Ring Reversal of *cis*-Cyclohexane-1,2,3,4,5,6-hexacarboxylic Acid and its Hexamethyl Ester

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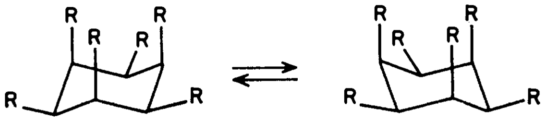
cis-Cyclohexane-1,2,3,4,5,6-hexacarboxylic acid and its hexamethyl ester have been synthesized and shown, by n.m.r., to exist in solution at room temperature as an equilibrium of slowly exchanging chair conformations. From complete line shape analysis of the ^{13}C n.m.r. spectra measured at different temperatures the activation parameters have been determined. A relatively high value (*ca.* 17 kcal mol^{-1}) † of free energy of activation has been found for both molecules, by analogy with the hexamethylcyclohexane case. The energy barrier of the acid has been calculated with the method of molecular mechanics and the computer program MOLBD3: the value obtained (16 kcal mol^{-1}) is a slight overestimate by comparison with the observed value of 13—14.5 kcal mol^{-1}.

RING reversal of six-membered carbocyclic rings has been experimentally investigated by dynamic n.m.r. spectroscopy,[1] and theoretically studied by conformational energy calculations.[2] Although a relatively large set of data is available in the literature [1a] for di- and tetra-substituted cyclohexanes, only five cases have been reported [3a] for vicinal hexa-substituted rings. The free energy barriers range from 10.5 to 17.3 kcal mol^{-1}. However the highest observed values seem to be typical of the *cis*-configuration, *i.e.* 15.4 for inositol and 17.3 kcal mol^{-1} for hexamethylcyclohexane. In order to test this hypothesis with additional experimental data, we have studied *cis*-cyclohexane-1,2,3,4,5,6-hexacarboxylic acid (1) and its hexamethyl ester (2).

The occurrence of a chair conformation in both (1) and (2) has been confirmed by diffractometric analysis; [4] this shows that 1,3 interactions are mainly released by deformation of the valence angles.



(1) R = CO_2H
(2) R = CO_2Me

In this paper we present the results of an n.m.r. determination [5] of the activation parameters of ring reversal of (1) and (2), together with a calculation of the conformational energy of (1), with a view to ascertaining the possible presence in the acid of intramolecular interactions, such as hydrogen bonding.

EXPERIMENTAL

Materials.—Compound (1) was prepared as a trihydrate from bicyclo[2.2.2]oct-7-ene-2,3:5,6-tetracarboxylic dianhydride by nitric acid oxidation promoted by NH_4VO_3 [6] and was crystallized from MeOH, δ(DMSO) 2.97 (3 H, t) and 3.45 (3 H, t). Compound (2) was prepared from (1) by esterification with MeOH and H^+ and crystallized from MeOH, m.p. 238 °C,‡ enantiotropic phase transition at 166 °C (differential thermal analysis), δ(DMSO) 3.13 (3 H, t), 3.55 (3 H, t), 3.44 (9 H, s, Me), and 3.64 (9 H, s, Me).

Spectra.—^{13}C N.m.r. spectra were measured in the pulsed Fourier mode on a Bruker HFX-90 spectrometer operating at 22.63 MHz, equipped with a 1085 Nicolet computer. The deuterium signal of the solvent was used for the frequency-field stabilization. A pulse width of 8 μs was used, the width for the 90° pulse being 22 μs. The broad-band decoupling parameters were: power 10 W, modulation 4, and frequency optimized in order to obtain the minimum line width of the ^{13}C signals.

TABLE 1

^{13}C Chemical shifts of (1) and (2) at 35 °C

Compound	Solvent	δ(p.p.m.) CO	CH	CH_3
(1)	D_2O	174.81	39.44	
		175.63	46.44	
(1)	DMSO	172.50	39.53	
		174.70	46.14	
(2)	DMSO	170.14	38.69	51.28
		170.41	45.31	51.62

The computer dwell time was 135 μs, corresponding to a spectral window of 3 703 Hz. The f.i.d. was accumulated on 16 k of memory so that the acquisition time was 2.2 s. Zero filling with additional 16 k of memory raised the effective digital resolution to 0.2 Hz per point. No exponential filtering was applied to the f.i.d. before Fourier transformation.

The samples were 0.6M solutions in $(^{12}CD_3)_2SO$ and D_2O, contained in 10 mm o.d. tubes. A trace of ethylene glycol was added to the solution for measuring the line width in absence of exchange. Chemical shifts were measured from the methylene group of glycol and then referred to Me_4Si by the relationship $\delta(\text{glycol}) - \delta(Me_4Si) = 63.0$ p.p.m.

