# THE CONFORMATIONS IN SOLUTION OF *trans*-CYCLOHEXENE DIHALIDES AND *cis*- AND *trans*-1,2-CYCLOHEXANEDIOLS AND DERIVATIVES

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## ABSTRACT

*trans*-1,4,4-Trideuteriocyclohexene dichloride, dibromide, and diiodide and the 1,4,4-trideuterio-*cis*- and *trans*-1,2-cyclohexanediols together with their *O*-acetyl, *O*-tosyl, and *O*-isopropylidene derivatives were synthesized. Their nuclear magnetic resonance (NMR) spectral parameters were obtained with a spectrometer operating at 100 Mc.p.s. and employing double irradiation to establish the chemical shifts and the signs of the coupling constants. The interpretation of the data according to expectations based on the Karplus relationship, for dihedral angles and coupling constants, support the conformational equilibria assigned to the *trans*-dichloride and *trans*-dibromide of cyclohexene on the basis of dipole moment measurements (previously published results). The results indicate that *trans*-cyclohexene diiodide exists to about 84% in the diaxial conformation. In the case of the 1,2-cis-disubstituted cyclohexanes, the occurrence of the signal for the 3-hydrogen in trans relation to the 2-hydrogen at lower field than its geminal 3-hydrogen is assigned to the deshielding influence on the 3-hydrogen when in axial orientation by an opposing axial oxygen at the 1-position. Support for this contention was obtained by determination of the chemical shifts of the geminal hydrogens at the 3- and 5-positions of the *cis*- and *trans*-4-*t*-butyl-2,2,6,6-tetradeuterio-1-methylcyclohexanols. The conformational equilibria indicated for the 1,2-diol, 1,2-diacetoxy, and 1,2-ditosyloxy trans derivatives of 1,4,4-trideuteriocyclohexane by NMR parameters obtained from the spectrum of the *O*-isopropylidene derivatives of the *trans*-diol allowed conclusions regarding the non-bonded interaction energies involved. The Karplus relation had to be adjusted to the form, $J_\phi = 14.7 \cos^2\phi - 0.2$ (0°–$\phi$–90°) and $J_\phi = 11.2 \cos^2\phi - 0.2$ (90°–$\phi$–180°), to accommodate the results. Solvent effects on conformation are noted. Also, the investigation provided further evidence for the opposite signs of the coupling constants for geminal and vicinal hydrogens. A consideration of the chemical shifts observed for a variety of derivatives of cyclohexanol appears to indicate that intramolecular shielding effects are better accounted for on the basis of neighboring atomic groupings than on the basis of individual chemical bonds.

Attempts have been made previously to study the conformational equilibria of the *trans*-cyclohexene dihalides in benzene solution by the measurement of dipole moments (1) and by observation of the chemical shifts of protons adjacent to the halogen atoms (2). Both of these methods suffer from disadvantages; in the first, it is impossible to estimate the molecular dipole in the diaxial conformation, i.e. of allowing for dipolar contributions from the cyclohexane skeleton (3). The second method requires the assumption that the usual orientational effects on chemical shifts apply (4, 5). This latter assumption, as it transpired, proved to be justified in the case of the *trans*-dihalides but could not have been foreseen and would not have applied to the series of *cis*-1,2-cyclohexane derivatives. Moreover, it would be impossible to study the conformational equilibrium of the diiodide by the dipole method since this compound exists in solution in chemical equilibrium with cyclohexene and iodine. A more attractive approach was to use nuclear magnetic resonance (NMR) spectroscopy to measure appropriate coupling constants. By preparing specifically deuterium-labelled cyclohexene, the NMR spectra of the dihalides could be simplified sufficiently to measure coupling constants which could then be related by the Karplus (6) expression to the corresponding dihedral angles. The actual shape of the molecules could then be examined. It was realized that the theoretical Karplus

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relation, which has been supported by experimental observations (7), has its own limitations (8, 9). However, it was thought to be of interest to show that the two procedures afforded consistent results. This was found to be the case and in addition the NMR coupling constant method gave information on the conformational equilibrium of the diiodide. The method also appeared to provide interesting new insight on ring distortions, conformational equilibria, solvent effects, and orientation effects on chemical shift in the case of the *cis*- and *trans*-1,2-cyclohexanediols and their *O*-acetyl, *O*-tosyl, *O*-*p*-toluenesulphonate, and *O*-isopropylidene derivatives.

1,4,4-Trideuteriocyclohexene was selected as a suitable starting material for the preparation of the corresponding *trans*-dihalides and *cis*- and *trans*-glycols. These afford spectra of the ABX type (10) arising from the protons at the 2,3,3-positions. It turned out that the paramagnetic shift of the substituent at the 2-position on the 2-proton was always sufficient to render the ABX approximation valid. Analysis of the ABX spectra then gave the conformationally averaged coupling constants $J_{AX}$ and $J_{BX}$ from which the dihedral angles could be deduced. Except for the diacetate, the trans compounds gave spectra in good approximation to the AMX type (11).

Cyclohexane-1,4-dione was reduced in tetrahydrofuran with lithium aluminum deuteride, and the resulting 1,4-dideuteriocyclohexane-1,4-diols were dehydrated over alumina (12) to provide 1,4-dideuterio-1,4-epoxycyclohexane, which produced virtually no detectable signal (at 4.6 p.p.m. from internal tetramethylsilane) in the NMR spectrum for hydrogens at the 1- and 4-positions. The maximum hydrogen content at these positions was estimated to be 5%. The epoxide was cleaved in 87% yield to the 1,4-dideuterio-*trans*-4-bromocyclohexanol using hydrogen bromide in diethyl ether at room temperature. Again the NMR spectrum was devoid of signals (at 3.7 and 4.1 p.p.m.) for hydrogens at the 1- and 4-positions. This reaction was found to be much cleaner than that involving the direct action of hydrogen chloride to the epoxide (12). The bromine atom was replaced by deuterium through very rapid deuterolysis in the presence of a palladium-on-charcoal catalyst in methanol containing sodium methoxide. It is noteworthy that no difference in the deuterium content of the product was observed when methanol-*O-d* was used as solvent. The resulting 1,4,4-trideuteriocyclohexanol showed no detectable absorption at the position in the NMR spectrum for the 1-hydrogen of cyclohexanol.

