Kinetics of Thermal Racemization of Some 1,2-Dihalides

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The first-order rate constants for the thermal racemization of *trans*-1,2-dibromocyclopentane, -cyclohexane, -cycloheptane, and -cyclo-octane, 1,2-dibromopentane, *threo*-2,3-dibromopentane, and *trans*-2-chloro-1-bromocyclohexane have been measured at different temperatures and the activation parameters have been determined. Values of the activation energies ranging between 29·2 and 33·2 kcal mol^{-1} have been found for the dibromides, the activation entropies being very low; the chloro-bromide had the highest activation energy (35·9 kcal mol^{-1}). A parallelism has been observed between the racemization and the iodide-promoted debromination of *trans*-1,2-dibromocycloalkanes. All data are consistent with a racemization mechanism identical with that proposed for the diaxial–diequatorial rearrangement of steroidal and cyclohexyl *trans*-1,2-dibromides.

In the course of previous work on the asymmetric bromination of alkenes [1-4] it was observed that optically active acyclic and cyclic *trans*-1,2-dibromides racemize on heating. It was suggested [2,5] that the mechanism of this racemization is the same as that involved in the interconversion of diaxial and diequatorial steroidal and cyclohexyl vicinal dibromides, a type of ' 1,2-interchange ' which has been studied in some detail before.[5,6] With the aim of obtaining more conclusive information on the analogy between these two processes and particularly on their structural and conformational requirements, we undertook a kinetic investigation of the thermal racemization of a group of vicinal dibromides, including dibromoalkanes and dibromocycloalkanes of different ring size. Moreover, in order to assess the influence of the halogen involved in the process, we also included *trans*-2-chloro-1-bromocyclohexane.

RESULTS AND DISCUSSION

The optically active dibromides were easily obtained by asymmetric bromination of the appropriate alkenes in the presence of dihydrocinchonine. The additions occurred exclusively in an *anti*-fashion (g.l.c.). The active *trans*-chloro-bromide (7) was similarly prepared by addition of bromine chloride to cyclohexene in the presence of the same alkaloid; only a small amount of *trans*-dibromide was formed beside the desired adduct (7). All dihalogenocycloalkanes obtained by the above method were laevorotatory, while the acyclic dibromoalkanes were dextrorotatory, in agreement with previous findings.[1-4] The optical yields of these asymmetric transformations were probably rather low, even if no precise estimate can be made since the maximum optical rotations of these dihalides are unknown. Anyway, the rotations obtained were always high enough to permit accurate measurements on neat liquids (Experimental section). All compounds (1)—(7) racemized cleanly on heating in sealed tubes under nitrogen and the rates were measured at three temperatures. The occurrence of side reactions was excluded, since the i.r. and n.m.r. spectra and the gas chromatograms were identical before and after complete racemization. In the case of the chloro-bromide (7), the presence of the compound (2), as a by-product with higher optical rotation, would have interfered in the rate measurements. However the racemization was much slower for the chloro-bromide than for the dibromide, so that brief heating at 175° of samples of (7) contaminated by (2) caused complete racemization of the latter without appreciable loss of optical purity of the former. Thereafter the rate of racemization of (7) was easily measured without interference by (2).

In all cases the racemizations exhibited clean, first-order kinetics at the temperatures studied. Rate constants are reported in Table 1, which also includes literature data [7] on the second-order rate constants for the debrominations of cyclic dibromides by iodide ion in methanol. The data of Table 1 fit the Arrhenius equation satisfactorily; the activation parameters thus obtained are quoted in Table 2, which also includes those reported for the debrominations.[7]

The first conclusion drawn from the data of Tables 1 and 2 is that the kinetics of the thermal racemization of dibromocycloalkanes (1)—(4) are only slightly affected by the structural and conformational features of the substrates. The rates fall within a narrow range, the extremes (for *trans*-1,2-dibromocyclohexane and *trans*-1,2-dibromocycloheptane) differing at 120°, for example, only by a factor of 5·09. The activation parameters are accordingly of comparable magnitude. However, the differences observed, although subtle, may provide some useful mechanistic information.

The thermal interconversion between diaxial and diequatorial cyclohexyl and steroidal vicinal dibromides is considered as a ' 1,2-interchange ' [6] occurring through an intermediate state having a polar bromonium–bromide type character (8) or a bicyclic non-polar structure (9), depending on the polarity of the reaction medium [8,9] (Scheme). Intermediate (8) would be involved in polar solvents; (9), which could be a non-classical intermediate or the transition state of a single step process, in the less polar ones.

The activation parameters of these transformations,

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[1] G. Berti and A. Marsili, *Tetrahedron*, 1966, **22**, 2977.

[2] G. Bellucci, C. Giordano, A. Marsili, and G. Berti, *Tetrahedron*, 1969, **25**, 4515.

