Structure and Conformation of Heterocycles. Part VI.[1] The *cis*-1,4,5,8-Tetraoxadecalin (Hexahydro-*p*-dioxino[2,3-*b*]-*p*-dioxin) System: A Chemical, Conformational, and Crystallographic Study[2]

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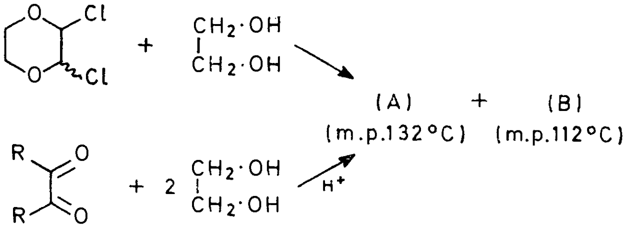
The title system (1) (a, b, c: R = H, CH_2Br, or Me respectively) is subject of a multilateral investigation. *cis*-9,10-Bisbromomethyl-1,4,5,8-tetraoxadecalin (4a,8a-bisbromomethylhexahydro-*p*-dioxino[2,3-*b*]-*p*-dioxin) (1b) was obtained along with its bi(dioxolan-2-yl) isomer (2b) from the acid-catalysed condensation of 1,4-dibromobutane-2,3-dione with ethylene glycol. Chemical correlation between derivatives in both series, *viz.* (1b → 1c) and (2b) → (2c). was achieved. Dynamic conformational analysis in solution was performed in a variable-temperature n.m.r. study of the octadeuteriated derivative, $[^2H_8]$-(1b), which was found to exist in solution as an inverting system with $\Delta G^\ddagger_{226}$ 11·2 kcal mol^{-1}, $\Delta H^\ddagger$ 9·0 ± 0·9 kcal mol^{-1} and $\Delta S^\ddagger$ − 9 ± 4 e.u.

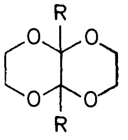
Three-dimensional *X*-ray studies of (1a) and (1b) proved these tetraoxadecalins to be *cis* and to adopt a double-chair conformation. The crystal and molecular structure of (1a), analysed in greater detail [space group *C*2/*c*, Monoclinic, a = 16·003(1), b = 7·077(1), c = 11·654(1) Å, β = 92·81°, Z = 8], was solved by direct methods and was refined anisotropically by a full-matrix least-squares method to R = 0·07. The mean standard deviation of the co-ordinates of C, O, and H atoms are 0·004, 0·003, and 0·04 Å respectively.

Departures from the ideal chair–chair geometry were found which did not disturb the C_2 molecular symmetry. The mean C–O distances along the C–O(1)(ax)–C–O(8)(eq)–C moiety of *cis*-1,4,5,8-tetraoxadecalin (1a) are 1·441, 1·429, 1·408, and 1·446 Å and the corresponding mean bond angles are C–O(8)–C 113·3° and C–O(1)–C 109·9°. These results are discussed in terms of the influence of intramolecular interactions on the conformation of (1a) and on the inversion parameters of (1b) with particular reference to the anomeric effect. The system appears to be a unique example of two adjacent anomeric moieties incorporated in a bicyclic system with C_2 symmetry.

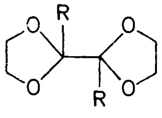
THIS was initiated as part of a study of the structure and conformational analysis of bi- and poly-cyclic heterocycles bearing multiple heteroatoms in the ring-skeleton. This particular field has been scarcely investigated, although aspects of many monocyclic heterocycles have recently received considerable attention.[3,4] The interest in such bi- and poly-cyclic systems is enhanced by the extension of cyclohexane conformational analysis to decalin and related carbocycles.[3d,4]

We started with six-membered oxygen derivatives and chose the 1,4,5,8-tetraoxadecalin system. In spite of considerable synthetic,[5,6] and more limited structural [6-8] studies, the series was devoid of unequivocal and ultimate structural proof as well as of chemical correlation between its members. In fact, several investigations have dealt with the products [(A) and (B)] of the condensation of 2,3-dichlorodioxan or of glyoxal with ethylene glycol and ended with contradictory structural assignments. Thus, mainly on the strength of chemical arguments and dipole-moment measurements, Boeseken *et al.*,[6] concluded that they dealt with the *trans*- and *cis*-1,4,5,8-tetraoxadecalins. Furberg and Hassel [8a] showed, by *X*-ray analysis, that the low melting isomer (B) is, in fact, bi(dioxolan-2-yl) (2a). Furthermore, Hassel and Romming [8b] confirmed the *trans*-tetraoxadecalin structure (3) of the high-melting isomer (A), on the basis of a two-dimensional *X*-ray study of its $HgCl_2$ complex. In two independent n.m.r. studies [7] this structure was found to be incompatible with the coupling constants of the peripheral





(1)



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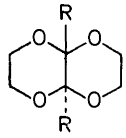
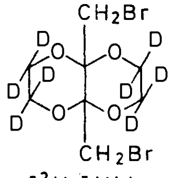
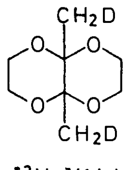


(3)

a; R = H b; R = CH_2Br c; R = Me



$[^2H_8]$(1b)



$[^2H_2]$(1b)

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[1] Part V, M. Erez and B. Fuchs, *Tetrahedron Letters*, in the press.

[2] For preliminary accounts of parts of this work, see: (*a*) B. Fuchs, *Tetrahedron Letters*, 1969, 3571; (*b*) I. Goldberg and U. Shmueli, *Proc. Ann. Meeting Israel Crystallography Soc.*, April, 1971, Rehovoth.

[3] (*a*) C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Topics Stereochem.*, 1969, **4**, 39; (*b*) F. G. Riddell, *Quart. Rev.*, 1967, 364; (*c*) R. K. Harris and R. A. Spragg, *J. Chem. Soc.* (*B*), 1968, 684; (*d*) W. A. Thomas, *Ann. Rev. Magn. Res.*, 1967, **1**, 33 and references therein.

[4] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Interscience, New York, 1965, ch. 4.

[5] For a review see G. Banmeyer, G. Dittus, and E. Müller in 'Methoden der Organischen Chemie,' ed. E. Müller, vol. 6/4, Georg Thieme Verlag, Stuttgart, 1966, p. 410.

[6] J. Boeseken, F. Tellegen, and P. Cohen-Henriquez, *Rec. Trav. chim.*, 1931, **50**, 909; 1935, **54**, 733; 1938, **57**, 143, and further related papers.

[7] (*a*) C. Altona and E. Havinga, *Tetrahedron*, 1966, **22**, 2275; (*b*) R. R. Fraser and C. Reyes-Zamora, *Canad. J. Chem.*, 1967, **45**, 1012.

[8] (*a*) S. Furberg and O. Hassel, *Acta Chem. Scand.*, 1950, **4**, 1584; (*b*) O. Hassel and Chr. Romming, *ibid.*, 1956, **10**, 136.

methylene protons, and (A) was assigned the *cis*-configuration (1a) with two rapidly inverting chairs.

A method of structural assignment for this type of compound, which also permits differentiation between them and their bi(dioxolan-2-yl) isomers, is based on n.m.r. and mass spectral features.[9]

For dynamic conformational analysis of the system (1), the analogy with *cis*-decalin is obvious. In the latter case, quantitative investigations of the conformational inversion have been performed by using variable-temperature n.m.r. measurements of suitable derivatives.[3d] We sought similar approach for our system. An independent, three-dimensional *X*-ray analysis of the tetraoxadecalin system was also required in order to put the so far existing structural assignments on a sound basis.