Recently, Premuzic and Reeves (13) described the preparation of 1,3,3-trideuteriocyclohexene by the conventional dehydration of 2,2,6,6-tetradeuteriocyclohexanol with orthophosphoric acid, but gave no indication of the extent of deuteration of the product. A similar trial dehydration of our 1,4,4-trideuteriocyclohexanol resulted in complete loss of deuterium by acid-catalyzed exchange, so that this method was abandoned in favor of base-catalyzed cleavage of the tosylate. The *O*-tosyl derivative of the alcohol was treated with potassium hydroxide in dry diethylene glycol to yield 1,4,4-trideuteriocyclohexene (I). Gas–liquid partition chromatography showed the presence of cyclohexene only and integration of the NMR spectrum showed the relative intensities of the ethylenic and methylenic hydrogens to be 1:5.8 (expected for I, 1:6). The spectrum (see Fig. 1) clearly required that the reductions in the intensities of the signals relative to those in cyclohexene be at the 1- and 4-positions. Compound I was converted to the dichloride and the dibromide by halogenations in benzene. The diiodide was prepared by mixing equimolar amounts of I and iodine at about −70°. On warming of the mixture to room temperature, the iodine had dissolved and the resulting mixture was taken up in benzene for the NMR experiment. The *cis*-diol was prepared by osmium tetraoxide oxidation in pyridine (14) and decomposition of the osmiate with sodium bisulphite (15).

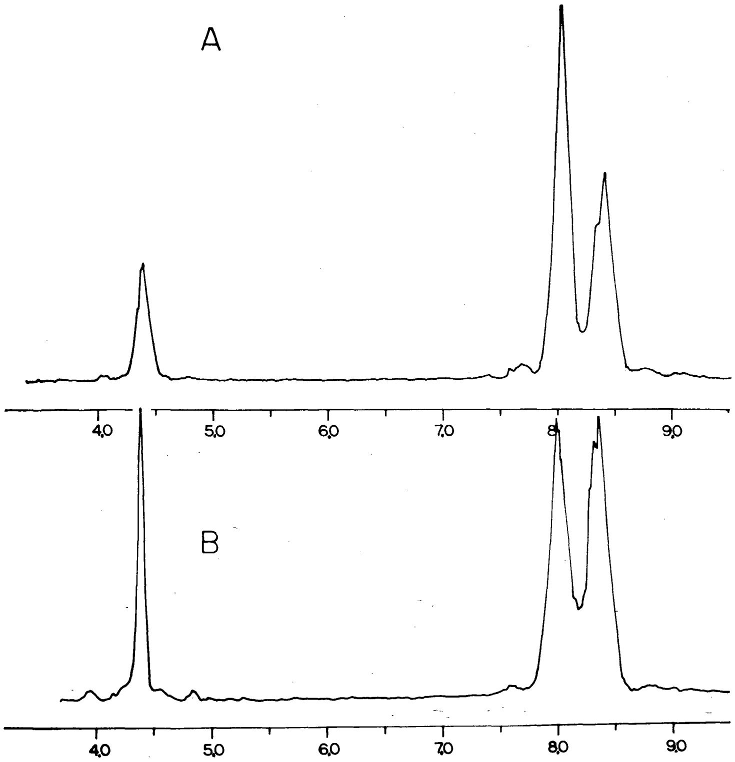


FIG. 1. (A) 1,4,4-Trideuteriocyclohexene. (B) Cyclohexene. Both 5% solutions in $CCl_4$ at 60 Mc.p.s. with tetramethylsilane (1%) as internal reference. The scale is in $\tau$ units.

Performic acid oxidation followed by hydrolysis gave the *trans*-diol (14). Each spectrum showed a clearly resolved triplet or quartet due to the X-proton (which was broadened by neighboring deuterium coupling) but a direct ABX analysis was not possible owing to the overlap of the AB signals by the equivalent protons at the 6-position. The ABX parameters could, however, be determined by the spin decoupling or double resonance method (16–19).

By this means it could be shown that the X-proton was coupled to two and only two other protons at higher field in the methylene envelope, thereby confirming the structures. By measuring the decoupling frequencies, the chemical shifts of the A- and B-protons could be found within two cycles per second. Spin decoupling has been used with considerable success in assigning relative signs of coupling constants in spectra which approximate to first order (16, 17). In view of the theoretical interest in the relative signs of the vicinal and geminal couplings (20–22), it was of interest to determine the relative signs of the coupling constants in these systems. This refinement had added advantages in that it provided an additional consistency check on the measured decoupling frequencies and allowed a rationalization of those experiments (see below) where anomalous double resonance effects occurred owing to a small AB chemical shift as described by Freeman (23). Also the method provided a reasonable estimate of the third coupling constant $J_{AB}$ and so provided all the spectral parameters including the relative signs of the coupling constants. Thus, it was possible to derive better approximations to the true coupling constants and chemical shifts by iterative calculations of theoretical spectra. By using the values for the coupling constants and chemical shifts to predict the appearance of the experimentally observable X-part of the ABX spectrum at both 60 and 100 Mc.p.s., an additional check on the accuracy of the derived parameters was obtained.

Valuable qualitative information is obtained directly by this selective decoupling of the individual groups of A and B transitions in that one can tell from the appearance of a decoupled quartet which proton, high field or low field (B or A by definition), gives rise to the larger coupling.

Spin decoupling may be carried out with the integrator of the Varian 100 Mc.p.s. spectrometer (24). The observed frequency difference, $\Delta w$, which produces optimum decoupling is not exactly equal to the chemical shift difference of the two spin-decoupled nuclei. Anderson and Freeman (25) have shown that, for two sets of nuclei whose chemical shifts are $w_A$ and $w_X$, the condition for optimum decoupling is given by the expression,

$$\Delta w = w_A - w_X - (\gamma H_2)^2/2(w_A - w_X),$$

where $H_2$ is the decoupling radio-frequency field strength and $\gamma$ is the magnetogyric ratio of the proton. For nuclei with large relative chemical shifts such as are considered here the correction term $(\gamma H_2)^2/2(w_A - w_X)$ is small and $\Delta w \simeq (w_A - w_X)$. An estimate of the magnitude of the correction to be made in the least favorable case gave a value of 0.2 c.p.s., which was considered negligible.

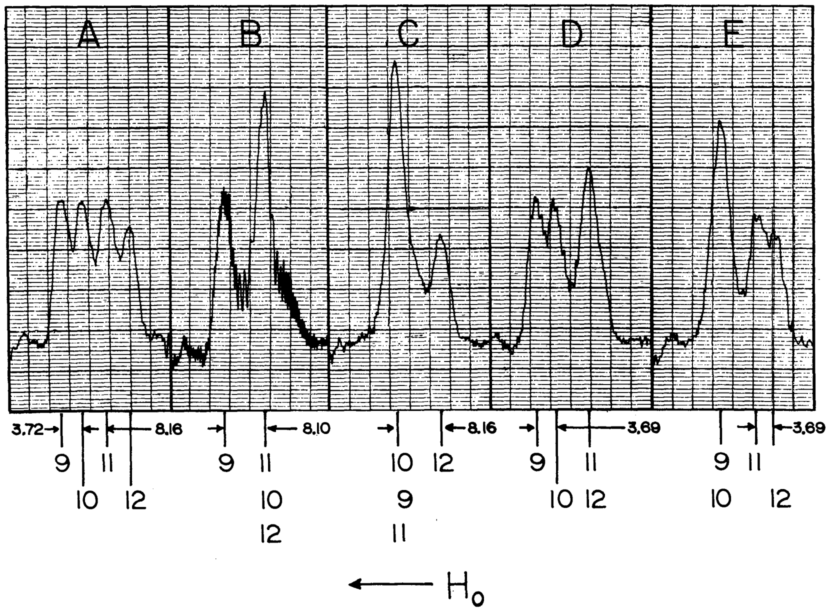


FIG. 2. The signal for the 2-hydrogen (X-part) of *trans*-1,4,4-trideuteriocyclohexene dichloride, taken at 100 Mc.p.s. in benzene at room temperature, showing the effects of double irradiation performed with first lower sideband. (A) Single resonance spectrum. (B) With double irradiation frequency at 239.8 c.p.s. (C) With double irradiation frequency at 223.7 c.p.s. (D) With double irradiation frequency at 179.8 c.p.s. (E) With double irradiation frequency at 160.8 c.p.s.

