

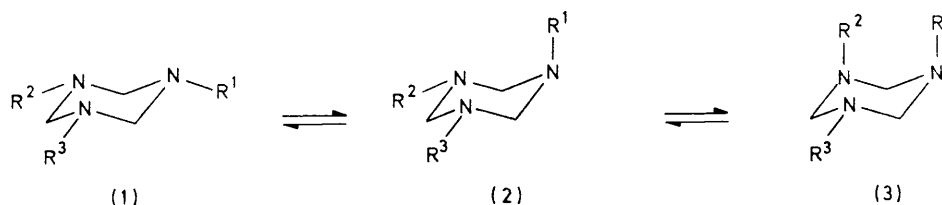
The Conformational Analysis of Saturated Heterocycles. Part LIII.¹ Further 1,3,5-Trialkylhexahydro-1,3,5-triazines

By R. Philip Duke, Richard A. Y. Jones,* Alan R. Katritzky,* and Roger Scattergood, School of Chemical Sciences, University of East Anglia, Norwich NOR 88C
Frank G. Riddell, Department of Chemistry, University of Stirling, Scotland

The dipole moments of mixed isopropyl-*t*-butyl- and methyl-*t*-butyl-hexahydrotriazines allow the calculation of the conformational free energies of placing one or two *N*-alkyl groups axial in this system. The results are compared for those in other six-membered ring systems.

In an earlier study² of hexahydro-1,3,5-triazines, we concluded that equilibria of type (1) \rightleftharpoons (2) \rightleftharpoons (3) were involved, but that the proportion of triequatorial

derivatives the diaxial conformer (3) could be neglected. The availability³ of unsymmetrically substituted trialkylhexahydrotriazines now allows a test of these con-



form (1) was small for the trimethyl and triethyl compounds, whereas for the tri-isopropyl and tri-*t*-butyl

derivatives the diaxial conformer (3) could be neglected. The availability³ of unsymmetrically substituted trialkylhexahydrotriazines now allows a test of these con-

TABLE I

Dielectric and specific volume measurements^a at 25° in cyclohexane

	10 ⁶ <i>w</i>	10 ⁶ (ε ₁₂ - ε ₁)	10 ⁶ (v ₁ - v ₁₂)
1-Isopropyl-3,5-di- <i>t</i> -butylhexahydro-1,3,5-triazine			
	1697	1349	278.5
	3758	2889	623.3
	5149	3973	840.8
	5353	4079	877.8
1,3-Di-isopropyl-5- <i>t</i> -butylhexahydro-1,3,5-triazine			
	4624	3654	719
	6536	5140	1058
	7723	6107	1235
	8833	6977	1395
1-Methyl-3,5-di- <i>t</i> -butylhexahydro-1,3,5-triazine			
	3813	2797	628.8
	4253	3171	694.6
	5621	4224	922.0
1,3-Dimethyl-5- <i>t</i> -butylhexahydro-1,3,5-triazine			
	2041	1793	320.8
	2897	2496	485.1
	2978	2532	493.5
	3530	3160	

^a *w* = Weight fraction, ε₁ and ε₁₂ are the dielectric constants for solvent and solution respectively, and v₁ and v₁₂ are the corresponding specific volumes.

EXPERIMENTAL

Compounds.—Preparative details will be published elsewhere.³

Dipole Moments.—These were measured at 25° in cyclohexane as previously described;⁴ the results are recorded in Tables 1 and 2.

Calculations.—The dipole moments expected for the individual conformers were calculated using the optimised geometry for hexahydro-1,3,5-triazine,⁵ and the results are given in Table 3.

DISCUSSION

We made the following assumptions regarding the conformational equilibria. (a) The equilibrium constant $K_{3e} = [2]/[1]$ depends only on R¹ and not on R² or R³. The corresponding free energy difference we depict as

¹ Part LII, R. P. Duke, R. A. Y. Jones, and A. R. Katritzky, *J.C.S. Perkin II*, 1973, 1553.

² R. A. Y. Jones, A. R. Katritzky, and M. Snarey, *J. Chem. Soc. (B)*, 1970, 135.

³ F. G. Riddell, to be submitted to *J.C.S. Perkin II*.

⁴ L. Angiolini, R. P. Duke, R. A. Y. Jones, and A. R. Katritzky, *J.C.S. Perkin II*, 1972, 674.

⁵ I. D. Blackburne, R. P. Duke, R. A. Y. Jones, A. R. Katritzky, and K. A. F. Record, *J.C.S. Perkin II*, 1973, 332.