Temperatures were measured before and after recording the spectrum with a thermocouple inserted in the sample solution. During the adjustment and reading of the potentiometer the f_2 decoupling frequency was temporarily switched off in order to avoid reading errors due to strong radiofrequency irradiation.

The room temperature ^{13}C chemical shifts of (1) and (2) are collected in Table 1. Very large shift differences between the two exchanging forms were observed for the CH resonances for both (1) and (2) and also for CO resonances

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† 1 cal = 4.184 J.
‡ °C = K − 273.15.

for (1) in both solvents D_2O and DMSO. Relatively small shift differences were detected for the CH_3 and CO signals of (2). Consequently the latter two resonances were not used for the line shape analysis, in order to obtain reliable results in the determination of the activation parameters from the study of the temperature dependence of the rate constant.

The calculations of the exchanging spectra were carried out with the CLATUX computer program [7] for the classical two-spin system without coupling.

The values of $k = 1/2\tau$ correspond to the transition from one chair form (C) to the other. Following the mechanism of ring reversal usually proposed for cyclohexane it was assumed there was a pathway through a flexible boat (B) form as intermediate. This description involves a rate constant for chair to boat transition which is twice the observed k. The temperature dependence of k was analysed by the Eyring equation.

Weighted least squares analysis was used to determine the activation parameters and their standard errors, by allowing for the variances of both dependent and independent variables.[8]

The variance of k was estimated for each experimental point from a range of rate constants which give satisfactory agreement between the simulated and the observed line shape. The variance of T was obtained by the method of Binsch.[9] The errors in the new variables of the linearized Eyring equation were calculated by the rule of the propagation of errors.[8] The standard error of ΔG^* was obtained from the relationship $\sigma^2(\Delta G^*) = \sigma^2(\Delta S^*) + T^2\sigma^2(\Delta G^*) - 2T\text{cov}(\Delta H^*, \Delta S^*)$ where cov is the covariance.

RESULTS AND DISCUSSION

The observed activation parameters are collected in Table 2.

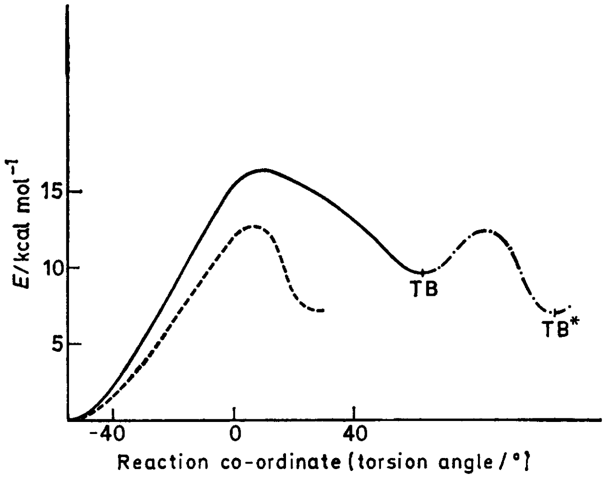
The values of ΔG_{CB}^* observed at 25 °C are of the same order of magnitude as the values previously determined for hexamethylcyclohexane.[3a] This suggests that by increasing the number of substituents in the cyclohexane ring the transition state for ring reversal is more destabilized than the ground state, relative to the unsubstituted molecule which has a value of ΔG_{CB}^* of 10.1 kcal mol^{-1}.

Moreover the ΔG_{CB}^* value of acid (1) shows dependence on the solvent, increasing from 16.7 kcal mol^{-1} in D_2O to 17.4 kcal mol^{-1} in DMSO. This observation can be accounted for by assuming the presence in the acid dissolved in DMSO of a partial hydrogen bond which would stabilize the ground state. However such a bond is not present in the water solution of (1) which accordingly shows the same free energy barrier as the ester dissolved in DMSO. Solvent effects of the same sign on the barrier to ring reversal of (1) are observable in the value of the enthalpy of activation ΔH_{CB}^* which increases on going from water to DMSO (13.1 to 14.5 kcal mol^{-1}).

Finally the ΔS_{CB}^* parameter shows a small, consistently negative value in every case. A negative entropy of activation is not infrequent in the conformational isomerization of cyclohexane derivatives. It must involve an activated state more symmetric or more rigid than the ground state.