It was anticipated that the geminal coupling $J_{AB}$ would be large, ca. 12 c.p.s., and experience showed that $\delta_{AB}$ was about 50 c.p.s. for the *trans*-dihalides at 100 Mc.p.s. Consequently, the general appearance of the ABX spectra would be three widely separated sets of quartets. For reference purposes, the 12 transitions are numbered with decreasing field from 1 to 12. The possibility arises of irradiating the branches of the A- and B-quartets selectively so that four decoupling frequencies are measured. The relative signs of the coupling constants may be deduced from the appearance of the decoupled multiplet (18). The determination of relative signs of coupling constants in this way is illustrated by the appearance of the X-proton quartet of the *trans*-dichloride in Fig. 2. It can be seen from Fig. 2 that when the largest decoupling frequency, which must necessarily correspond to the 1- and 2-transitions, is employed there resulted a collapse of lines 10 and 12. The next lowest decoupling frequency irradiates the 3- and 4-transitions and caused the collapse of lines 9 and 11. This showed that $J_{AX}$ and $J_{AB}$ are of opposite sign and also that $J_{BX}$ is greater than $J_{AX}$. This result is in accordance with the usual orientational effects on chemical shifts in 6-membered rings (4). A similar experiment carried out by irradiating in the region of the A-nucleus confirmed that $J_{AB}$ and $J_{BX}$ are opposite in sign and that $J_{AX}$ was the smaller constant. It thus followed that, as expected (20–23), the signs of the coupling constants for vicinal hydrogens were opposite to that for the geminal hydrogens.

It follows that the four decoupling frequencies observed will be given by the following expressions:—

| Lines irradiated | | Decoupling frequency (c.p.s.) | |
|---|---|---|---|
| 1 and 2 | B-quartet | $\delta_{BX}+\frac{J_{AB}}{2}+\frac{J_{AX}}{2}$ | (1) |
| 3 and 4 | | $\delta_{BX}-\frac{J_{AB}}{2}-\frac{J_{AX}}{2}$ | (2) |
| 5 and 6 | A-quartet | $\delta_{AX}+\frac{J_{AB}}{2}+\frac{J_{BX}}{2}$ | (3) |
| 7 and 8 | | $\delta_{AX}-\frac{J_{AB}}{2}-\frac{J_{BX}}{2}$ | (4) |

where $\delta_{BX}$ etc. represent the chemical shifts in c.p.s. Therefore, the difference between expressions 1 and 2 equals $J_{AB}+J_{AX}$; similarly the difference between expressions 3 and 4 equals $J_{AB}+J_{AX}$. It can be shown that the calculated separations of the X-quartet are very insensitive to the magnitude of $J_{AB}$, therefore an estimate of $J_{AB}$ could be obtained from the differences in decoupling frequencies by subtracting the corresponding spacings of the quartet measured at 100 Mc.p.s.

Thus, two estimates of $J_{AB}$ are obtained from decoupling of the B- and A-protons, respectively. Now by substituting the approximate values of $J_{AB}$, $J_{AX}$, and $J_{BX}$ in equations 1 to 4, values could be obtained for the positions of the four branch lines of the unperturbed AB-quartet, the simple AB analysis then furnished the chemical shifts of the A- and B-protons.

It is seen from Tables I and II that the chemical shifts of the A-, B-, and X-protons were usually large. However, for certain compounds, particularly the *trans*-diacetate and the *cis*-*O*-isopropylidene compounds, $\delta_{AB}$ was quite small. Consequently, transitions 3 and 4, and 5 and 6, of the ABX spectrum tended to overlap or at least be so close together that irradiation of transitions 5 and 6, for example, tended to perturb transitions 3 and 4 (26). Thus, no precise decoupling frequencies could be measured in this region of the spectrum. However, clear-cut spin decoupling was achieved at the outer regions, that is, by irradiation of transitions 1 and 2 of the B-proton and transitions 7 and 8 of the A-proton. The values for $\delta_A$ and $\delta_B$ were then derived by using the value for $J_{AB}$ obtained

TABLE I

NMR spectral parameters for *trans*-1,4,4-trideuteriocyclohexene dihalides*

| Compound | X-spacings, c.p.s. | Chemical shifts, p.p.m. (TMS) | | | Calc. coupling constants, c.p.s.† | | |
|---|---|---|---|---|---|---|---|
| | | $\delta_A$ | $\delta_B$ | $\delta_X$ | $J_{AX}$ | $J_{BX}$ | $J_{AB}$ |
| 1. Dichloride | 3.72, 8.16 | 1.99 | 1.39 | 3.70 | 3.72 | 8.16 | −12 |
| 2. Dibromide | 3.69, 5.57 | 2.10 | 1.50 | 4.11 | 3.69 | 5.57 | −11 |
| 3. Diiodide | 3.36, 3.36 | 2.00 | 1.56 | 4.73 | 3.36 | 3.36 | −12 |

*Determined in benzene at 100 Mc.p.s. and room temperature (about 25°).
†The negative sign is based on the evidence recently presented by Anet (28).

TABLE II

NMR spectral parameters for the *cis*- and *trans*-1,4,4-trideuterio-1,2-cyclohexanediols and derivatives*