[3] G. Bellucci, G. Berti, F. Marioni, and A. Marsili, *Tetrahedron*, 1970, **26**, 4627.

[4] G. Bellucci, F. Marioni, and A. Marsili, *Tetrahedron*, 1969, **25**, 4167.

[5] P. L. Barili, G. Bellucci, G. Berti, F. Marioni, A. Marsili, and I. Morelli, *J.C.S. Perkin II*, 1972, 58.

[6] D. N. Kirk and M. P. Hartshorn, ' Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, p. 373.

[7] J. Weinstock, S. N. Lewis, and F. G. Bordwell, *J. Amer. Chem. Soc.*, 1956, **78**, 6072.

[8] C. A. Grob and S. Winstein, *Helv. Chim. Acta*, 1952, **35**, 782.

[9] J. F. King and R. G. Pews, *Canad. J. Chem.*, 1965, **43**, 847.

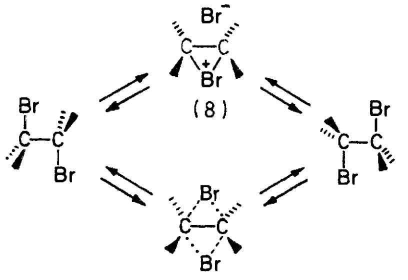
which have been recently evaluated[5] for a group of substituted cyclohexyl dibromides, were found to be *independent* of remote alkyl substituents on the ring. The values found in the present work for the racemization of *trans*-1,2-dibromocyclohexane are practically identical with those reported for the equilibration of 4-methyl- and 4-t-butyl-*r*-1,*t*-2-dibromocyclohexanes, a fact that strongly points to similar reaction paths and transition states for either the equilibration or the racemization, as already suggested.[5]

TABLE 1

Rates of racemization of vicinal dihalides

Substrate	t/°C	10^5k_1/s^{-1}	Relative rates at 120·0°	Relative rates of debromination *
trans-1,2-Dibromocyclopentane (1)	100·3	1·40 ± 0·03		
	120·0	10·30 ± 0·40	2·04	3·88
	140·1	68·40 ± 0·40		
trans-1,2-Dibromocyclohexane (2)	100·5	0·58 ± 0·01		
	120·0	5·05 ± 0·07	1·00	1·00
	140·3	35·30 ± 0·50		
trans-1,2-Dibromocycloheptane (3)	100·5	3·54 ± 0·07		
	120·0	25·70 ± 0·70	5·09	15·60
	135·3	108·00 ± 2·80		
trans-1,2-Dibromocyclo-octane (4)	100·2	1·02 ± 0·14		
	120·0	6·40 ± 0·32	1·27	3·20
	140·3	47·10 ± 1·40		
1,2-Dibromopentane (5)	120·0	0·54 ± 0·01	0·11	
	140·2	4·33 ± 0·05		
	155·0	17·50 ± 0·70		
threo-2,3-Dibromopentane (6)	100·2	0·76 ± 0·01		
	120·0	6·70 ± 0·01	1·33	
	133·8	45·40 ± 0·35		
trans-2-Chloro-1-bromocyclohexane (7)	165·0	1·55 ± 0·06		
	180·0	6·64 ± 0·28		
	199·8	34·09 ± 3·13		

* Data taken from ref. 7 are for rates of debromination on treatment with iodide ion in 99% methanol at 110°.



(9)

SCHEME

The racemization rates in the dibromocycloalkane series are in the order $C_7 > C_5 > C_8 > C_6$. Although less marked, this trend is analogous to that found[7] for the rates of debromination of the same compounds with iodide ion in methanol. The data of Table 2 show that the activation entropies are very low for the racemization, in agreement with the intramolecular process shown in the Scheme, and more negative but practically identical for the debrominations. However, the activation energies for compounds (1)—(3) [those for the debromination of (4) have not been reported] are in the same order for both reactions. This parallel between the kinetics of racemization and of debromination strongly suggests similar requirements for the respective transition states.

The debromination of vicinal dibromides with iodide is a bimolecular process requiring an antiparallel approach to the transition state, as shown by the much higher reactivity of diaxial than diequatorial steroidal[10-12] and cyclohexyl 1,2-dibromides.[13] This reaction has been considered[14] as a concerted $E2$-type elimination proceeding through a transition state similar to (10); however, a stepwise mechanism has recently been proposed,[15] involving the rate-determining formation of 'onium species of type (11). Even if the latter mechanism seems more attractive on the basis of the analogy between the kinetics of debromination and of racemization, it must be pointed out that a choice between these two mechanisms appears immaterial for the present discussion. In fact their transition states

TABLE 2

Activation parameters for the racemization and debromination of vicinal dihalides [a]

	Racemization			Debromination [b]	
Substrate	E_a	ΔH	ΔS‡	E_a	ΔS‡
(1)	29·9	29·2	−3·1	23·2	−14·7
(2)	31·7	30·9	−0·1	24·8	−13·8
(3)	29·7	29·0	−1·8	22·5	−13·8
(4)	29·2	28·4	−5·7		
(5)	33·2	32·4	−0·7		
(6)	31·6	30·8	+0·2		
(7)	35·9	35·0	−1·3		

[a] E_a and ΔH‡ are expressed in kcal mol^{-1}, ΔS‡ in cal K^{-1} mol^{-1}.
[b] Taken from ref. 7.