RESULTS

Chemistry.—The foregoing considerations led us to choose a suitably substituted member of the series *viz.* 9,10-bisbromomethyl-1,4,5,8-tetraoxadecalin (4a,8a-bisbromomethylhexahydro-*p*-dioxino[2,3-*b*]-*p*-dioxin) (1b) for investigation. This, together with its isomeric bi(dioxolan-2-yl) derivative (2b) was obtained from the acid-catalysed condensation of 1,4-dibromobutane-2,3-dione with ethylene glycol in boiling toluene, with continuous removal of water. While the desired isomer (1b) crystallized readily from the reaction mixture, the second one (2b) could be isolated and separated from residual (1b) only by chromatography followed by repeated crystallization. The known unsubstituted isomers (1a, 2a; R = H) and dimethyl derivatives (1c, 2c; R = Me) [6] were obtained similarly.

Although there have been considerable synthetic efforts in this field,[5,6] no chemical correlation so far exists between compounds in the series. Several attempts of displacement of the bromine in (1b) by sulphide, cyanide, or iodide ions were unsuccessful, probably owing to its being α to a neopentylic centre bound to two oxygens. Eventually, $LiAlH_4$ reduction of (1b) and (2b) in boiling tetrahydrofuran yielded, respectively, the known dimethyl derivatives (1c) and (2c).[6] Thus, a closed cycle is obtained, whereby the reliability and generality of our approach [9] to assignment and differentiation between compounds of type (1) and (2) is tested. By use of $[^2H_8]$ethylene glycol the deuteriated derivative $[^2H_8]$-(1b) was obtained, while $[^2H_2]$-(1c) resulted from $LiAl^2H_4$ reduction of (1b). The differentiation between (1) and (2) was readily accomplished by n.m.r. and mass spectral techniques.[9]

X-Ray Studies.—We then determined the structure of (1b) by *X*-ray analysis.

Crystal data for (Ib). $C_8H_{12}Br_2O_4$ Orthorhombic, a = 9·544(2), b = 13·140(2), c = 8·535(4) Å, D_m = 2·0 (by flotation), Z = 4, D_c = 2·05, $F(000)$ = 648. Space group *Pbcn*. Cu-K_α radiation, λ = 1·5418 Å.

Determination of the structure of (Ib). The structure was solved by the heavy-atom method using the bromine parameters obtained from Patterson–Harker sections. A three-dimensional bromine-phased electron-density synthesis clearly revealed the positions of all the non-hydrogen atoms. The approximate atomic positions so obtained conformed with the *cis*-configuration of 9,10-bisbromomethyl-1,4,5,8-tetraoxadecalin with both rings in the chair conformation, the molecule being located on a crystallographic two-fold axis. Subsequent three cycles of isotropic refinement led to R 0·16. The electron-density synthesis computed at this stage is presented in Figure 1. This analysis confirmed the above-mentioned structural assignments for (1b). However, the accuracy of the atomic parameters obtained was relatively low, presumably because of the predominant contribution of the heavy-atom to the refinement. The use of these parameters in connection with the detailed conformational analysis of (1b) in the solid state, was therefore not warranted. It was therefore decided to undertake a detailed structure investigation of (1a) itself.

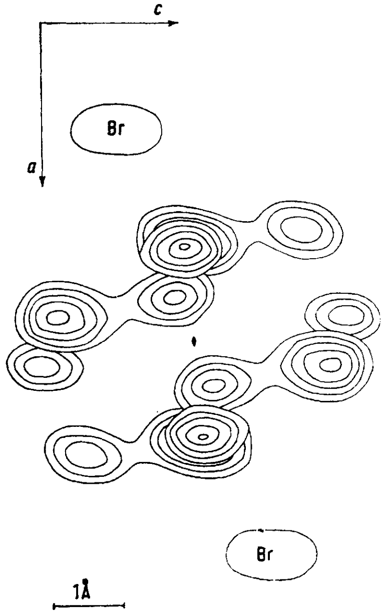

FIGURE 1 Three overlapped sections of electron-density synthesis of the tetraoxadecalinic skeleton of (1b)

Crystal structures of (Ia). (1a) Crystallizes in the monoclinic system, space group *Cc* or *C*2/*c* (systematic absences: *hkl* with $h + k$ odd and *h*0*l* with l odd).

The crystal data are given in Table 1 and compared with these reported by Danö *et al.*[10] The unit-cell dimensions were obtained from their least-squares fit to about 40 measurements of high-angle reflections on Weissenberg [λ(Cu-$K_{\alpha,1}$) = 1·5405, λ(Cu-$K_{\alpha,2}$) = 1·5443 Å] and precession [λ(Mo-K_α) = 0·7107 Å] photographs. The *h*0*l* Weissenberg photograph used was calibrated with powder lines from an

TABLE 1

Crystal data

	Ref. 10	Present work
Space group	*A*2/*a* or *Aa*	*C*2/*c* or *Cc*
a/Å	11·55	16·003 (1)
b/Å	7·04	7·077 (1)
c/Å	15·88	11·654 (1)
β/deg.	92·5	92·81 (1)
D_m/g cm^{-3}	1·46	
D_c/g cm^{-3}	1·50	1·43
Z	8	8
Tests for centre of symmetry	Piezoelectric test (negative)	$N(z)$ distribution (hypercentric)

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[9] B. Fuchs, *Tetrahedron Letters*, 1970, 1747.

[10] M. Danö, S. Furberg, and O. Hassel, *Acta Chem. Scand.*, 1950, **4**, 965.

0·2 mm copper wire. A crystal with dimensions *ca.* 0·3 × 0·3 × 0·4 mm, was selected for intensity measurements. Because of a tendency to sublime when exposed to radiation, it was mounted in a thin-walled (0·1 mm) glass capillary. The intensity data were obtained from microdensitometer measurements of integrated precession photographs, taken with Mo-K_α radiation. The intensities of 1498 reflections were recorded from the layers 0—5*kl* and *hk*0—5 and were reduced to structure amplitudes in the usual manner. No absorption corrections were applied to the data. [μ(Mo-K_α) = 1·3 cm^{-1}]. 130 Observed reflections, common to different layers, were used to place the data on a common scale by a least-squares procedure [11a] similar to that of Sparks and Rollett.[11b] The processing and reduction of the data resulted in the structure amplitudes of 1304 independent reflections which included 646 reflections whose intensities were too weak to be measured. Each reflection was assigned a weighting parameter given by $w_0(I) = I^2/\sigma^2(I)$ where I is the intensity of the reflection in arbitrary units and $\sigma(I)$ is the corresponding error estimate. This parameter was later incorporated into the weighting scheme used during the refinement of the structure. The intensities of the ' unobserved ' reflections were estimated as $\frac{1}{3}I_{\text{min.}}$, where $I_{\text{min.}}$ is the weakest observed intensity.

The presence of the centre of symmetry in crystals of (1a) was indicated by the absence of the piezoelectric effect [10] as well as by the $N(z)$ distribution evaluated from the three-dimensional data. The consequent choice of $C2/c$ space group was later confirmed by the structure determination.

Approximate scale and temperature factors were obtained by the Wilson method [12] and normalized structure amplitudes were computed as: [13]

$$|E(\boldsymbol{h})| = \{|F_o(\boldsymbol{h})|^2/[K^2p(\boldsymbol{h})\sum_{n=1}^{N} f_n{}^2(\boldsymbol{h})]\}^{\frac{1}{2}}\exp\,(B\,.\,\sin^2\theta/\lambda^2)$$

where K^2 and B are the scale and temperature factors respectively, $p(\boldsymbol{h})$ is the average-intensity multiple [14] and $|F_o(\boldsymbol{h})|$ is the observed structure amplitude of the reflection $\boldsymbol{h}(hkl)$. The extrapolated value of K^2, obtained from the Wilson plot, was readjusted so that $\langle|E|^2\rangle = 1$. The temperature factor, however, was left intact, as the slope of the plot was fairly well defined.

The average values of some functions of E and the distribution of the E values among the data are compared in Table 2 with the corresponding theoretical results.