TABLE 2
Measured dipole moments ^a

dε/dw	-dv/dw	τP _{2∞}	εP	μ/D	
1-Isopropyl-3,5-di-t-butylhexahydro-1,3,5-triazine	0.753 ± 0.008	0.163 ± 0.002	112.61	74.41	1.37 ± 0.01
1,3-Diisopropyl-5-t-butylhexahydro-1,3,5-triazine	0.791 ± 0.007	0.161 ± 0.006	108.25	69.86	1.37 ± 0.01
1-Methyl-3,5-di-t-butylhexahydro-1,3,5-triazine	0.749 ± 0.009	0.164 ± 0.0007	99.26	65.32	1.29 ± 0.01
1,3-Dimethyl-5-t-butylhexahydro-1,3,5-triazine	0.876 ± 0.023	0.166 ± 0.005	84.87	51.70	1.27 ± 0.02

^a Errors quoted for dε/dw and dv/dw are standard deviations based on the least-squares plot. These errors are combined to give the quoted error in μ.

TABLE 3
Calculated dipole moments (μ/D) for
hexahydro-1,3,5-triazines

Compound	Bu ^t ₃	Bu ^t ₂ -Pr ⁱ	Bu ^t -Pr ⁱ ₂	Pr ⁱ ₃
Measured	1.45	1.37	1.37	1.36
All eq	2.08	2.08	2.07	2.07
One Bu ^t ax	1.26	1.24	1.20	
One Pr ⁱ ax		1.34	1.32	1.29
Two Pr ⁱ ax			0.76	0.67

Compound	Me ₃	Me ₂ -Bu ^t	Me-Bu ^t ₂
Measured	1.19	1.27	1.32
All eq	2.31	2.24	2.16
One Me ax	1.44	1.40	1.36
One Bu ^t ax		1.35	1.30
Two Me ax	0.74	0.70	

ΔG^0_{3e} . (b) The equilibrium constant $K_{2a} = [3]/[2]$ depends on R¹ and R² but not on R³. The corresponding free energy difference we depict as ΔG^0_{2a} . (c) Conformers (3) with two axial groups are negligibly populated if either R¹ or R² is t-butyl.

Free Energy Differences ΔG^0_{3e} and ΔG^0_{2a} for t-Butyl and Isopropyl.—Recalculation of the previous ² result for the tri-t-butyltriazine using the revised geometry ⁵ gives $N(\text{Bu}^t_3 \text{ eq}) = 0.188$; hence $K_{3e}(\text{Bu}^t) = 4.32$ and $\Delta G^0 = -0.87$ kcal mol⁻¹. Correcting for the higher entropy of the three-fold degenerate monoaxial-t-butyl compound gives $\Delta G^0_{3e}(\text{Bu}^t) = -0.22$ kcal mol⁻¹.

TABLE 5

Relative free energies (kcal mol⁻¹) of axial N-alkyl groups in the hexahydro-1,3,5-triazine and related systems ^{*}

System	Ref.	Bu ^t	Pr ⁱ	Et	Me
Hexahydrotriazine ΔG^0_{2a}	a	≥ 4 ^b	3.0 ± 0.5	(0.8) ^c	0.20 ± 0.05
Hexahydrotriazine ΔG^0_{3e}	a	-0.3 ± 0.1	-1.0 ± 0.1	(-1.8) ^c	-2.5 ± 0.2
Hexahydropyrimidine	5	Large	≥ 1.5	0.6	0.4
Piperidine	5	Large	1.6	1.0	0.7
Cyclohexane ^d	e	ca. 5	2.1	1.8	1.7

^a This work. ^b Assumed value, see text. ^c Provisional, see text. ^d C-Alkyl groups. ^e E. L. Eliel, N. L. Allinger, S. J. Angyal, and C. A. Morrison, 'Conformational Analysis,' Interscience, New York, 1965, p. 44.

^{*} In a previous paper (ref. 2) we used the opposite sign convention, but we believe that the present one ($\Delta G^0 = \Delta G^0_{ax} - \Delta G^0_{eq}$) is preferable.