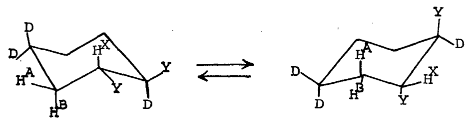
| | Solvent | X-spacings, c.p.s. | | Chemical shifts, c.p.s.† (TMS) | | | Calculated coupling constants | | | $J_{AX}+J_{BX}$, c.p.s. |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 100 Mc.p.s. | | $\delta_A$ | $\delta_B$ | $\delta_X$ | $J_{AX}$ | $J_{BX}$ | $J_{AB}$ | |
| *cis-Compounds* | | | | | | | | | | |
| Di-*O*-acetyl | $CCl_4$ | 3.62 | 6.98 | 180 | 157 | 492 | 7.1 | 3.6 | −11 | 10.7 |
| Diol | $CHCl_3$ | 3.79 | 7.11 | 177 | 153 | 375 | 7.1 | 3.8 | −11 | 10.9 |
| Diol | $D_2O$ | 4.29 | 6.50 | 218 | 194 | 421 | 6.7 | 4.1 | −11 | 10.8 |
| Di-*O*-tosyl | $CHCl_3$ | 2.77 | 7.72 | 196 | 154 | 451 | 7.8 | 2.7 | −12 | 10.5 |
| *O*-Isopropylidene | $CCl_4$ | 5.4 | 5.4 | 181 | 154 | 396 | 5.4 | 5.4 | −12 | 10.8 |
| *trans-Compounds* | | | | | | | | | | |
| Di-*O*-acetyl | $CCl_4$ | 4.20 | 10.15 | 141 | 129 | 468 | 3.5 | 11.0 | −11 | |
| Diol | $CHCl_3$ | 4.55 | 11.06 | 192 | 123 | 330 | 4.5 | 11.0 | −11 | |
| Diol | $D_2O$ | 4.26 | 10.91 | 240 | 171 | 384 | 4.1 | 10.5 | −12 | |
| Di-*O*-tosyl | $CHCl_3$ | 3.62 | 7.82 | 196 | 148 | 440 | 3.6 | 7.9 | −12 | |
| *O*-Isopropylidene | $CCl_4$ | 3.46 | 10.99 | 205 | 137 | 310 | 3.5 | 11.0 | −12 | |

*The parameters are expressed to the nearest significant figure.
†At 100 Mc.p.s.

for the isomers. It was found that the calculated values for $J_{AX}$ and $J_{BX}$ were quite insensitive to the value of $J_{AB}$ in the range 11 to 12 c.p.s.

$$nJ_{aa}+(1-n)J_{ee} = J_{BX} \tag{5}$$

$$nJ_{ae}+(1-n)J_{ea} = J_{AX} \tag{6}$$



II III

The NMR results obtained for the *trans*-dihalides allow the following conclusions to be drawn. With respect to their relative magnitudes, $J_{AX}$ and $J_{BX}$ represent the weighted averages of the coupling constants for the *cis*- and *trans*-hydrogens, respectively (equations 5 and 6). Judging from structurally closely related compounds wherein the halogens (Y) are axial, only the chair conformations II and III need be considered (27). Bender, Flowers, and Goering (1) have estimated by dipole moment studies that the fraction, *n*, in the diequatorial form (II) is 0.75 and 0.43 for the dichloride and dibromide, respectively. Substitution of these values for *n* and the appropriate values for $J_{AX}$ and $J_{BX}$

given in Table I into expressions 5 and 6 provides the values $J_{aa} = 10.2$, $J_{ee} = 2.04$, $J_{ae} = 3.74$, and $J_{ea} = 3.66$ c.p.s. These values are in excellent agreement with those to be expected (28) and thus provide confirmation of the significance attached to the dipole moment data. To the extent to which the results from the two methods are in agreement, the assumption that the cyclohexane skeleton makes a negligible contribution to the molecular dipole in the diaxial conformation is justified (1, 3).

Substitution of the above values for $J_{aa}$ and $J_{ee}$ and the value for $J_{BX}$ obtained from the diiodide in equation 5 suggests that this compound exists in benzene at room temperature to an extent of about 84% in the conformation wherein both iodines are in axial orientation. Since the chemical shift for the A- and B-hydrogens (44 c.p.s.) is more than three times greater than $J_{AB}$ the condition is met that the triplet is not degenerate and $J_{AX}$ does equal $J_{BX}$ (29). It is pertinent in this regard that the coupling constant of the 1-hydrogen with the vicinal hydrogens in a number of 2,6-disubstituted cyclohexyl iodides were found (30) to be of the magnitude (necessarily greater than the observed spacings, 9 and 2.5 c.p.s., for hydrogens in trans and gauche relations, respectively) expected on the basis of the present results.

It must be noted that the NMR data taken together with the dipole moment data can only indicate that the hydrogens at the 1- and 2-positions of the *trans*-1,2-dihalogenocyclohexanes are both well staggered with the hydrogens on the vicinal carbon atoms when the halogens are in axial orientation (III). It seems likely that the erection of the halogens into axial orientation to achieve conformation III will cause some distortion of the opposite side of the ring in the direction which will increase the internuclear distance between the halogens and the opposing axial hydrogens. This condition seems likely in view of the results, discussed below, obtained with the di-*O*-tosyl-*cis*-1,2-cyclohexanediol.

TABLE III

Effect of solvent on the conformational equilibria for *trans*-cyclohexene dihalides

| Compound | Solvent | Dielectric constant at 20°* | Approx. coupling constants, c.p.s. | | n† |
|---|---|---|---|---|---|
| | | | $J_{AX}$ | $J_{BX}$ | |
| Dichloride | $CCl_4$ | 2.24 | 3.6 | 6.8 | 0.58 |
| Dichloride | $CH_3CN$ | 37.50 | 3.7 | 8.9 | 0.84 |
| Dibromide | $CCl_4$ | 2.24 | 3.9 | 4.0 | 0.24 |
| Dibromide | $CS_2$ | 2.64 | 4.1 | 4.1 | 0.25 |
| Dibromide | $CHCl_3$ | 4.81 | 4.1 | 4.2 | 0.26 |
| Dibromide | $CHBr_3$ | 4.39 | 3.7 | 5.7 | 0.45 |
| Dibromide | $(CH_3)_2CO$ | 20.7‡ | 3.7 | 6.7 | 0.57 |
| Dibromide | $CH_3CN$ | 37.5 | 4.1 | 7.1 | 0.62 |

*National Bureau of Standards Circular 514.

†Fraction of conformation II calculated from expression 6, with $J_{aa} = 10.2$ and $J_{ee} = 2.04$ c.p.s.

‡Value at 25° C.

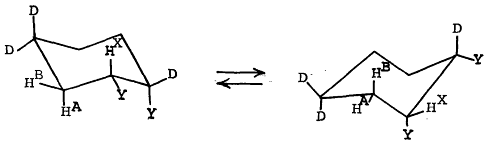
Having established the close correspondence between the results obtained from the dipole moment and NMR studies, it would be predicted that the conformationally averaged spacings would be dependent on the dielectric constant of the solvent. The greater the dielectric constant the greater should be the population of the more polar diequatorial conformation (II). Accordingly, the spacings of the X-quartet for the dichloride and the dibromide dissolved in a number of solvents were determined at

60 Mc.p.s. (Table III). Since it has been established that the spectra in benzene are close to the AMX type, the spacings can be expected to be approximately equal to $J_{AX}$ and $J_{BX}$. On this basis, the values for the fraction $n$ of the compounds in the diequatorial conformation II were estimated. It is seen that the quantitative prediction is borne out and illustrates the advantage of the NMR technique for the study of conformational equilibria in highly polar solvents (31).