TABLE 2

Some functions of $|E|$ and the % distribution of their magnitudes

		Calc.	
	Found	Centro-symmetric	Noncentro-symmetric
$\langle\lvert E\rvert\rangle$	0·767	0·798	0·886
$\langle\lvert E^2 - 1\rvert\rangle$	1·055	0·968	0·736
$\langle\lvert E^2\rvert\rangle$	1·000	1·000	1·000
$\lvert E\rvert > 3$	1·1	0·3	
$\lvert E\rvert > 2$	5·0	5·0	
$\lvert E\rvert > 1$	25·5	32·0	

Determination of the structure of (Ia). The structure was solved by a reiterative application of the Sayre equation [15] employing the multisolution routine of Long.[16] The choice of the starting set of signs (two signs specifying the origin of the non-primitive space group [17] and four signs to be permuted) was based on a survey of the Σ_2 listing [18] computed from 231 largest E values with $E > 1·2$.

The multisolution routine, operating with the starting set shown in Table 3, yielded sixteen sets of signs for the 231 E values which were input. One of the solutions was associated with a consistency index [16] (C = 0·84) appreciably higher than the others; it was achieved in the smallest number of cycles and had a reasonable sign balance. In addition, the sign of the very intense 400 reflection was indicated as negative in this solution, which was consistent with previous indications of negative 400 based on packing and on intensity considerations. The E map computed from this set of signs revealed ten peaks, above a rather noisy background, which were readily seen to correspond to the positions of the non-hydrogen atoms of *cis*-tetraoxadecalin. Four cycles of overall isotropic refinement, with constant weights, of the trial structure so derived, led to R 0·162 and acceptable interatomic distances. All the observed reflections were included into this calculation.

TABLE 3

Starting set of signs

	h	k	l	E
Origin specifying reflections	15	7	5	+3·50
	4	6	$\overline{13}$	+3·20
Reflections whose signs were permuted	17	7	$\bar{5}$	3·79
	4	0	0	3·78
	7	5	$\bar{3}$	2·83
	1	7	$\overline{13}$	7·09

The criterion for this choice was the frequency of appearance of the reflections in the Σ_2 listing.

The full-matrix least-squares refinement of the structure was based on the minimalization of the function: $M = \sum_{\boldsymbol{h}} w(\boldsymbol{h})[|F_o(\boldsymbol{h})| - K|F_c(\boldsymbol{h})|]^2$ with the weighting function given by $w(\boldsymbol{h}) = [aK^2 + b|F_o(\boldsymbol{h})|^2/4w_0(\boldsymbol{h})]^{-1}$ where $w_0(\boldsymbol{h})$ is the experimental weighting parameter assigned to each reflection during the processing of the data, $a = 1$ and $b = 0$ in calculations with constant weights (apart from the dependence on the scale-factor K), and $a = 0$ and $b = 1$ in weighted calculations. The various stages of the refinement are summarized in Table 4.

The co-ordinates of the hydrogen atoms, introduced after the completion of anisotropic refinement of the heavy-atom parameters were calculated assuming standard C–H bond distances and tetrahedral angles. The isotropic temperature factors of the hydrogen atoms were kept fixed with $U_0 = 0·06$ Å^2.

During the final stage of the refinement those unobserved reflections, for which $|F_c|$ exceeded the (scaled) threshold value of F_o, were included into the calculation. The final agreement factors based on 845 reflections are R 0·071 (observed only) and R 0·083 (including 192 unobserved reflections). The final value of the weighted residual is given by: $(\Sigma w\Delta^2/n - m)^{\frac{1}{2}} = 1·60$ where $n = 845$ and $m = 121$.

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[11] (*a*) D. Rabinovich, personal communication; (*b*) J. S. Rollett and R. A. Sparks, *Acta Cryst.*, 1960, **13**, 273.

[12] A. J. C. Wilson, *Nature*, 1942, **150**, 152.

[13] D. Rogers, 'Computing Methods in Crystallography,' ed. J. S. Rollett, Pergamon, London, 1965, p. 133.

[14] D. Rogers, *Acta Cryst.*, 1950, **3**, 455.

[15] D. Sayre, *Acta Cryst.*, 1952, **5**, 60.

[16] R. Long, Ph.D. Thesis, 1965, University of California, Los Angeles.

[17] H. Hauptman and J. Karle, *Acta Cryst.*, 1959, **12**, 93.

[18] J. Karle and I. L. Karle, *Acta Cryst.*, 1966, **21**, 849.

The atomic scattering factors used were taken from ref. 19 for carbon, from ref. 20 for oxygen, and obtained from an exact calculation [21a] for hydrogen.

TABLE 4

Summary of refinement process

Stage	Parameters refined	a	b	R_{hkl}
(1)	x, y, z of non-H atoms, overall vibration and scale	1	0	0·162
(2)	x, y, z, U (isotropic) of non-H atoms, overall scale	1	0	0·159
(3) [a]	x, y, z, U_{ij} of non-H atoms, overall scale	0	1	0·112
(4)	x, y, z of all the atoms, U_{ij} of non-H atoms, overall scale	0	1	0·071
(5)	As in stage 4, but including unobserved reflections with $\lvert F_c\rvert > K^{-1}\lvert F_o\rvert$	0	1	0·071 (0·083) [b]

[a] The 002 reflection which was probably affected by extinction and the very strong 400 reflection, whose intensity could be only qualitatively estimated (and was overestimated), were excluded from the refinement at this stage. [b] R factor including unobserved reflections.

Observed and final calculated structure amplitudes are listed in Supplementary Publication No. SUP 20258 (5 pp., 1 microfiche).*

The final atomic positional and thermal parameters with their estimated standard deviations are given in Tables 5 and 6 respectively.

TABLE 5

Atomic co-ordinates as fractions of the cell edges with estimated standard deviations in parentheses

Atom	x	y	z
O(1)	0·1233(2)	0·5347(3)	0·0654(2)
C(2)	0·1263(3)	0·4570(5)	0·1796(3)
C(3)	0·1552(3)	0·6047(5)	0·2653(4)
O(4)	0·0994(2)	0·7645(3)	0·2580(2)
O(5)	0·1648(2)	0·9327(3)	0·1218(2)
C(6)	0·1583(3)	1·0097(5)	0·0083(4)
C(7)	0·1404(3)	0·8553(5)	−0·0788(4)
O(8)	0·0649(2)	0·7585(3)	−0·0535(2)
C(9)	0·0657(2)	0·6874(4)	0·0595(3)
C(10)	0·0895(2)	0·8393(5)	0·1476(3)
H(2a)	0·073(3)	0·403(6)	0·199(4)
H(2e)	0·167(3)	0·356(6)	0·176(4)
H(3a)	0·211(3)	0·651(6)	0·250(4)
H(3e)	0·152(3)	0·559(5)	0·350(4)
H(6a)	0·115(3)	1·111(6)	−0·001(4)
H(6e)	0·216(3)	1·074(6)	−0·011(4)
H(7a)	0·188(3)	0·763(6)	−0·081(4)
H(7e)	0·134(3)	0·907(5)	−0·161(4)
H(9)	0·001(3)	0·636(5)	0·080(4)
H(10)	0·043(3)	0·948(5)	0·148(4)

Thermal motion. The anisotropic vibration parameters of the non-hydrogen atoms of (1a) were analysed in terms of the rigid-body motion parameters by the method of Schomaker and Trueblood [22] with the aid of a program written by one of us (U. S.). The results of this analysis are presented in Table 7.

