The Stereochemistry of Autoxidation of 2-Bromo-1-methylcyclohexane

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Autoxidation of *cis*-2-bromo-1-methylcyclohexane and subsequent reduction of the resulting hydroperoxide with lithium aluminium hydride gave only *t*-2-bromo-1-methyl-*r*-1-cyclohexanol to the exclusion of the *c*-2-bromo-isomer. The reactivity ratio of the C–1 hydrogen in *cis*-2-bromo-1-methylcyclohexane to that in 1, *c*-3, *c*-5-trimethylcyclohexane towards abstraction was estimated to be about 4 by competitive oxidation experiments. An explanation for the acceleration of hydrogen abstraction and the stereospecific oxygen attack on the intermediate radical is given in terms of a bromine bridged radical. Autoxidation of a sample of 2-bromo-1-methylcyclohexane, containing about 90% of the *trans* isomer, took place very slowly as compared with the *cis* isomer.

In previous papers,[1,2] it was shown that oxygen attacks the bromocyclohexyl radicals generated by addition of a bromine atom to cyclohexene and 1-methylcyclohexene exclusively from the *trans* direction to the bromine atom, while an almost random attack of oxygen occurs on both sides of the methylcyclohexyl radicals formed by hydrogen abstraction from a variety of methylcyclohexanes. This paper is concerned with the autoxidation of 2-bromo-1-methylcyclohexane carried out in order to examine the effect of the neighbouring bromine substituent on the reactivity of the hydrogen at position 1 towards abstraction as well as the stereochemical course of oxygen attack on the intermediate radical.

Results and Discussion

cis-2-Bromo-1-methylcyclohexane (**1**) was prepared by radical addition of hydrogen bromide to 1-methylcyclohexene in heptane followed by partial hydrolysis and fractionation for separation from 1-bromo-1-methylcyclohexane, a by-product. The NMR spectrum indicated that the product obtained was free of the *trans* isomer (**2**), as evidenced by the absence of the signal (doublets of a triplet) centered at δ 3.61 due to a Br–C–H proton in the *trans* isomer.[3]

The *cis* bromide (**1**) was autoxidized with oxygen in the presence of azobisisobutyronitrile at 60 °C, and the resulting hydroperoxide was reduced with lithium aluminium hydride to the corresponding alcohol. Gas-liquid partition chromatographic analysis showed that *t*-2-bromo-1-methyl-*r*-1-cyclohexanol (**3**) was the sole detectable alcohol, the retention time agreeing with that of an authentic specimen on each of three different columns (diisodecyl phthalate, polyethylene glycol, and cyanosilicone). The *cis* isomer could not be detected. The results are summarized in Table 1.

In order to estimate the relative rate of abstraction of the C-1 hydrogen in *cis*-2-bromo-1-methylcyclohexane (**1**), competitive oxidation experiments with 1, *c*-3, *c*-5-trimethylcyclohexane (**4**) were performed. The results are shown in Table 2. Treatment of these data with the same method as described previously[1] gave a reactivity ratio of the C-1 hydrogen in bromomethyl-

TABLE 1. AUTOXIDATION OF 2-BROMO-1-METHYLCYCLOHEXANE[a]

Bromide (mmol)		AIBN[b] (mmol)	Reaction time (hr)	Hydroperoxide (mmol)	Bromohydrin (mmol)	
					cis	*trans* (**3**)
cis (**1**)	7.18	0.024	22	0.21	0	Formed[c]
cis (**1**)	7.21	0.048[e]	24	0.28	0	0.22[d]
cis+*trans* (**1**+**2**)[f]	7.09	0.025	22	0.040		

a) At 60.0 °C. b) Azobisisobutyronitrile. c) After reduction with sodium borohydride. The amount was not determined. d) After reduction with lithium aluminium hydride. e) AIBN was added in two portions. f) **1** : **2**=10 : 90.

TABLE 2. COMPETITIVE AUTOXIDATION OF *cis*-2-BROMO-1-METHYLCYCLOHEXANE (**1**) WITH 1,*c*-3,*c*-5-TRIMETHYLCYCLOHEXANE (**4**)[a]

1 (mmol)	**4** (mmol)	AIBN[b] (mmol)	Hydroperoxide (mmol)	Alcohols[c] (mmol)		
				trans-Bromohydrin **3**	1,3,5-Trimethyl-cyclohexanol	Total
7.20	6.05	0.148	0.491	0.227	0.137	0.364
7.19	6.04	0.143	0.485	0.217	0.144	0.361

a) At 60.0 °C for 24 hr. b) Azobisisobutyronitrile. c) After reduction with lithium aluminium hydride.