An inspection of a conformational Barton model allows the conclusion that the dihedral angles defined by the 2-hydrogen of *O*-isopropylidene-*trans*-1,2-cyclohexanediol with the hydrogens at the 3-position are very close to 60° and 180°. Therefore it was concluded from the data in Table III that for this compound $J_{AX} = J_{60°} = 3.5$ c.p.s. and $J_{BX} = J_{180°} = 11.0$ c.p.s. These values are in excellent agreement with those observed by Anet for similar groupings in cyclohexane rings (28). The above value for $J_{60°}$ requires an upward displacement in this region of the original Karplus curve (6) by 1.65 c.p.s. A simple upward displacement of the whole curve would yield $J_{90°} = 1.37$ c.p.s., a value which is not acceptable in view of the evidence that $J_{90°}$ invariably is very small (6, 7, 32).

For the cis compounds listed in Table III, the observed coupling constants must represent the average coupling of the *cis*- and *trans*-3-hydrogens with the 2-hydrogen, respectively, in the two energetically equivalent chair conformations IV and V. Therefore,

$$J_{ae}+J_{ea} = 2J_{BX} \text{ and } J_{aa}+J_{ee} = 2J_{AX}.$$



IV V

In view of the near linearity of the Karplus curve in the vicinity of 60°, the sum $J_{ee}+J_{ea}$ should be near constant, and $J_{aa}$, being only slightly dependent upon dihedral angle in the region 170° to 180°, should have very nearly the same value for all the compounds. Therefore, assuming $J_{ae} = J_{60°} = 3.5$ c.p.s. and $J_{aa} = J_{180°} = 11.0$ c.p.s. it would be expected that for the cis compounds,

$$J_{AX}+J_{BX} = (J_{180°}+3J_{60°})/2 = 10.75 \text{ c.p.s.}$$

It is seen in Table II that the values found for $J_{AX}+J_{BX}$ are in excellent general agreement with this expectation. Evidence has been obtained that the cis compounds exist in solution in the chair forms (33). The slight difference between the shift for unbonded and bonded hydroxyl infrared frequency of 39 $cm^{-1}$ for the *cis*-diol and 32 $cm^{-1}$ for the trans isomer has been ascribed (34) to deformation of the cis compound from the perfect chair. The hydroxyl groups are said to be able to approach each other more readily in the *cis*- than in the *trans*-diol. A similar explanation has been advanced to explain the slightly greater reactivity of the *cis*-diol towards cleavage by lead tetraacetate (35).

Should the cis compounds exist in undistorted chair forms, one would expect $J_{AX} = 7.25$ c.p.s. and $J_{BX} = 3.5$ c.p.s. Indeed, values very close to these were found in the case of the *cis*-diacetate and of the *cis*-diol when dissolved in chloroform. However, the high value for $J_{BX} = 4.1$ c.p.s. and the low value for $J_{AX} = 6.7$ c.p.s. for the *cis*-diol when dissolved in deuterium oxide infer appreciable distortion of the chair for this compound in aqueous solution. The result, as expected, seems best explained on the basis of a dihedral angle of less than 60° for the oxygen atoms. However, it is to be noted that the distortion is probably related to the hydration of the hydroxyl groups rather than simple intramolecular hydrogen bonding since the distortion was not present for the compound dissolved in chloroform. Thus, the apparent ring distortion brought on by intramolecular hydrogen bonding when the compound is dissolved at high dilution in carbon tetrachloride (34) must be imposed on the molecule by the state of dilution which has rendered intermolecular hydrogen bonding unfavorable.

The value, 5.4 c.p.s., found for both $J_{AX}$ and $J_{BX}$ in the case of the *cis*-isopropylidene compound requires considerable distortion of the cyclohexane ring (36, 37). Because of unusually strong deuterium broadening of the signal, these coupling constants are not known to better than ±0.2 c.p.s. Should expressions of the type proposed by Karplus allow an interpretation of these results, in view of the data contained in Table II and the above considerations regarding $J_{90°}$, the following expressions are indicated.

$$J_\phi = 14.7 \cos^2\phi - 0.2 \ (0° \leq \phi \leq 90°), \tag{7}$$

and

$$J_\phi = 11.2 \cos^2\phi - 0.2 \ (90° \leq \phi \leq 180°). \tag{8}$$

On this basis, with $\phi_{ae} = \phi_{ea} = 50°$, $\phi_{aa} = 170°$, and $\phi_{ee} = 70°$, the values $J_{AX} = J_{BX} = 5.9$ c.p.s. are obtained. Although these values are in reasonably close agreement with those determined experimentally, a somewhat greater distortion was anticipated on the basis of a conformational model.

The values for $J_{AX}$ and $J_{BX}$ found for the ditosylate appear to require $J_{ee} > J_{60°}$ and $J_{ea} < J_{60°}$. The only distortion apparent from a study of conformational models that can provide such a condition is that wherein the 3-, 4-, and 5-carbons have moved toward coplanarity with the 1-carbon (the position of the axial tosyloxy group). Such a distortion is plausible since it provides a relief of the congestion between the axial tosyloxy group and the opposing axial hydrogens.

The values of $J_{BX}$ ($\simeq J_{aa}$) for the *trans*-diol when dissolved in chloroform and deuterium oxide require the compound to exist almost entirely in the diequatorial orientation in both solvents. This situation could not necessarily be anticipated from the published values for the non-bonded interaction energies involved. The experimentally determined free-energy differences between equatorial and axial hydroxyl groups in aprotic solvents have been estimated (3, p. 236) to be 0.5 (pyridine), 0.4 (carbon disulphide), and 1.0 (carbon tetrachloride) (28) kcal/mole. The differences (so-called A-values) seem greater in protic solvents (3, p. 236); 0.8 (75% aqueous acetic acid), 0.9 (water), 0.96 (isopropanol), 1.25 (deuterium oxide) (28). This change in A-value on change from aprotic to protic solvents has been assigned to solvation phenomena (38, 39). For the purpose of illustrating the present status of our appreciation of the conformation of the *trans*-diol, it is useful to assume average A-values for the hydroxyl group of 0.6 kcal/mole (aprotic solvent) and 1.0 kcal/mole (protic solvent). Only one value has been reported for the non-bonded interaction free energy of hydroxyl groups in gauche relation, namely, 0.35 kcal/mole (40) (we propose the term G-value for this type of non-bonded interaction free energy). On this basis, it was to be anticipated that the conformational equilibrium constant toward the diequatorial conformation (II) at ordinary temperatures for *trans*-1,2-cyclohexanediol should be about 4 for aprotic solvents and about 16 for protic solvents. These constants would require $J_{BX}$ to have values of 9.5 and 10.7 c.p.s., respectively. The value of 9.5 c.p.s. is significantly lower than the experimentally determined value of 11.0 c.p.s. for the *trans*-diol dissolved in chloroform. Clearly, however, because of the possibility of intramolecular hydrogen bonding the G-value for hydroxyl groups can be expected to be appreciably dependent on solvent. However, the values found for $J_{AX}$ suggest that such intramolecular bonding effects are negligible at the concentrations required for the NMR experiments. That is, the values of 4.5 and 4.1 c.p.s. observed for $J_{AX}$ reflect a distortion of the cyclohexane ring in the direction which will decrease the dihedral angle defined by the A- and X-hydrogens in the diequatorial conformation (II). This situation can only be achieved by the hydroxyl groups moving somewhat further apart than in the ideal chair form. On the basis of the expressions 7 and 8, only very slight distortions are necessary. Thus, for the *trans*-diol, a dihedral angle of about 58° is indicated for the A- and X-hydrogens when the solvent is either chloroform or water. Our results are best explained using the A-values for the hydroxyl group of 1.25 kcal/mole in deuterium oxide and 1.0 kcal/mole in carbon tetrachloride determined by Anet (28). This conclusion rests on the assumption that the non-bonded interaction energy between two hydroxyl groups in gauche relation (G-value) has the value of 0.35 kcal/mole estimated by Angyal and McHugh (40). The above noted distortions require a repulsion between the hydroxyl groups in the *trans*-diol. It does not seem likely that this repulsion can be substantially less than 0.35 kcal/mole.