The root-mean-square discrepancy between both sets of tensor components is given by: $[\Sigma(V_{ij}^{\text{obs}} - V_{ij}^{\text{calc}})^2/n - m]^{\frac{1}{2}} = 0{\cdot}0026$ Å^2, with $n = 60$ and $m = 20$. The agreement between the individual components of the observed and calculated vibration tensors is also rather satisfactory, and it appears that the treatment of a (1a) molecule in the crystal as a rigid body is a valid approximation. Moreover, the description of the average motion is physically reasonable, as the markedly anisotropic libration tensor has its principal axes nearly parallel to those of the tensor of inertia, the largest libration amplitude being associated with the smallest principal moment of inertia and *vice versa*. The translational motion, on the other hand, is nearly isotropic.

TABLE 6

Anisotropic * vibration parameters $U_{ij} \times 10^4$ (Å^2), with estimated standard deviations in parentheses

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{23}	U_{13}
O(1)	697(18)	431(12)	447(16)	57(13)	−13(10)	99(15)
C(2)	774(31)	480(20)	536(26)	44(21)	51(18)	83(27)
C(3)	588(25)	644(23)	507(26)	29(22)	78(19)	27(28)
O(4)	597(17)	573(14)	405(16)	18(13)	−38(11)	39(16)
O(5)	564(16)	469(13)	501(16)	−82(13)	9(11)	−42(14)
C(6)	661(28)	533(22)	493(25)	−13(20)	57(17)	3(28)
C(7)	665(29)	549(21)	456(23)	10(22)	60(17)	70(26)
O(8)	601(18)	620(14)	377(15)	21(13)	−15(11)	−105(16)
C(9)	488(22)	508(18)	372(32)	29(18)	−43(16)	−45(22)
C(10)	445(22)	476(18)	477(24)	2(18)	−27(16)	64(23)

* In the form: $\exp\{-2\pi^2[h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2hka^*b^*U_{12} + 2klb^*c^*U_{23} + 2lhc^*a^*U_{31}]\}$.

Packing. The projection of the structure down the c axis (Figure 2) shows that the (1a) molecules are arranged in a layer-like pattern with the layers nearly perpendicular to the a axis. It is seen that the unit cell is crossed by four similarly spaced layers, avoiding the special positions, which is consistent with the high intensity and the negative sign of the important 400 reflection (*vide supra*).

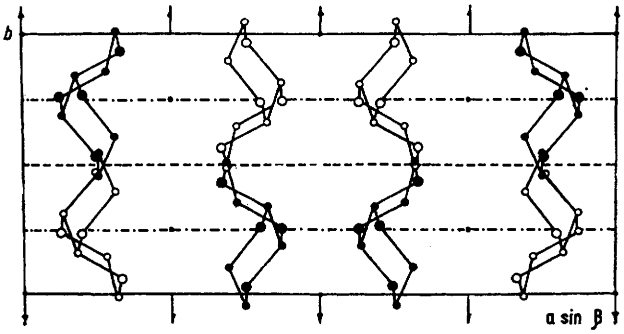

FIGURE 2 Projection of the crystal structure down the c axis

An examination of the intermolecular distances shows that the molecules are very efficiently packed, which correlates well with the relatively high density of the crystal. However, none of the inter- or intra-layer close approaches (Table 8) appears to be unusual. Some of the C · · · O distances are somewhat short, yet the relevant O · · · H distances exceed 2·60 Å which is a normal van der Waals separation between oxygen and hydrogen atoms.

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* For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc. (A)*, 1970, Issue No. 20 (items less than 10 pp. will be supplied as full-size copies).

[19] J. Berghuis, I. J. H. Haanappel, M. Potters, B. O. Loopstra, C. H. MacGillavry, and A. L. Veenendaal, *Acta Cryst.*, 1955, **8**, 478.

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[21] (*a*) 'International Tables for *X*-Ray Crystallography,' vol. III, 1962, Kynoch Press, Birmingham, p. 208; (*b*) *Chem. Soc. Special Publ.*, No. 12, 1956; No. 18, 1965.

[22] V. Schomaker and K. N. Trueblood, *Acta Cryst.*, 1968, **B24**, 63.

Molecular structure. The bond lengths and angles derived from the final atomic co-ordinates (Table 5) are given with their estimated standard deviations in Tables 9 and 10 respectively and are also illustrated in Figure 3. The parallel projection of the molecular framework (Figure 3), shows that in the crystal the (Ia) molecule has the *cis*-configuration and adopts the double chair conformation.

The chemically equivalent, but crystallographically different, bond lengths and angles (Figure 3) imply that the (Ia) molecule has a two-fold axis of symmetry, within the

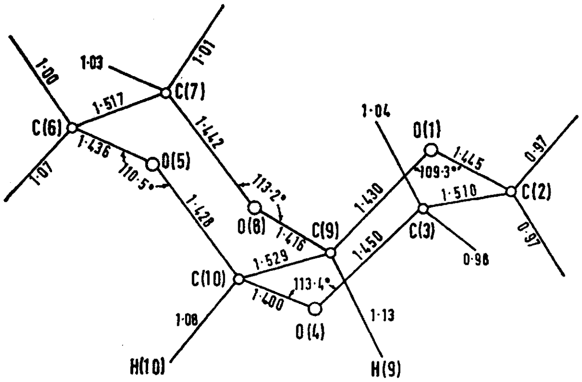


FIGURE 3 A parallel projection of the molecular framework of (1a). The bond lengths and angles are corrected for libration (excluding the C–H bonds)

TABLE 7

Results of the rigid-body-motion analysis

All the tensors in this Table are referred to the axial system of the tensor of inertia defined in (*d*); $\boldsymbol{l}_i$ and $\boldsymbol{t}_i$ are unit vectors along the principal axes of the libration tensor $\boldsymbol{L}$ and translation tensor $\boldsymbol{T}$ respectively. The translation tensor is referred to the origin with respect to which the screw tensor $\boldsymbol{S}$ is symmetric.

(*a*) Rigid-body tensors

	Tensor elements × 10^5		
	11	*22*	*33*
$\boldsymbol{L}$/rad^2	1061(117)	429(44)	317(36)
$\boldsymbol{T}$/Å^2	4294(89)	4220(116)	4015(190)
$\boldsymbol{S}$/rad Å	77(50)	−64(41)	−12(65)

	Tensor elements × 10^5		
	12	*23*	*13*
$\boldsymbol{L}$/rad^2	−29(31)	−16(32)	97(39)
$\boldsymbol{T}$/Å^2	338(81)	188(106)	168(89)
$\boldsymbol{S}$/rad Å	−177(36)	−17(20)	−38(26)

(*b*) Root-mean-square amplitudes and orientation of the axial systems of $\boldsymbol{L}$ and $\boldsymbol{T}$ with respect to the axial system of the tensor of inertia

	Amplitudes		Principal axes		
			$\boldsymbol{m}_1$	$\boldsymbol{m}_2$	$\boldsymbol{m}_3$
	5·9°	$\boldsymbol{l}_1$	172·2°	87·3°	97·3°
$\boldsymbol{L}$	3·8	$\boldsymbol{l}_2$	93·4	173·9	84·9
	3·2	$\boldsymbol{l}_3$	97·1	84·5	9·0
			$\boldsymbol{m}_1$	$\boldsymbol{m}_2$	$\boldsymbol{m}_3$
	0·220 Å	$\boldsymbol{t}_1$	133·6°	129·4°	110·4°
$\boldsymbol{L}$	0·199	$\boldsymbol{t}_2$	130·5	70·9	46·6
	0·197	$\boldsymbol{t}_3$	108·8	45·6	129·6

(*c*) Atomic vibration tensors (Å^2 × 10^4) *

	V_{11}	V_{22}	V_{33}	V_{12}	V_{23}	V_{31}
O(1)	452	476	640	−5	140	−23
	476	*482*	*649*	*−3*	*130*	*−14*
O(5)	483	447	611	−19	−78	16
	489	*469*	*594*	*10*	*−62*	*6*
C(2)	469	585	731	−44	109	−4
	454	*602*	*714*	*−41*	*118*	*−4*
C(6)	453	567	670	1	−4	15
	463	*560*	*683*	*−37*	*−15*	*5*
C(3)	479	677	583	39	1	7
	430	*651*	*594*	*61*	*−12*	*33*
C(7)	428	594	645	17	48	−32
	426	*594*	*635*	*47*	*64*	*−3*
O(4)	494	500	580	90	46	−22
	496	*489*	*576*	*89*	*33*	*−37*
O(8)	476	509	626	140	−34	91
	494	*514*	*641*	*95*	*−29*	*56*
C(9)	460	422	492	93	2	52
	483	*440*	*480*	*50*	*−21*	*8*
C(10)	500	461	433	3	21	−35
	484	*438*	*445*	*43*	*46*	*17*

* The italicized values refer to vibration tensors calculated from the rigid body model.