To try and rationalize these observations conformational analysis has been carried out by the method of molecular mechanics and using the MOLBD3 program of Boyd.[10] The presence of the carboxylic groups required the definition of new potential function constants; therefore we transferred to the force field of Boyd (restricted to hydrocarbons) the potential function constants for the carboxy-group introduced by Brooks and Haas [11] and modified by Allinger and Chang.[12]

A further question concerned the torsional barrier around the aliphatic C–C bond; we decided to choose 3.0 instead of 2.5 kcal mol^{-1}, the most recent value used by Boyd.[13] We have already adopted this modification in a conformational study of the stereoisomers of hydrogenated triptycene, obtaining a good agreement between observed and calculated energies.[14] In order to check this choice further we repeated with the new torsional barrier the calculations of Wiberg and Boyd [15] for cyclohexane conformational inversion. The obtained energy path is shown in the Figure. The calculated value of the



Calculated energy profile for the acid (1) (solid line) and for cyclohexane (short-dashed line). The energy profile for the acid (1), between TB and TB* is rotational rearrangement of the pendant groups (see text)

TABLE 2

Activation parameters for ring reversal in (1) and (2)

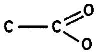
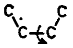
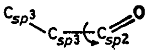
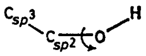
Compound	Solvent	ΔH_{CB}^*/ kcal mol^{-1} (kJ mol^{-1})	ΔS_{CB}^*/ kcal mol^{-1} K^{-1} (kJ mol^{-1} K^{-1})	ΔG_{CB}^* (25 °C)/ kcal mol^{-1} (kJ mol^{-1})
(1)	D_2O	13.13 ± 0.20	−12.00 ± 0.60	16.71 ± 0.03
		(54.96 ± 0.84)	(−50.23 ± 2.51)	(69.95 ± 0.13)
(1)	$[^2H_6]$DMSO	14.50 ± 0.53	−9.76 ± 1.50	17.42 ± 0.08
		(60.70 ± 2.22)	(−40.86 ± 6.28)	(72.92 ± 0.33)
(2)	$[^2H_6]$DMSO	14.79 ± 0.32	−6.33 ± 0.08	16.68 ± 0.07
		(61.91 ± 1.34)	(−26.50 ± 3.52)	(69.82 ± 0.29)

energy barrier, 12.5 kcal mol^{-1}, is higher than that of Wiberg and Boyd and in good agreement with the experimental [1b] ΔH^* value of 11.5 kcal mol^{-1}.

In order to conform to Boyd's interactions for hydrocarbons, non-bonded interactions involving the oxygen atoms have been parametrized according to exp-6 functions. The exponent has been kept equal to that of carbon (3.09 Å^{-1}) * since it appears to be rather insensitive to the kind of atom in the range He–Ne.[16] The attractive constant has been set at 3.29 mdyn Å^7 † due to the lower polarizability of oxygen relative to carbon (no difference was introduced between carbonyl and hydroxy oxygens) and the repulsive constant has been adjusted in order to have the minimum of the interaction energy at 3.0 Å. Mixed interactions have been treated by averaging the corresponding parameters. All strain energy parameters used are summarized in Table 3.

TABLE 3

Strain energy parameters

Stretching	$0.5\,K_s\,(l - l^0)^2$		
	K_s/mdyn Å^{-1}		l^0 (Å)
C–C	4.40		1.530
C–H	4.55		1.090
C_{sp2}–C_{sp2}	4.40		1.500
C=O	10.80		1.207
C_{sp2}–O	5.05		1.328
O–H	7.20		0.972
Bending	$0.5\,K_\theta\,(\theta - \theta^0)^2$		
	K_θ/mdyn Å rad^{-2}		θ^0 (°) [a]
C–C–C	0.800		111.0
C–C–H	0.608		109.5
H–C–H	0.508		107.9
C_{sp3}–C_{sp2}–O	0.702		108.0
C_{sp3}–C_{sp2}=O	0.570		122.8
O–C=O	1.128		124.0
C–O–H	0.736		106.5
Out of plane bending	$0.5\,K_\delta\,(\delta)^2$		
	K_δ/mdyn Å rad^{-2}		
	0.50		
Torsion	$0.5\,V^0\,[1 + \cos 3(\phi - \alpha)]$		
	V^0 (mdyn Å)		α (°)
	0.0209		0
	0.0133		180
	0.0417		0
			$A \exp(-B\,r) - C\,r^{-6}$
Non-bonded interactions	A/mdyn Å	B/Å^{-1}	C/mdyn Å^7
O·····O	31.0	3.09	3.29
O·····C	55.0	3.09	3.82
O·····H	17.0	3.415	0.79
C·····C	104.0	3.09	4.45
C·····H	30.0	3.415	0.92
H·····H	18.4	3.74	0.19

[a] 1° = (π/180) rad.

The above assumptions were checked by calculating the structural features of acetic and propionic acid. The resulting differences between calculated and experimental angles are within 1%, with the exception of the C–O bond whose calculated length was 1.33 Å against the observed values of 1.364 [16] and 1.367 Å: [17] this discrepancy is essentially due to the choice of 1.328 Å as the natural length of this bond.