A-values of 0.66 kcal/mole (28) and 0.7 kcal/mole (3, p. 236) have been reported for the acetoxy group. The values, $J_{AX} = 3.5$ c.p.s. and $J_{BX} = 10.9$ c.p.s., found for the *trans*-diacetate obviously require the compound to exist essentially only in the diequatorial orientation. Evidently, the G-value for acetoxy groups must be small. Setting this value at 0.35 kcal/mole (the value for the hydroxyl groups) and using an A-value of 0.7 kcal/mole, one would expect the compound to exist to an extent of 85% in the diequatorial orientation, in poor agreement with the NMR data. However, this G-value must be a maximum value in view of the correspondence of $J_{AX}$ with $J_{60°}$. On the other hand, it is difficult to conceive why the A-value for the acetoxy group should be substantially less than for the hydroxyl group. We therefore arbitrarily propose that A- and G-values for the acetoxy groups of 1.0 and 0.2 c.p.s., respectively, are in best agreement with the present data. On this basis, the compound would exist to an extent, 95%, compatible with the NMR data ($J_{BX} = 10.7$ c.p.s.). The low G-value presumably could arise from attractive dipole–dipole interactions between the acetyl groups tending to offset the repulsive non-bonded interactions.

In the case of the *trans*-ditosylate, assuming $J_{aa} = 11.0$ c.p.s. and $J_{ee}$ is in the range 2.6–3.5 c.p.s., since $J_{BX} = 7.9$ c.p.s., it would follow that 59% to 63% of the compound resides in the diequatorial conformation. There thus appears to be a considerably stronger repulsion between tosyloxy groups in *gauche*-orientation than in the case of acetoxy groups. On the basis of the reasonable assumption that the A-value of the tosyloxy group is the same as for the hydroxyl group in aprotic solvents, namely 1.0 kcal/mole, a G-value for the tosyloxy group of 1.8 kcal/mole is indicated. This high value is consistent with the conformational properties of the *trans*-dihalides and provided a basis for explaining the difficulty often experienced in attempts to completely tosylate carbohydrate structures.

It is seen in Table II that the A-protons of the cis compounds are more strongly coupled with the X-proton than are the B-protons. This difference in coupling must arise from the strong coupling to be expected between the 2- and 3-*trans*-hydrogens in conformation IV. Therefore, the A- and X-protons of the cis compounds must be in trans relation as shown in IV and V. The chemical shifts observed for the ring hydrogens of sugars and their derivatives were found to require the assignment of magnetic shielding of an axial hydrogen by an opposing, axially oriented C—O bond (41). On this basis, it could be anticipated that the A-protons of the cis compounds are deshielded relative to the B-protons because of the occurrence of this diaxial arrangement involving the A-protons when in conformation IV. To better assess the magnetic shielding of axial C—O bonds relative to C—$CH_3$ bonds on opposing axial hydrogens, it was decided to examine the NMR spectra of the *cis-* and *trans*-4-*t*-butyl-2,2,6,6-tetradeuterio-1-methylcyclohexanols. In the case of the *trans*-isomer, wherein the hydroxyl is equatorial, and using carbon tetrachloride as solvent, a rough doublet of intensity 2 centered at 1.7 p.p.m. was assigned to the two equivalent equatorial hydrogens at the 3- and 5-positions. The signals for the geminal axial hydrogens on the basis of intensity measurements appeared to be about 1.0 p.p.m., a position in the field about half-way between the signals for the two kinds of *C*-methyl peaks in the molecule. This chemical shift between the geminal hydrogens at the 3- or 5-positions of about 0.70 p.p.m. is assumed to arise mainly from the diamagnetic anisotropy of the neighboring C—C bonds (42). On the other hand, the spectrum of the *cis*-isomer required both the axial and equatorial hydrogens at the 3- and 5-positions to produce their signal at about the same positions, 1.47 p.p.m. Thus, as expected, the axial hydroxyl has a deshielding effect on the opposing axial hydrogens. The signals for the axial and equatorial hydrogens at the 3- and 5-positions of *trans*-4-*t*-butyl-2,2,6,6-tetradeuteriocyclohexanol under the same conditions were at about 1.0 and 1.8 p.p.m., respectively. A comparison of these chemical shifts with those given above for the 1-*C*-methyl derivative (1.0 and 1.7 p.p.m., respectively) shows the influence of an axial C—$CH_3$ bond on the chemical shift of an opposing axial hydrogen to be much less than that of a C—OH bond. Since substantially the same results were obtained with pyridine as the solvent, it seems clear that the shielding effects noted are intramolecular in origin.

In conclusion, it is of interest to note that the chemical shifts of the ring hydrogens of cyclohexane and its derivatives appear best rationalized as a first rough approximation (±0.1 p.p.m.) through a consideration of the inductive effects of substituent groups and of the shielding effects from neighboring *groups of atoms* rather than individual chemical bonds. Tau values are used in the following discussion to simplify the presentation. Shielding effects were derived by inspection of the chemical shifts observed in the variety of compounds considered using the chemical shift of the equatorial hydrogens of cyclohexane 8.35 $\tau$ (43), as the reference point in the magnetic field. Using Anet's data (28),* the inductive effect of an hydroxyl group on the chemical shift of a hydrogen situated on the same carbon was set at $-2.20$ $\tau$ and on a vicinal carbon at $-0.20$ $\tau$. Furthermore, the effect on the chemical shift of a hydrogen of projecting between H—C—H, H—C—OH, H—C—CH, and CH—C—OH groupings was estimated to be about 0.0, 0.0, 0.25, and 0.50 $\tau$, respectively. Also, the effect on the chemical shift of an axial hydrogen of being opposed by an axial hydroxyl was set at 0.50 $\tau$. On this basis, it would be anticipated that the equatorial hydrogens at the 2- and 6-positions of the *cis-* and *trans*-4-*t*-butylcyclohexanols and at the 3- and 6-positions of *trans*-1,2-cyclohexanediol would produce their signals at 8.15 $\tau$. The chemical shifts actually observed were 8.23, 8.08, and 8.08 $\tau$, respectively. The 1-hydrogen of *cis*-4-*t*-butylcyclohexanol would be expected to give its signal at 6.15 $\tau$; the observed position was 6.06 $\tau$. The calculations of the chemical shifts for these equatorial hydrogens involved only the inductive effects. However, the shielding effects of neighboring groups influence strongly the chemical shifts of axially oriented hydrogens. Thus, the chemical shifts for the axial hydrogens at the 2- and 6-positions of *trans*-4-*t*-