(*d*) The orthogonal unit vectors $\boldsymbol{m}_1$, $\boldsymbol{m}_2$, and $\boldsymbol{m}_3$, taken along the principal axes of the molecular tensor of inertia, are referred below to the reciprocal lattice vectors $\boldsymbol{a}^*$, $\boldsymbol{b}^*$, and $\boldsymbol{c}^*$

	$\boldsymbol{a}^*$	$\boldsymbol{b}^*$	$\boldsymbol{c}^*$	Description
$\boldsymbol{m}_1$	0·534	3·996	−9·617	Nearly perpendicular to the C–C bonds
$\boldsymbol{m}_2$	3·507	5·667	6·361	Nearly parallel to the C–C bonds
$\boldsymbol{m}_3$	15·604	−1·410	−1·686	Parallel to the molecular two-fold axis of symmetry

TABLE 8

Intermolecular distances <3·8 Å (excluding hydrogen atoms)

Interlayer		Intralayer	
O(4) $\cdots$ C(10$^{\rm I}$)	3·311 Å	C(2) $\cdots$ C(7$^{\rm IV}$)	3·577 Å
O(4) $\cdots$ C(10$^{\rm I}$)	3·515	C(3) $\cdots$ C(7$^{\rm IV}$)	3·741
O(4) $\cdots$ O(4$^{\rm I}$)	3·179	O(4) $\cdots$ C(6$^{\rm V}$)	3·417
C(9) $\cdots$ C(9$^{\rm II}$)	3·619	O(4) $\cdots$ C(7$^{\rm V}$)	3·341
C(3) $\cdots$ C(5$^{\rm III}$)	3·338	C(2) $\cdots$ C(6$^{\rm VI}$)	3·789

Roman numerals as superscripts refer to the following co-ordinates of equivalent positions relative to the reference molecule at x, y, z:

I $-x, y, \frac{1}{2} - z$	IV $x, 1 - y, \frac{1}{2} + z$
II $-x, 1 - y, -z$	V $x, 2 - y, \frac{1}{2} + z$
III $\frac{1}{2} - x, y - \frac{1}{2}, \frac{1}{2} - z$	VI $x, y - 1, z$

TABLE 9

Bond lengths (Å) with estimated standard deviations in parentheses

C(2)–C(3)	1·503(6) [1·510]	C(7)–O(8)	1·432(5) [1·442]
C(6)–C(7)	1·509(5) [1·517]	C(9)–O(8)	1·409(4) [1·416]
C(9)–C(10)	1·522(5) [1·529]	C(10)–O(4)	1·393(4) [1·400]
C(2)–O(1)	1·438(5) [1·445]	C(9)–O(1)	1·419(4) [1·430]
C(3)–O(4)	1·440(5) [1·450]	C(10)–O(5)	1·418(4) [1·428]
C(6)–O(5)	1·429(5) [1·436]		

Values in square brackets are corrected for the effects of librational motion by the method of ref. 22.

TABLE 10

Bond angles (deg., uncorrected), with estimated standard deviations in parentheses

O(1)–C(2)–C(3)	110·1(3)	O(8)–C(9)–O(1)	107·1(3)
O(5)–C(6)–C(7)	110·4(3)	O(4)–C(10)–C(9)	111·6(3)
C(2)–C(3)–O(4)	109·8(3)	O(8)–C(9)–C(10)	111·6(3)
C(6)–C(7)–O(8)	110·0(4)	C(10)–C(9)–O(1)	111·4(3)
C(3)–O(4)–C(10)	113·2(3)	C(9)–C(10)–O(5)	111·9(3)
C(7)–O(8)–C(9)	113·2(3)	C(9)–O(1)–C(2)	109·2(3)
O(4)–C(10)–O(5)	108·3(3)	C(10)–O(5)–C(6)	110·7(3)

The twenty-six bond angles involving hydrogen atoms range from 103·7—112·3°, mean 109·1°; mean σ 2·7°.

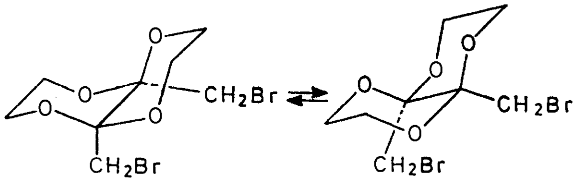
experimental error of the structure determination. It can be seen, however, that the ideal chair–chair conformation is somewhat distorted since the C(3)–O(4)–C(10) and C(7)–O(8)–C(9) angles (113·4 and 113·2°) are significantly larger than those in the other pair of symmetry-related C–O–C groups. Considering separately each of the fused dioxan rings it is found that the four carbon atoms are nearly coplanar (the maximum deviation from the best plane of either carbon quartet is 0·025 Å), while the degree of ring puckering is different for the C–O–C groups involved; defining the acute angle between the C–O(i)–C plane and the best plane of the four carbon atoms, by $\gamma_{[O(i)]}$, the following values are obtained: $\gamma_{[O(1)]} = 53{\cdot}4$, $\gamma_{[O(4)]} = 48{\cdot}6$, $\gamma_{[O(5)]} = 51{\cdot}8$, and $\gamma_{[O(8)]} = 48{\cdot}5°$. Apparently flattening occurs at O(4) and O(8) and is therefore associated with the larger C–O–C angles.

This distortion is probably due primarily to the intramolecular non-bonded interactions which are reflected in the short C(3) · · · O(5) and C(7) · · · O(1) distances (2·87 and 2·84 Å). However, a possible contribution of the tight packing to this distortion cannot be excluded.

The mean C–C bond distance in (1a) is 1·519 Å which agrees well with that for single bonds observed in several related heterocyclic compounds.[3a] It is possible however that the C–C bonds in (1a) still appear foreshortened since the direction of highest libration is nearly perpendicular to these bonds and the correction for the librational motion amounted to only 0·007 Å.

The mean of the two pairs of C–O bonds which share a common carbon atom [*e.g.* C(9)–O(8) and C(9)–O(1)] is 1·419 Å which is somewhat less than the value of 1·428 Å for a normal C–O bond distance.[21b] On the other hand the mean value of the remaining C–O bond distances is 1·443 Å.

Dynamic Conformational Analysis.—In order to study the conformational aspects of (1b) in solution a variable-temperature n.m.r. study was undertaken. Assuming an inverting double-chair, the two extreme conformers are related by a mirror-image. When they are frozen out, the bromomethyl protons are no longer enantiotopic and magnetically equivalent, but diastereotopic. The 60 MHz n.m.r. spectrum of (1b) (Figure 4) exhibits two overlapping patterns: a singlet at τ 6·31 assigned to the bromomethyl protons and an AA′BB′ system of the peripheral methylene protons centred at τ 6·07 with $w_{\frac{1}{2}}$ 56 Hz. Isomer (2b) on the other hand, exhibits two well resolved signals: a singlet at τ 6·32 and a sharp multiplet centred at τ 4·85 with $w_{\frac{1}{2}}$ 7 Hz, assigned to the bromomethyl- and dioxolan-protons respectively.[9] Since the signal of the CH_2Br protons in (1b) overlaps with those of the peripheral methylene protons, the octadeuteriated derivative $[^2H_8]$-(1b) was chosen for this investigation. Its room-temperature n.m.r. spectrum (Figure 4) consists of a singlet at τ 6·30.