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[11] D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1951, 1048.

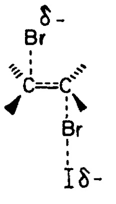
[12] G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, 1954, 4284.

[13] W. Hückel and H. Wablinger, *Annalen*, 1963, **666**, 16.

[14] D. V. Banthorpe, 'Elimination Reactions,' Elsevier, New York, 1963, p. 140.

[15] C. S. Tsai Lee, I. M. Mathai, and S. I. Miller, *J. Amer. Chem. Soc.*, 1970, **92**, 4602.

have similar geometric requirements, *i.e.* antiparallel orientation of the halogen atoms and an approximately planar arrangement of the carbon atoms bearing bromine. The dibromocycloalkanes (1)—(4) can easily assume the necessary *anti*-conformation, which is the more stable one at least in the five- and six-membered ring compounds (1) and (2).[16,17] Nevertheless both the racemization and the debromination of *trans*-1,2-dibromocyclohexane show an activation energy higher by *ca.* 2 kcal mol^{-1} than the other cyclic dibromides. This trend, typical of reactions of cyclic compounds involving a change from a tetrahedral to a planar arrangement at the reaction sites on passing from the ground to the transition state, has been attributed to *I* strain relief in the transition states of the C_5, C_7, and C_8 rings.[18] Again, the observed activation energy order ($C_6 > C_5 \simeq C_7 \simeq C_8$) is therefore consistent with a racemization mechanism such as one of the types shown in the Scheme, in which the transition state should have an approximately planar, olefin-like geometry, which is more favourable in the C_5, C_7, and C_8 than in the C_6 ring, as shown, for example, by the relative heats of hydrogenation and heats of bromination of these cycloalkenes.[7]



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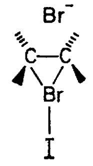
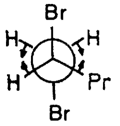


(11)

In the acyclic series, *threo*-2,3-dibromopentane has activation parameters practically identical with those of *trans*-1,2-dibromocyclohexane, whereas 1,2-dibromopentane has an activation energy higher by 1·5 kcal mol^{-1}. This difference between the two dibromoalkanes can hardly be ascribed to conformational factors, since they would instead suggest an opposite order. In fact the *anti*-rotamer of dibromide (5) should be more stable than that of (6) and the difference should increase on passing to approximately planar transition states, since steric compression between the methyl and ethyl groups of (6) should be higher than between hydrogen and n-propyl group of (5).



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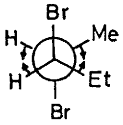

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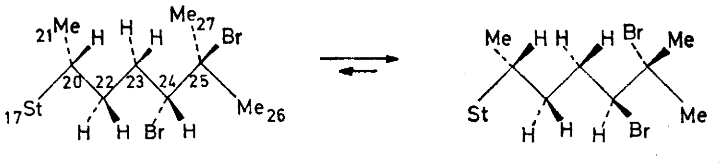

24*R* 24*S*

On the other hand, (6) is a bis-secondary vicinal dihalide, whereas (5) is a primary–secondary one. Easier C–Br bond breaking in the transition state for (6), outweighing the steric effects, could be responsible for the faster racemization of (6) than (5). In fact, even if in both dibromides bond breaking occurs at a secondary carbon atom, the electronic effect of the vicinal secondary group in (6) might accelerate S_N1 fission at the other carbon atom. There are no data on the kinetics of racemization of secondary–tertiary vicinal dihalides. However the easy conversion of lanosteryl acetate 24*R*,25-dibromide into the 24*S*-diastereoisomer ($\Delta G^{\ddagger}$ 25·5 kcal mol^{-1}) has been reported recently.[19] While the higher thermodynamic stability of the 24*S*- over the 24*R*-diastereoisomer has been attributed to steric interaction between the 20-methyl group and the 24-bromine atom in the latter, we believe that the large increase in the reaction rate with respect to the racemization of our dibromoalkanes should be due mostly to easier breaking of the C(25)–Br bond, owing to its tertiary character.