The ground state of (1) was optimized by starting from the crystal structure of the molecule determined by X-ray diffraction.[4] The reaction co-ordinate for the transition from chair to twisted boat was described by driving one torsional angle of the ring from its initial value of —55.4° toward positive values, by steps of 10°. The activated state, with an energy of 16.0 kcal mol^{-1}, corresponds to a conformation with five ring carbons approximately in a plane. This value of the calculated energy barrier is compared with the observed value of ΔH^* of 13—14.5 kcal mol^{-1}. Apparently the method overestimates the barrier as in the cyclohexane case.

After the constrained torsion angle reached 50.6° the strain energy of the molecule was minimized without restrictions and the (TB) conformation was obtained with an energy of 9.6 kcal mol^{-1}. In Table 4 some rotation angles are reported for C, TB, and the activated state.

TABLE 4

Description of some conformers of compound (1) and of cyclohexane. For compound (1) we report the torsion angles for the cyclohexane moiety and the torsion angles which define the orientation of carboxy-groups

Compound (1)

	Conformers			
Torsion angle	C	Activated complex	TB	TB*
6 1 2 3	−55.4	3.7	58.7	63.6
1 2 3 4	55.5	26.9	−31.8	−35.4
2 3 4 5	−55.4	−60.8	−27.6	−24.1
3 4 5 6	55.5	66.3	64.0	59.8
4 5 6 1	−55.4	−36.9	−36.9	−31.6
5 6 1 2	55.5	1.3	−22.3	−28.1
6 1 7 13	9.8	−94.4	−115.1	−8.4
1 2 8 15	−3.5	−105.5	−74.9	2.5
2 3 9 17	9.8	16.8	−11.7	121.8
3 4 10 19	−3.5	−7.5	−11.7	−116.5
4 5 11 21	9.8	0.2	4.3	−47.8
5 6 12 23	−3.5	118.1	121.1	−6.7

Cyclohexane

	C	Activated complex	TB
6 1 2 3	−56.1	2.6	30.4
1 2 3 4	56.1	10.5	−63.2
2 3 4 5	−56.1	−49.7	30.4
3 4 5 6	56.1	70.1	30.4
4 5 6 1	−56.1	−49.6	−63.2
5 6 1 2	56.1	10.4	30.4

While in the cyclohexane case the energy of the transition C ⟶ TB completely accounts for the energy of the C–C′ ring reversal (where C′ is the inverted chair form), this is not necessarily true in substituted cyclohexanes. There must be a rotational rearrangement of the carboxy-substituents around their C–C bonds in order to obtain a TB′ conformation related to TB by rotation of 180° of the mean plane of the ring. Obviously the TB′–C′ transition, symmetrically related to TB–C, does not provide any additional contribution to the energy of the overall process. Following this criterion the orientations of the carboxy-groups relative to

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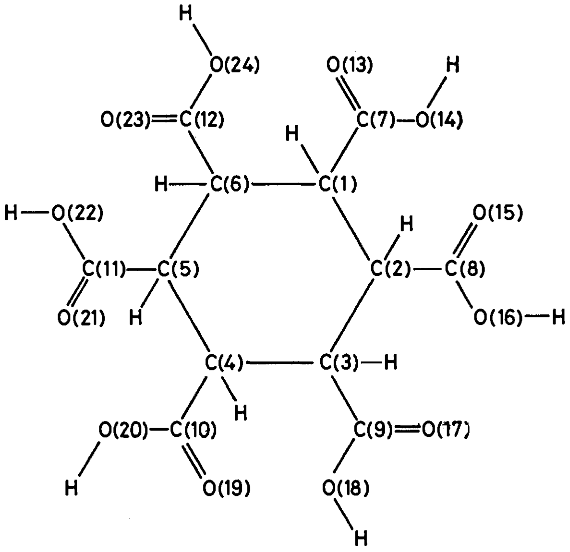
* 1 Å = 10^{-10} m.

† 1 dyn = 10^{-5} N.

the ring were changed one at a time, the process never overcoming barriers higher than 12.5 kcal mol^{-1}, *i.e.* lower than the energy of the activated state. In the course of this reorientation a TB* conformation was obtained; this is the most stable form in the boat region, with an energy of only 6.9 kcal mol^{-1}. It is reported in Table 4.



The calculations for ring reversal for unsubstituted cyclohexane show some differences concerning the TB conformation. As can be seen from Table 4 and the Figure, after the activated state is reached a wide rearrangement of torsional angles occurs and the conformation evolves along a different geometrical path from that of (1). From a qualitative point of view this could be interpreted as an indication that the flexibility of the transition state of cyclohexane is higher than that of (1). This feature is in agreement with the observed negative value of ΔS^* of (1) in contrast with the positive value for cyclohexane.

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