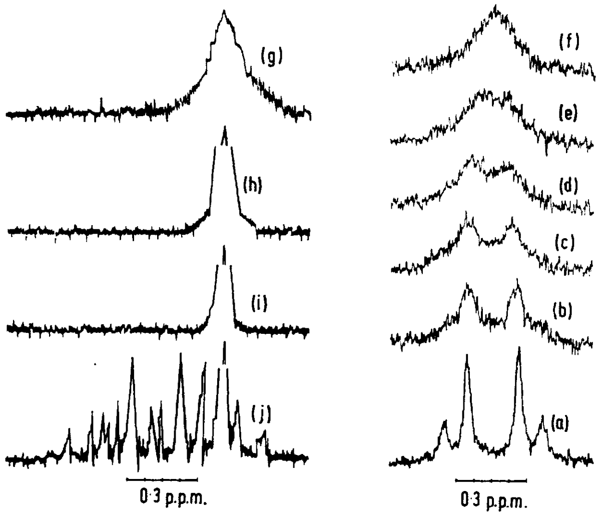


FIGURE 4 The temperature-dependent 60 MHz n.m.r. spectra of $[^2H_8]$-(1b) at: a, −70; b, −60; c, −56; d, −53; e, −50; f, −47; g, −40; h, −20; and i, 40 °C; j, room-temperature spectrum of (1b)

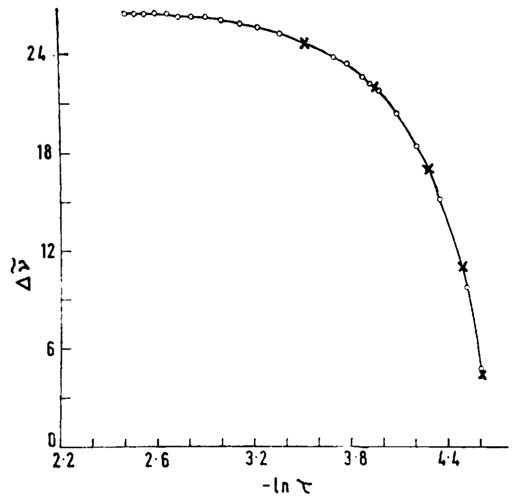


FIGURE 5 The dependence of the mean lifetime (expressed as (−log τ)) on the separation of the inner lines $\Delta\bar{\nu}$: circles, calculated; crosses, experimental values

On lowering the temperature, the n.m.r. spectrum of $[^2H_8]$-(Ib) reveals a developing AB quartet (Figure 4) unchanged down from −70 °C, with δ_{AB} 36·8 Hz and J_{AB} 12·0 Hz. The coalescence temperature is −47 °C.* This intramolecular interchanging two-site problem[23] was analysed at slow exchange with the aid of a computer program of Professor M. Saunders, and at fast exchange, *i.e.* after coalescence, using the linewidths of the coalesced singlet (w) relative to that at $\tau \rightarrow 0$ (w_0). Thus, below coalescence a plot of the separation between the inner lines *vs.* $-\ln \tau$, as τ emerged from the calculation, yielded the experimental values (Figure 5). Above the coalescence temperature, the τ values were evaluated from $\tau = 2(w - w_0)/\pi\delta_{AB}$.[2] At coalescence, τ_c was evaluated from $\tau_c = \sqrt{2}/\pi\sqrt{(\delta^2 + 6J^2)}$ to have the value of 0·01, corresponding to an inversion rate of 50 s^{-1}. From the absolute reaction

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* These values differ somewhat from those given previously in ref. 9, owing to temperature recalibration and renewed evaluation of the kinetic parameters.

[23] C. S. Johnson, jun., *Adv. Magn. Res.*, 1965, **1**, 33.

rate theory $k = (Kf/h) \,.\, T \exp(-\Delta G^{\ddagger}/RT)$ and using a transmission coefficient of $f = 1$ (*vide infra*), at −47 °C, $\Delta G^{\ddagger}_{226}$ is calculated as $4{\cdot}57T(10{\cdot}2 + \log T/k)$, which is 11·2 kcal mol^{-1}. A plot of $\ln(k/T)$ *vs.* $1/T$ (Figure 6) yielded $\Delta H^{\ddagger} = 9{\cdot}0 \pm 0{\cdot}9$ kcal mol^{-1} and $\Delta S^{\ddagger} = -9 \pm 4$ e.u.*

DISCUSSION

Interpretation of both static and dynamic conformational analysis should be carried out first with respect to decalin, and secondly in connection with *p*-dioxan and with various heterocyclic features.

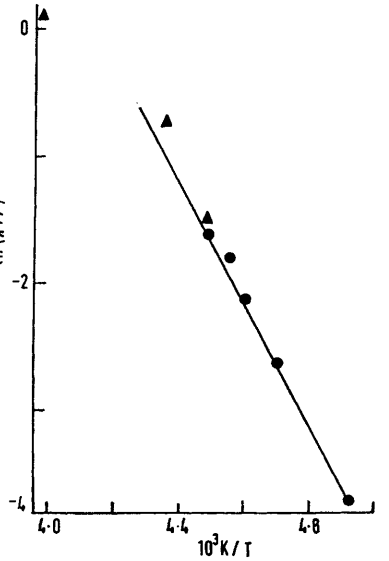

FIGURE 6 Evaluation of kinetic parameters from the absolute reaction rate expression. The slope yields $\Delta H^{\ddagger}$ 9·0 ± 0·9 kcal mol^{-1}; the intercept yields $\Delta S^{\ddagger}$ −9 ± 4 e.u.; circles, below coalescence; triangles, above coalescence

As described, the different bond lengths and angles do not appreciably alter the shape of (1a) as compared to *cis*-decalin [24] except for some partial ring flattening at C–O(4)–C and C–O(8)–C. Evidently, increased 1,3-diaxial ' cross-ring ' interactions exist, due mainly to the shorter C–O bond lengths. The resulting strain might be alleviated to some extent by the aforementioned partial ring flattening. Altogether, these effects may be thought to contribute to a lowering of the inversion barrier as compared to *cis*-decalin (*vide infra*). However, another important phenomenon operating in this system, appears to be the anomeric effect. The latter is long known in carbohydrate chemistry [25], where it was defined in terms of preference of an axial polar substituent (*e.g.* OR) in position α to the heteroatom over an equatorial one,[26a] contrary to the expected order of conformational stability. More recent *X*-ray structure analyses of sugars revealed another interesting aspect,[27] that in α-X substituted heterocycles, *viz.* containing the C–O–C–X moiety X = OR,[27] halogen [28,3a], *etc.*[26a]) the equatorial C–X bond is markedly shorter than the ' normal ' accepted value of 1·428 Å. When C–X is, however, axial the endocyclic [27] anomeric O–C bond is shorter whereas the adjacent C–O bond in the ring is longer.†

Several explanations and attempts at evaluation of the anomeric effects in its various aspects have been offered: dipole–dipole (electrostatic) interactions; [25,29] the ' rabbit-ear effect,' [26] *i.e.* the destabilization of conformations with parallel lone-pair orbitals; assignment of increased bond-order to an equatorial C–X bond due to *n*-electron delocalization into the adjacent σ* orbital; [3a,28,30] and detailed *ab initio* calculations [31] which led to the conclusion of interactions between bonded electron pairs, essentially as in the first explanation mentioned.[25] (1a) Constitutes a first and interesting example of two adjacent anomeric moieties incorporated in a bicyclic system and related by C_2 symmetry, and all the aforementioned explanations accomodate these features; we are not in a position to choose between them.