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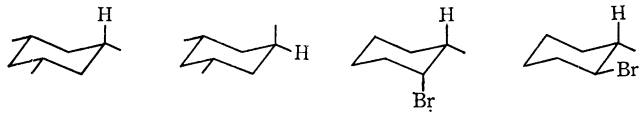
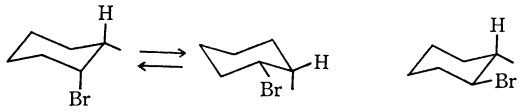
Table 3. Relative rates of hydrogen abstraction



1.0	2.6[a)]	4	*ca.* 0.4
4	**5**	**1**	**2**

a) Ref. 1.



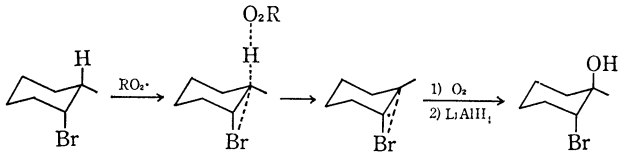
1a **1e** **2**

Fig. 1. Conformation of 2-bromo-1-methylcyclohexanes.

cyclohexane **1** to that in trimethylcyclohexane **4** towards abstraction of about 4 (Table 3), a considerably large value compared with that for an axial hydrogen atom in the ordinary situation.

Although the *cis* bromide (**1**) is not conformationally uniform, conformer **1a** should predominate largely over **1e** (Fig. 1), since the conformational equilibrium constant of **1**, the *gauche* interactions between the methyl and bromine substituent cancelling out for the pair of conformers, is considered to be almost equal to 0.1 for *cis*-4-bromo-1-methylcyclohexane.[4)] The large reactivity of the C-1 hydrogen in the *cis* bromide (**1**) may be in part due to steric acceleration caused by relief, in the transition state, of a *gauche* interaction between the C-1 methyl group and the C-2 bromine in conformer **1a**. However, the contribution of this effect would be of minor importance, since the observed reactivity ratio of 4 corresponds to a difference of 0.9 kcal/mol in free energy of activation, while the *gauche* interaction between a methyl group and a bromine atom is only 0.25 kcal/mol.[5)] The contribution of conformer **1e** would also be insignificant; the equatorial C-1 hydrogen in **1e** would be hindered by the C-2 equatorial bromine substituent, whereas there is no such hindrance suffered by the hydrogen at C-5 in 1, *c*-3,*t*-5-trimethylcyclohexane (**5**). Moreover, the abstraction of the C-1 hydrogen in **1e** would be less favoured than that at C-5 in **5** because of the incipient eclipsing of the methyl and bromine substituent, as the methyl tends to be planar with the other two bonds at carbon atom 1 in the course of abstraction. Even if the relative reactivity of the equatorial hydrogen in **1e** should be equal to 2.6 for compound **5**, the contribution of **1e** to the relative reactivity is only 0.26, since the conformational population of **1e** is estimated to be about 10%.

The relative reactivity of 4 found for *cis*-2-bromo-1-methylcyclohexane (**1**) is thus attributed mainly to the hydrogen in axial position at carbon atom 1, and apparently the value is higher than that expected for a hydrogen in similar steric environments. A special effect causing such an acceleration must be due to the bromine substituent at position 2, although the halogen substituent is known to retard the hydrogen abstraction



1 **3**

Fig. 2. Autoxidation of *cis*-2-bromo-1-methylcyclohexane.

reaction because of electron-attracting inductive effect.[6)] A possible explanation of both the acceleration of hydrogen abstraction and the stereospecific oxygen attack in *cis* bromo-compound **1** may be that the axial bromine substituent anchimerically delocalizes an incipient odd electron in the transition state of hydrogen abstraction and then forms a bridged intermediate radical[7)] (Fig. 2).

Although a mixture of *cis*- and *trans*-2-bromo-1-methylcyclohexane (**1** and **2**) was obtained in a ratio of about 10 : 90 by the Hunsdiecker reaction of silver 2-methylcyclohexanecarboxylate,[3)] attempts to isolate the pure *trans* isomer from this mixture were unsuccessful. Autoxidation of a sample of the mixture took place very slowly, as shown in Table 1. From comparison of the amount of hydroperoxide formed from this mixture with that from the pure *cis* isomer, the approximate reactivity ratio of the C-1 hydrogen in *trans*-2-bromo-1-methylcyclohexane (**2**) to that in trimethylcyclohexane **4** towards abstraction was estimated to be about 0.4. The observed retardation may be ascribed to inductive effect of a bromine substituent and/or a sterically unfavourable transition state with the methyl group and bromine substituent tending to eclipse each other.