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*The authors wish to thank Professor Anet for providing them prior to publication with the chemical shifts of the ring hydrogens of the cis- and trans-4-t-butylcyclohexanols deuterated at the 3-, 4-, and 5-positions.*

butylcyclohexanol and at the 3- and 6-positions of *trans*-1,2-cyclohexanediol would both be expected to be at $8.35 + 0.50 + 0.25 - 0.20 = 8.90\ \tau$. The values observed are 8.88 and 8.77 $\tau$, respectively. The position of the 1-hydrogen of *trans*-4-*t*-butylcyclohexanol would be expected at $8.35 + (2\times0.25) - 2.20 = 6.65\ \tau$, found 6.62 $\tau$. The signal of the 1- (or 2-) hydrogen of *trans*-1,2-cyclohexanediol would be expected to occur at $8.35 + 0.50 + 0.25 - 2.20 - 0.20 = 6.70\ \tau$, the chemical shift actually observed. In the case of the axial 2- or 6-hydrogens of *cis*-4-*t*-butylcyclohexanol, a chemical shift of $8.35 + (2\times0.25) - 0.20 = 8.65\ \tau$ is expected. The shift found for this hydrogen was 8.63 $\tau$. A consideration of the chemical shifts for the A-, B-, and X-hydrogens of *cis*-1,2-cyclohexanediol in equal populations of the conformations IV and V gave the following results. The A-hydrogen would be expected to produce its signal at $8.35 + 0.50 + 0.25 - 0.50 - 0.20 = 8.40\ \tau$ and at $8.35 - 0.20 = 8.15\ \tau$ in conformations IV and V, respectively. Thus, an averaged value of 8.28 $\tau$ would be expected which compared well with the observed value of 8.23 $\tau$. In the case of the B-hydrogen, chemical shifts of $8.35 - 0.20 = 8.15\ \tau$ and $8.35 + (2\times0.25) - 0.20 = 8.65\ \tau$ would be expected for conformations IV and V, respectively, with an averaged value of 8.40 $\tau$. The value observed was 8.47 $\tau$. Thus, the relative positions of the A- and B-hydrogens are rationalized. The X-hydrogen would be expected to produce its signal at $8.35 + (2\times0.25) - 2.20 - 0.20 = 6.45\ \tau$ and $8.35 - 2.20 - 0.20 = 5.95\ \tau$ in the IV and V conformations, respectively. The average of these values 6.20 $\tau$, is in good agreement with that observed, 6.25 $\tau$. The agreement could be improved by the introduction of further parameters. However, such refinements would only obscure the main point of the discussion, which is to indicate that reasonably good agreement can be achieved by the addition of shielding effects arising from neighboring groups of atoms. This was not possible when only individual neighboring bonds were considered. The same situation was found to be the case in an attempt to rationalize the chemical shifts observed (4) for the ring hydrogens of isomeric benzene hexachlorides. Reasonable agreement was only obtained when shielding effects were assigned to H—C—Cl, H—C—CH, CH—C—Cl, and axial C—Cl groups in the manner described above for the alcohols.

## EXPERIMENTAL

### *Nuclear Magnetic Resonance Spectra and Double Irradiation Experiments*

Solutions, 5–10% (w/v), were prepared in suitable solvents containing 0.5% tetramethylsilane as internal reference. Spectra were first recorded conventionally at 60 Mc.p.s. on a Varian Associates A-60 spectrometer and at 100 Mc.p.s. on a Varian model H.R. 100 spectrometer and line positions calibrated in both cases by the sideband technique using a Hewlett-Packard audiofrequency oscillator model 200AB and electronic counter model 521C. It is possible to operate in the sideband mode by altering the modulation level and altering the audio phase by 90°. Ordinary absorption spectra differing only in sign are then obtained by using the upper or lower 2 kc.p.s. sideband ($w_1$). Additional field modulation at a variable frequency $w_2$ c.p.s. can make a portion of the residual rf power available for selective nuclear saturation in the $w_1$ sideband spectrum. In this way, proton–proton spin decoupling is obtained (24). When operating on the first lower $w_1$ sideband (which was used throughout these experiments) protons with chemical shifts at higher applied fields (the A- and B-protons) may be decoupled in turn from the X-proton by setting $(w_2-w_1)$ approximately equal to the chemical shifts $\delta_{AX}$ or $\delta_{BX}$. Due care was taken to reduce the modulation amplitude so that the observed X-lines were not broadened by saturation. To confirm that successful decoupling had been accomplished, a check was made that the X-quartet or triplet regained its original shape as $(w_2-w_1)$ was increased beyond the optimum decoupling value. Several determinations were made of decoupling frequency for each substance and the results are summarized in Tables IV, V, and VI. In general, as seen from Table II, the agreement between the sums of the X-spacings and the calculated coupling constants $(J_{AX} + J_{BX})$ was as good as the measurement of the spacings (±0.2 c.p.s.). Judging from results with other compounds involving similar chemical shifts, the discrepancy in the case of the *trans*-diol in deuterium oxide must be the result of experimental errors and $J_{AX}$ and $J_{BX}$ likely have values closer to the values reflected by the X-spacings for this compound.

All melting points were determined in capillaries and are uncorrected.

TABLE IV

Double irradiation experiments on *trans*-1,4,4-trideuteriocyclohexene dihalides* in benzene

| Compound | Proton and lines irradiated | Decoupling frequencies,† c.p.s. | Lines collapsed | Appropriate measured spacings,‡ c.p.s. | $J_{AB}$, c.p.s. | Chemical shifts,§ c.p.s. | |
|---|---|---|---|---|---|---|---|
| | | | | | | $\delta_A$ | $\delta_B$ |
| Dichloride | B (1 and 2) | 239.8 | 10, 12 | 3.72 | 12.38 | 199 | 139 |
| | B (3 and 4) | 223.7 | 9, 11 | | | | |
| | A (5 and 6) | 179.8 | 11, 12 | 8.16 | 10.84 | | |
| | A (7 and 8) | 160.8 | 9, 10 | | | | |
| Dibromide | B (1 and 2) | 268.7 | 10, 12 | 3.69 | 11.20 | 210 | 150 |
| | B (3 and 4) | 253.8 | 9, 11 | | | | |
| | A (5 and 6) | 208.2 | 11, 12 | 5.57 | 11.00 | | |
| | A (7 and 8) | 191.6 | 9, 10 | | | | |
| Diiodide | B (1 and 2) | 325.3 | 10, 12 | 3.36 | 11.10 | 200 | 156 |
| | B (3 and 4) | 309.1 | 9, 11 | | | | |
| | A (5 and 6) | 279.4 | 11, 12 | 3.36 | 12.80 | | |
| | A (7 and 8) | 264.9 | 9, 10 | | | | |

*In each case the measurements were made on the signal for the X-proton.
†Average of three to four determinations.
‡These spacings were substituted in either expressions 1 and 2 or 3 and 4 to obtain $J_{AB}$.
§These shifts are those deduced as described in the text.

