[4] P. T. Lansbury, J. F. Bieron, and M. Klein, *J. Am. Chem. Soc.*, **88**, 1477 (1966).

[5] P. T. Lansbury, J. F. Bieron, and A. J. Lacher, *ibid.*, **88**, 1482 (1966).