The reason why (1a) is the only 1,4,5,8-tetraoxadecalin isomer isolated under conditions of thermodynamic control is that the *trans*-isomer is presumably also the more strained one (because of two parallel dipole-pairs, *i.e.* an *anti*-periplanar bond interaction [31] or a severe double ' rabbit-ear ' effect [26]) and can be thought to form only in a kinetically controlled process.

Gerig and Roberts [32] have analysed the temperature-dependence of the ^{19}F n.m.r. spectra of 2,2-difluoro-*cis*-decalin and found an activation energy of 14·0 ± 0·8 kcal mol^{-1} ($\Delta G^{\ddagger}$ 12·0 kcal mol^{-1}, $\Delta S^{\ddagger}$ 8 ± 5 e.u.). This is in fair agreement with the value (17 kcal mol^{-1}) obtained from (Wiberg type) potential-energy calculations which also indicated a double-chair ground state for *cis*-decalin, in disagreement with a previous suggestion,[33] that it might alternatively occur in a double-twist-boat form.

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* See previous footnote concerning values in ref. 9.

† While the differences in C–O bond length are in general within a few standard deviations, their systematic occurrence in a host of widely differing structures which also exhibit the anomeric effect, strongly supports their correlation under this heading.

[24] M. I. Davis and O. Hassel, *Acta Chem. Scand.*, 1964, **18**, 813.

[25] (*a*) J. T. Edward, *Chem. and Ind.*, 1955, 1102; (*b*) J. T. Edward, P. F. Morand, and I. Puskas, *Canad. J. Chem.*, 1961, **39**, 2069; (*c*) R. V. Lemieux and N. J. Chü, *Abstracts*, 133rd Meeting Amer. Chem. Soc., San Francisco, April, 1958, p. 31N; (*d*) S. J. Angyal, *Angew. Chem.*, 1969, **81**, 172 and references therein.

[26] (*a*) A. L. Eliel and C. A. Giza, *J. Org. Chem.*, 1968, **33**, 3754; (*b*) R. O. Hutchins, L. D. Kopp, and E. L. Eliel, *J. Amer. Chem. Soc.*, 1968, **90**, 7174; (*c*) E. L. Eliel, *Svensk. kem. Tidskr.*, 1969, **81**, 22; (*d*) E. L. Eliel, *Accounts Chem. Res.*, 1970, **3**, 1.

[27] M. Sundaralingam, *Biopolymers*, 1968, **6**, 189 and references therein.

[28] For such a behaviour in dihalogeno-*p*-dioxans and -*p*-thioxan, *cf.* ref. 3*a* and (*a*) C. Altona and C. Romers, *Acta Cryst.*, 1963, **16**, 1225; (*b*) *ibid.*, *Rec. Trav. chim.*, 1963, **82**, 1080; (*c*) C. Altona, C. Knobler, and C. Romers, *Acta Cryst.*, 1963, **16**, 1217; (*d*) N. DeWolf, C. Romers, and C. Altona, *ibid.*, 1967, **22**, 715.

[29] C. B. Anderson and D. T. Sepp, *Tetrahedron*, 1967, **24**, 1707.

[30] (*a*) J. F. A. Williams, *Tetrahedron*, 1962, **18**, 1477; (*b*) E. A. C. Lucken, *J. Chem. Soc.*, 1959, 2954.

[31] S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, *J. Chem. Soc.* (*B*), 1971, 136.

[32] J. T. Gerig and J. D. Roberts, *J. Amer. Chem. Soc.*, 1966, **88**, 2791.

[33] P. Geneste and G. Lamaty, *Bull. Soc. chim. France*, 1964, 2439.

Extensions of the investigation to angularly monosubstituted difluorodecalins has revealed an interesting trend.[32] A lower activation energy was found but the entropy of activation became negative; this resulted in $\Delta G^{\ddagger}$ values, virtually identical to that of the parent system (for 9-alkyl-2,2-difluorodecalins E_a 9·2, $\Delta G^{\ddagger}$ 12·0 kcal mol^{-1} and $\Delta S^{\ddagger}$ −12 e.u.; for 10-methyl-2,2-difluorodecalin E_a 10·5, $\Delta G^{\ddagger}$ 12·4 kcal mol^{-1}, and $\Delta S^{\ddagger}$ −10 e.u.[32]). No explanation was offered for this phenomenon.

Recently,[34] decalins bearing two prochiral substituents ($-CH_2X$) in the 9- and 10-positions were investigated by variable-temperature n.m.r. techniques in order to study, as in our case, the hydrogen pairs of the angular substituents. A typical result is, for X = Br: E_a 19, $\Delta G^{\ddagger}$ 14·7 kcal mol^{-1} and $\Delta S^{\ddagger}$ 11 e.u.[34]

The increase in activation energy can be readily understood as reflecting the increased barrier due to eclipsing of the two $-CH_2X$ groups in the transition state. In the energy profile postulated by Gerig and Roberts,[32] this would mean that the ' central ' movement around the 9,10-bond might reach or even overshoot the second (*B*) barrier, thus constituting the true barrier to inversion of 9,10-disubstituted decalins.* On the other hand, the reasons for the changes recorded in the entropy of activation when comparing the un-, mono-, and di-substituted decalins are not easy to understand. Simple symmetry arguments are, in our opinion, untenable since most of the decalin derivatives examined are asymmetric and even the symmetrically substituted ones (or the parent system) have a low symmetry number of 2, which could contribute only little to the total entropy term. Recently, Pickett and Strauss [35] relied on potential functions derived from vibrational and geometrical data to calculate and construct detailed conformational energy maps for cyclohexane and some related oxanes. They concluded, that particularly for the more symmetric molecules, a positive $\Delta S^{\ddagger}$ for the chair-to-twist-boat process is required by the existence of pseudorotation in the transition state. A similar effect might operate in the bicyclic compounds but in that case the only rationalization of the cases with negative entropies of activation, is to assume flexible ground-state conformations, *i.e.* double-twist-boat [33] or chair-twist-boat, (see also preceding footnote).

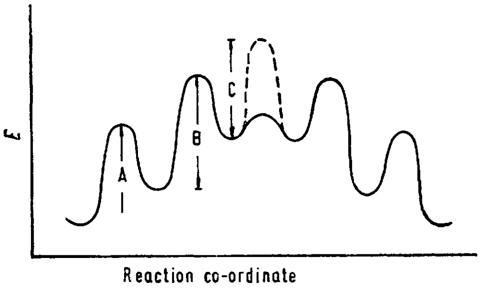

FIGURE 7 Energy profile for inversion of *cis*-decalin-type molecules

Considering now the heterocyclic aspects, replacement of the methylene group in propane by a hetero-atom, say oxygen, considerably lowers the torsional barrier.[3b,36] This has been invoked to account for the slightly but consistently lower values of $\Delta G^{\ddagger}$ for ring inversion of several six-membered heterocycles as compared to that of cyclohexane.[3c] Thus, for tetrahydropyran [37], 1,3-dioxan,[38] and 1,4-dioxan [39] the $\Delta G^{\ddagger}_{200}$ values are 9·9, 9·9, and 9·7 kcal mol^{-1}, respectively. The inversion process of 1,4-dioxan systems which is of particular interest in the context of this paper is extremely poorly documented. The only other instance for a substituted derivative is, *cis*-2,3-dichloro-1,4-dioxan with an estimated $\Delta G^{\ddagger}_{155}$ 7·5 kcal mol^{-1}.[40] This drastic lowering of the barrier is perhaps an additional result of the anomeric effect by destabilization of the ground state.