Experimental

All melting points and boiling points are uncorrected. Glpc work was carried out with a Perkin-Elmer model 154 D instrument. NMR data were obtained with a Varian A-60 spectrometer using tetramethylsilane as an internal standard. IR spectra were recorded on a Nihon-Bunko DS-402 G spectrometer.

cis-2-Bromo-1-methylcyclohexane (1). Hydrogen bromide, dried by passing through a trap cooled at −50 °C and a tube packed with anhydrous calcium sulphate, was bubbled through a solution of 80 ml (64.8 g) of 1-methylcyclohexene and 8.2 g of benzoyl peroxide in 600 ml of heptane for 4 hr at 65—75 °C with stirring. After removal of excess of hydrogen bromide with solid sodium hydrogencarbonate, the solution was filtered and the solvent removed from the filtrate under reduced pressure. Distillation of the residual material in vacuum furnished 77 g of a crude addition product, bp 35—38 °C/3 mmHg. To this material was added 500 ml of water and the mixture stirred for 24 hr at room temperature. The organic layer was separated, mixed with 1 l of a 4 : 1 acetone-water mixture, and allowed to stand for 48 hr at room temperature to hydrolyse accompanying 1-bromo-1-methylcyclohexane. Hygrogen bromide liberated amounted to 8.2 mol% based on the starting addition product. After dilution with water, the organic layer was separated and dried over anhydrous magnesium sulphate. A portion (25 g) of this material (66 g) was fractionally distilled through a

spinning band column to yield 19 g of the *cis* bromide (**1**), bp 68 °C/19 mmHg, n_D^{30} 1.4888 (Found: C, 47.53; H, 7.69; Br, 45.17%. Calcd for $C_7H_{13}Br$: C, 47.48; H, 7.40; Br, 45.12%), ν_{max} 656 cm^{-1} (axial C–Br).[8] The NMR spectrum indicated three methyl protons at δ 0.99 (d; J, 5 Hz), a Br–C–H proton at 4.40 (unresolved multiplet), and ring protons at 0.8—2.3 (a complex series of peaks).

A Mixture of cis- *and* trans-*2-Bromo-1-methylcyclohexane.* Methyl *trans*-2-methyl-4-cyclohexene-1-carboxylate[9] (70 g) was hydrogenated with hydrogen at 1 atm on 9 g of 5% palladium-charcoal catalyst in 300 ml of methanol at room temperature. The resulting saturated ester was hydrolysed by boiling with 10% aqueous sodium hydroxide solution, and acidification of the reaction mixture gave 56 g of *trans*-2-methylcyclohexanecarboxylic acid, mp 53—54 °C (lit,[10] mp 51—52 °C). The acid (50 g) was dissolved in a solution of 15.5 g of sodium hydroxide in 160 ml of water. Nitric acid was added dropwise until turbidity appeared; then a solution of 59.7 g of silver nitrate in 96 ml of water was added. The precipitated silver salt was collected on a filter, washed with water and ethanol, air-dried, and then dried over phosphorus pentoxide in a vacuum desiccator. The silver salt (64 g) was treated with bromine (41 g) in carbon tetrachloride (420 ml) according to the directions of Marvel and Sexton.[3] After working up the reaction mixture, fractionation with a spinning band column gave 12.1 g of a middle fraction, bp 62.5 °C/18 mmHg −61.5 °C/15.5 mmHg, ν_{max} 681 cm^{-1} (equatorial C–Br).[8] The NMR spectrum showed an unresolved multiplet at δ 4.40 due to the presence of the *cis* isomer, a sextet (doublets of a triplet; J, 4.5 and 10 Hz) at 3.61 due to the *trans* isomer, a doublet (J, 6 Hz) at 1.11, and a complex series of peaks at 0.8—2.6. The ratio of *cis*-(**1**) to *trans*-2-bromo-1-methylcyclohexane (**2**) was estimated to be 10 : 90 by comparing the areas of the peaks at δ 4.40 and 3.61.

Autoxidation and Reduction of the Oxidates. The experimental procedures for autoxidation have been described previously.[1] After a portion of the oxidate had been titrated iodometrically for hydroperoxide,[11] the rest was dissolved in dry ether and added to a suspension of lithium aluminium hydride (2—3 times the theoretical amount) in dry ether. The mixture was stirred for 30 min at room temperature, and excess of lithium aluminium hydride destroyed with dilute sulphuric acid. The ether layer was separated, washed with water, and dried over anhydrous sodium sulphate. The ether was removed and the residue analysed by glpc.

Product Analysis. The preparations of authentic samples of *c*-2- and *t*-2-bromo-1-methyl-*r*-1-cyclohexanol have been described previously.[2] Qualitative analyses by glpc were carried out using either a diisodecyl phthalate column 0.5 m long at 100 °C, a Carbowax column 1 m long at 111.5 °C, or a cyanosilicone column 1 m long at 112.5 °C. For quantitative analyses a Carbowax column 1 m long was used at 100 °C for 1,3,5-trimethylcyclohexanols and at 112 °C for *t*-2-bromo-1-methyl-*r*-1-cyclohexanol. In gas-liquid partition chromatography of the present bromine containing compounds the use of glass columns was necessary for reliable analyses.

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