The following order seems therefore to be valid for the racemization (or isomerization) rates of dibromoalkanes: tertiary–secondary > secondary–secondary > secondary–primary. We emphasize that this series, pointing to an S_N1-type process, suggests that incipient bromide formation is the important process in the rate-determining step of these reactions. This is more in agreement with a polarized than with a non-polar structure of type (9) for the transition state.

Finally, the racemization of the chloro-bromide (7) has an activation energy higher by *ca.* 4 kcal mol^{-1} than the corresponding dibromide (2). These findings are consistent with previous reports[20] on the relative rates of '1,2-interchange' in steroidal halogenohydrin esters, and stress the importance of the greater strength of the C–Cl relative to the C–Br bond and of the lower tendency of chlorine to nucleophilic participation in displacement reactions.

EXPERIMENTAL

Optical rotations were measured with a Perkin-Elmer 141 photoelectric polarimeter; the values given are observed

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[16] P. Laszlo, *Progr. N.M.R. Spectroscopy*, 1967, **3**, 231; H. Booth, *ibid.*, 1969, **5**, 149; C. Altona, H. R. Buys, H. J. Hageman, and E. Havinga, *Tetrahedron*, 1967, **23**, 2265.

[17] C. Altona, H. R. Buys, and E. Havinga, *Rec. Trav. chim.*, 1966, **85**, 973, 983, 998.

[18] E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, p. 265.

[19] D. H. R. Barton, H. MacGrillen, P. D. Magnus, C. H. Carlisle, and P. A. Timmins, *J.C.S. Perkin I*, 1972, 1584.

[20] D. H. R. Barton and J. F. King, *J. Chem. Soc.*, 1958, 4398.

rotations for neat liquids at 25° in 1 dm tubes and are accurate within ±0·005°.

G.l.c. analyses were performed on a Fractovap C. Erba G.V. instrument, fitted with a 1 m steel column, diam. 0·8 cm, packed with 1% neopentyl glycol succinate on Chromosorb W 80—100 mesh.

Chloroform was purified immediately before use by washing with concentrated sulphuric acid and water followed by distillation.

Olefins.—Commercial cyclopentene, cyclohexene, cycloheptene, *cis*-cyclo-octene, pent-1-ene, and *cis*-pent-2-ene were purified (99%) by fractionation through a spinning band column.

Asymmetric Halogenations.—Brominations were carried out in chloroform solution at 0° in the presence of dihydrocinchonine as already described.[1] The bromochlorination of cyclohexene was performed analogously by using 2M-bromine chloride in carbon tetrachloride. Solvents were evaporated and products distilled at temperatures low enough to prevent racemization. G.l.c. analyses of the dibromides always showed a single peak. The addition of bromine chloride to cyclohexene gave, besides (7), *ca.* 10% of (2) which was not completely removed by fractional distillation; however, (2) was racemized, the optical purity of (7) being slightly affected, by heating the mixture at 175° for 30—60 min. The optical rotations of the products are reported in Table 3.

Thermal Racemizations.—Samples of *ca.* 1·5 ml of each dihalide were sealed in Pyrex tubes under nitrogen and completely immersed in a thermostatted bath at the indicated temperatures (±0·2°). The samples were withdrawn at intervals and rapidly cooled in ice–water. Darkening occurred, especially at the higher temperatures, but n.m.r., g.l.c., and i.r. analysis did not reveal the formation of appreciable amounts of by-products. When necessary, the samples were decolourized by rapid distillation at temperatures much lower than those of the kinetic runs and their optical rotations measured at 589, 546, and 436 nm. No racemization occurred during these distillations, since the optical rotations remained unchanged after two or three identical operations. In the case of (4) the samples were decolourized by percolating through a silica gel column with pentane as eluant.

TABLE 3

Refractive indices and optical rotations of dihalides (neat, 1 dm, 25°)

Product	n_D^{25}	α_{589} (°)	α_{546} (°)	α_{436} (°)
(1)	1·5470	−4·100	−4·695	−8·270
(2)	1·5500	−3·850	−4·415	−7·950
(3)	1·5545	−0·940	−1·080	−1·915
(4)	1·5509	−0·950	−1·085	−1·935
(5)	1·5045	+0·585	+0·665	+1·125
(6)	1·5058	+3·190	+3·630	+6·260
(7) *	1·5198	−1·075	−1·230	−2·155

* Measured after racemization of the impurity (2).

All racemizations exhibited satisfactory first-order kinetics. Six or more measurements were carried out for each temperature and the first-order rate constants were calculated by the least-squares method by using the optical rotations at the three wavelengths. The errors given in Table 1 are standard deviations. Plots of ln *k* against $1/T$ gave good straight lines, the slopes of which were calculated by the least-squares method. The transition state activation parameters, $\Delta H^\ddagger$ and $\Delta S^\ddagger$, were calculated as described [5] for the average temperature of the range studied.

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