Our kinetic parameters may be interpreted for inversion of (1b) on the basis of the foregoing. That $\Delta G^{\ddagger}_{226}$ is considerably lower than that of the corresponding carbocyclic analogue [34] can be primarily understood in terms of higher ground-state energy due to lower torsional barriers coupled with the postulated anomeric effect. At the same time, it is greater than $\Delta G^{\ddagger}_{200}$ of mono- or peripherally substituted tetraoxadecalins ($\leqslant$10 kcal mol^{-1}) [41] due to the increased interaction between the $-CH_2Br$ groups in the transition state. On the other hand, the problem of the negative entropy of activation again arise. We cannot offer, at this stage, a clear answer. One possible explanation is the possibility of (1b) occurring in solution with a flexible double-twist-boat conformation as an appreciably populated ground state.† This is, in fact, supported by significant differences between the i.r. spectra for both solution and solid (1a) and (1b).

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* The postulated energy profile [32] is shown in Figure 7 including the suggested increase in the ' central ' barrier (broken line). This would imply a transmission coefficient of $f = 1$, which was actually used in our calculations (as compared to $f = \frac{1}{2}$ defined by the Gerig–Roberts profile). This constitutes a minor dilemma since the difference of $\frac{1}{2}$ in f, with the latter being part of a logarithmic term, affects the thermodynamic parameter only a little.

† Examination of Dreiding models reveals that the energy profile for double-chair (cc) interconversion of *cis*-1,4,5,8-tetraoxadecalin should in fact, differ from the one depicted for the *cis*-decalin (*vide supra*).[32] Thus, due mainly to the different C–C and C–O bond lengths the first and second minimum in the profile appear to be the chair-twist-boat (ct) and twist-boat-twist-boat (tt) conformations. The latter might in fact constitute the stable conformation of this system because of partial mitigation of nonbonded interaction relative to the carbocyclic *cis*-decalin. The energy profile would then take the form shown in Figure 8. The magnitude of the central barrier depends, of course, on the angular substituents (*cf.* previous footnote).

[34] J. Altman, H. Gilboa, D. Ginsburg, and A. Loewenstein, *Tetrahedron Letters*, 1967, 1329.

[35] H. M. Pickett and H. L. Strauss, *J. Amer. Chem. Soc.*, 1970, **92**, 7281.

[36] E. L. Eliel and M. Carmeline Knoeber, *J. Amer. Chem. Soc.*, 1968, **90**, 3444.

[37] G. Gatti, A. L. Segre, and C. Morandi, *J. Chem. Soc.* (*B*), 1967, 1203.

[38] B. Pederson and J. Schaug, *Acta Chem. Scand.*, 1968, **22**, 1705.

[39] F. R. Jensen and R. Neese, unpublished preliminary observation quoted in ref. 35, footnote 17.

[40] C. Altona, *Thesis*, Leiden, 1964, also quoted in ref. 7*a*.

[41] Y. Auerbach, M. Sprecher, and B. Fuchs, *Tetrahedron Letters*, 1970, 5207.

EXPERIMENTAL

M.p.s are corrected. Microanalyses were performed by A. Heller, Weizmann Institute Microanalytical Laboratory, Rehovoth. N.m.r. spectra were recorded at 100 MHz on a Varian HR 100 instrument or at 60 MHz on a Varian A 60A instrument equipped with a V 6040 variable-temperature controller. Mass spectra were measured with an Atlas CH4 spectrometer (70 eV) at the Israel Institute of Technology, Haifa (courtesy of Dr. A. Mandelbaum). G.l.c. was performed on an SAIB/Chromosorb P column at 140 °C (helium flow rate 100 ml min^{-1}) with a Perkin-Elmer 800 gas chromatograph equipped with a thermal conductivity detector.

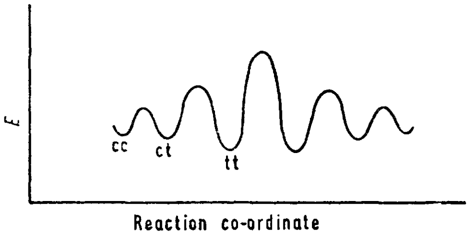

FIGURE 8 Alternative energy profile for inversion of *cis*-1,4,5,8-tetraoxadecalin, assuming a twist-boat-twist-boat (tt) ground state

cis-9,10-*Bisbromomethyl*-1,4,5,8-*tetraoxadecalin* (4a,8a-*Bisbromomethylhexahydro*-p-*dioxino*[2,3-b]-p-*dioxin*) (1b).—A solution of 1,4-dibromobutane-2,3-dione (Aldrich; 10 g, 0·041 mol), ethylene glycol (5·6 g, 0·09 mol), and toluene-*p*-sulphonic acid (0·2 g) in toluene (60 ml) was refluxed overnight (Dean–Stark head). When no more water was collected (total 1·6 ml), the mixture was evaporated to dryness. Crystallization from carbon tetrachloride afforded two crops (3·9 g) of *product* (1b), m.p. 230°. Recrystallization from dioxan gave colourless crystals m.p. 235°, $\nu_{max.}$ (KBr) 1090, 687, 657, and 520 cm^{-1}; τ ($CDCl_3$) 3·69 (4H, s, 2 × CH_2Br) and 3·93 (8H, m, $W_{\frac{1}{2}}$ 56 Hz, 4 × CH_2)[9] (Found: Br, 48·4. $C_8H_{12}Br_2O_4$ requires Br, 48·2%).

The mother liquor was evaporated to dryness and the residue chromatographed on neutral Alumina (Merck; 300 g). Elution with light petroleum–chloroform (3 : 1) yielded material (2·15 g) which was crystallized from dioxan to give a small amount of (1b) followed by colourless crystals of 2,2′-*bisbromomethylbi*(*dioxolan*-2-*yl*) (26) (1·7 g), m.p. 137—138°; $\nu_{max.}$ (KBr) 1168, 842, 626, and 580 cm^{-1}; τ ($CDCl_3$) 3·68 (4H, s, 2 × CH_2Br) and 4·15 (8H, m, $W_{\frac{1}{2}}$ 7 Hz, 4 × CH_2)[9] (Found: Br, 47·95%).

Reduction of the Tetraoxadecalin (1b) *with Lithium Aluminium Hydride*.—A solution of compound (1b) (1 g) in tetrahydrofuran was added to a suspension of lithium aluminium hydride (1 g) in the same solvent and the mixture was refluxed overnight. Standard work-up and crystallization from hexane yielded colourless crystals (142 mg) m.p. 80°, identical (g.l.c. retention time, i.r. n.m.r. and mass spectra) with authentic *cis*-9,10-dimethyl-1,4,5,8-tetraoxadecalin (1c).[6]

Reduction of the Bidioxolanyl (2b) *with Lithium Aluminium Hydride*.—A similar procedure gave a liquid product, which was isolated by preparative g.l.c. and identified (retention time and n.m.r. and mass spectra) as 2,2′-dimethylbi(dioxolan-2-yl) (2c).[6]

cis-9,10-*Bisbromomethyl*-1,4,5,8-*tetraoxa*[$^2H_8$]*decalin* {[$^2H_8$]-(1b)}.—This was prepared similarly to compound (1b) from [$^2H_4$]ethylene glycol (Merck). The product had m.p. 229—230°, $\nu_{max.}$ (KBr) 2100, 2230, 1065, 668, 622, and 528 cm^{-1}; τ ($CDCl_3$) 3·68 (s).

Variable-temperature N.m.r. Measurements.—These were performed at 60 MHz on a 5% solution in [^2H]chloroform with tetramethylsilane as internal standard. The latter was recorded in every spectrum for natural linewidth checks. The temperatures were monitored with a copper–constantan thermocouple inserted in the probe, but the actual temperatures of the solutions were taken from the methanol line separation and are believed to be accurate to *ca.* ±2 °C. The spectra are displaced in Figure 4 and the kinetic analytical procedure is described in the text.

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