For the isopropyl-di-t-butyl, di-isopropyl-t-butyl, and tri-isopropyl derivatives, the relative population of each conformer may be expressed in terms of $\Delta G^0_{3e}(\text{Bu}^t) = a$, $\Delta G^0_{3e}(\text{Pr}^i) = b$, and $\Delta G^0_{2a}(\text{Pr}^i) = c$. For example, for

⁶ For a full discussion see R. Scattergood, Ph.D. Thesis, University of East Anglia, 1972.

the di-isopropyl-t-butyl derivative we have equations (1)–(4).

$$N(\text{tri-}eq) = \frac{1}{1 + e^{(-a/0.59)} + 2e^{(-b/0.59)} + e^{[-(b+c)/0.59]}} \quad (1)$$

$$N(\text{Bu}^t \text{ ax}) = \frac{e^{(-a/0.59)}}{1 + e^{(-a/0.59)} + 2e^{(-b/0.59)} + e^{[-(b+c)/0.59]}} \quad (2)$$

$$N(\text{Pr}^i \text{ ax}) = \frac{2e^{(-b/0.59)}}{1 + e^{(-a/0.59)} + 2e^{(-b/0.59)} + e^{[-(b+c)/0.59]}} \quad (3)$$

$$N(\text{Pr}^i_2 \text{ ax}) = \frac{e^{[-(b+c)/0.59]}}{1 + e^{(-a/0.59)} + 2e^{(-b/0.59)} + e^{[-(b+c)/0.59]}} \quad (4)$$

These conformer populations may now be used with the calculated dipole moments of Table 3 to give ⁶ four equations connecting the expected dipole moment and the values a, b, and c. By trial and error the best fit (Table 4) was found using $\Delta G^0_{3e}(\text{Bu}^t) = -0.3$, $\Delta G^0_{3e}(\text{Pr}^i) = -1.0$, and $\Delta G^0_{2a}(\text{Pr}^i) = -3.0$ kcal mol⁻¹.

TABLE 4

Compound	Conformer populations				Dipole moment	
	Mole fractions				Calc.	Obs.
Compound	Tri- <i>eq</i>	Bu ^t <i>ax</i>	Pr ⁱ <i>ax</i>	Pr ⁱ ₂ <i>ax</i>		
Tri-t-butyl	0.17	0.83			1.43	1.45
Mono-isopropyl-di-t-butyl	0.10	0.34	0.56		1.40	1.37
Di-isopropyl-mono-t-butyl	0.07	0.12	0.80	<0.01	1.37	1.37
Tri-isopropyl	0.06		0.93	<0.01	1.34	1.36
	Tri- <i>eq</i>	Me <i>ax</i>	Me ₂ <i>ax</i>	Bu ^t <i>ax</i>		
Trimethyl	<0.01	0.58	0.42		1.20	1.19
Dimethyl-mono-t-butyl	<0.01	0.7?	0.26	<0.01	1.26	1.27
Mono-methyl-di-t-butyl	0.01	0.93		0.05	1.37	1.32

Free Energy Differences ΔG^0_{3e} and ΔG^0_{2a} for Methyl.—For the trimethyl, dimethyl-t-butyl, and methyl-di-t-butyl compounds, a treatment similar ⁶ to that used above gives three equations in the two unknowns, from

which the best values of $\Delta G^0_{3e}(\text{Me}) = -2.5$ and $\Delta G^0_{2a}(\text{Me}) = 0.2$ kcal mol⁻¹ were found (Table 4).

General Conclusions.—Free energy differences are summarised in Table 5: the values given for ethyl are tentative as they are derived from a measurement of the single triethyl compound only. The results show a smooth

progression and confirm the previous² semiquantitative conclusion that whereas for the *t*-butyl and isopropyl compound the equilibrium mixture contains mainly the triequatorial and monoaxial-diequatorial conformers, for the ethyl and methyl compounds the equilibrium is essentially between the monoaxial-diequatorial and diaxial-monoequatorial conformers. It is a little difficult to assess the errors in the reported ΔG^0 values because there is no simple relationship between the experimental dipole moments and ΔG^0 . The errors quoted are those which give rise to an approximate doubling of the least squares differences between observed and calculated moments (Table 4).

Table 5 also gives conformational ΔG^0 values for related systems: it is easier to place *N*-alkyl axial in piperidine than *C*-alkyl in cyclohexane because of the ease of deformation at nitrogen. A further small increase is observed for *N*-alkyl in hexahydropyrimidine: here there is less hindrance to the axial alkyl group as one β -hydrogen atom is replaced by a lone pair. A dramatic decrease in ΔG^0_{se} occurs for the hexahydro-1,3,5-triazines due both to decreased interaction in the *N*-alkyl axial conformer and to unfavourable interactions in the triequatorial conformer.

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