### *trans-1,4,4-Trideuteriocyclohexene*

A solution of 26 g of cyclohexane-1,4-dione (L. Lights and Co., purified by sublimation) in 100 ml of purified anhydrous tetrahydrofuran was added dropwise to a rapidly stirred suspension of 5 g of lithium aluminum deuteride (98%) in 100 ml of anhydrous tetrahydrofuran over a period of 1 hour. A considerable quantity of white insoluble complex separated and the mixture became very viscous. After complete addition of the dione the mixture was stirred at room temperature for 12 hours, cooled in ice, and treated cautiously with 20 ml of ice water with rapid stirring, followed by 100 ml of ice-cold 2 *N* sulphuric acid. The organic layer was removed and the aqueous layer saturated with sodium chloride and extracted three times with ether. The combined extract was dried over magnesium sulphate and filtered, and the solvents evaporated. The combined yield of *cis*- and *trans*-1,4-dideuteriocyclohexane-1,4-diols, obtained as a waxy solid from three similar preparations, was 70.5 g, 88%. The mixture of diols was used without further purification.

A mixture of 70 g of reagent aluminum oxide (which had been freshly roasted to drive off absorbed water, and cooled) and 70.5 g of *cis*- and *trans*-cyclohexane-1,4-diols was heated to 240–250° under a Vigreux column for 6 hours and the distillate collected. The organic layer of the distillate was removed and the aqueous layer extracted with ether (3×15 ml). The combined extract was dried over magnesium sulphate, filtered, and fractionated at atmospheric pressure through a spinning-band column. The 1,4-dideuterio-1,4-epoxycyclohexane distilled at 115° at 700 mm (b.p. for hydrogen analogue, 117–118° (12)). The yield was 12.05 g, 20.5%. Gas–liquid chromatographic analysis of the product on a silicone oil column at 80° showed the product to be pure. The NMR spectrum showed no detectable absorption at 4.66 p.p.m. from internal tetramethylsilane at the position expected for the hydrogens at the 1- and 4-positions.

A solution of hydrogen bromide in ether was prepared by passing the dry gas into ice cold anhydrous ether for ½ hour. The concentration of the hydrogen bromide was determined by titration. 1,4-Dideuterio-1,4-epoxycyclohexane (12 g, 0.12 *M*) was dissolved in 250 ml of the anhydrous ether solution of hydrogen bromide (0.18 *M*) and the mixture set aside in the dark at room temperature for 24 hours. The solution was refluxed for ½ hour, the solvent removed *in vacuo* and the residual pink oil purified by chromatography of silicic acid with light petroleum ether (b.p. 60–80°) as eluant. Evaporation of the eluate afforded 1,4-dideuterio-*trans*-4-bromocyclohexanol, 19 g (87%), as a white crystalline solid m.p. 80°. Rothstein (44) has described the preparation of the mixed cis- and trans-compounds.

### *1,4,4-Trideuteriocyclohexanol*

In a typical experiment 2.03 g of 1,4-dideuterio-*trans*-4-bromocyclohexanol was dissolved in a solution of 0.307 g of sodium in 20 ml of anhydrous methanol. The bromide was subjected to rapid deuterolysis over 0.312 g of 5% palladium-on-charcoal with deuterium generated electrolytically from sodium deuteroxide solution. A rapid uptake of gas was observed and when no more deuterium was absorbed the solution was filtered through Celite. The methanol was removed by fractional distillation with a small spinning-band column. The residue was poured into brine and the mixture was extracted several times with ether. The combined extracts from several similar experiments were dried over magnesium sulphate, filtered, and

TABLE V

Double irradiation experiments on *cis*-1,2-cyclohexanediols and their derivatives*

| Compound | Solvent | Proton and lines irradiated | Decoupling frequencies,† c.p.s. | Lines collapsed | Appropriate measured spacings,‡ c.p.s. | $J_{AB}$, c.p.s. | Chemical shifts,§ c.p.s. | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | $\delta_A$ | $\delta_B$ |
| Di-*O*-acetyl | $CCl_4$ | B (1 and 2) | 346.0 | 11, 12 | 6.98 | 11.2 | 180 | 157 |
| | | B (3 and 4) | 327.8 | 9, 10 | | | | |
| | | A (5 and 6) | 318.8 | 10, 12 | 3.62 | 11.4 | | |
| | | A (7 and 8) | 303.8 | 9, 11 | | | | |
| Diol | $CHCl_3$ | B (1 and 2) | 231.8 | 11, 12 | 7.00 | 10 | 177 | 153 |
| | | B (3 and 4) | 214.8 | 9, 10 | | | | |
| | | A (5 and 6) | 204.6 | 10, 12 | 3.80 | 11.6 | | |
| | | A (7 and 8) | 189.2 | 9, 11 | | | | |
| Diol | $D_2O$ | B (1 and 2) | 237.8 | 11, 12 | 6.50 | 11.5 | 218 | 194 |
| | | B (3 and 4) | 219.8 | 9, 10 | | | | |
| | | A (5 and 6) | 209.8 | 10, 12 | 4.29 | 10.7 | | |
| | | A (7 and 8) | 194.8 | 9, 11 | | | | |
| Di-*O*-tosyl | $CHCl_3$ | B (1 and 2) | 309.2 | 11, 12 | 7.72 | 12.2 | 196 | 154 |
| | | B (3 and 4) | 288.2 | 9, 10 | | | | |
| | | A (5 and 6) | 261.7 | 10, 12 | 2.77 | 12.4 | | |
| | | A (7 and 8) | 246.5 | 9, 11 | | | | |
| *O*-Isopropylidene | $CCl_4$ | B (1 and 2) | 252 | {11, 12 | 5.40 | 11.6 | 181 | 154 |
| | | B (3 and 4) | 234 | 9, 10} | | | | |
| | | A (5 and 6) | 222 | {10, 12 | 5.40 | 12.6 | | |
| | | A (7 and 8) | 205 | 9, 11} | | | | |

*In each case the measurements were made on the signal for the X-proton.
†Average of three to four determinations.
‡These spacings were substituted in either expressions 1 and 2 or 3 and 4 to obtain $J_{AB}$.
§These shifts are those deduced as described in the text.

TABLE VI

Double irradiation experiments on *trans*-1,2-cyclohexanediols and their derivatives*

| Compound | Solvent | Proton and lines irradiated | Decoupling frequencies,† c.p.s. | Lines collapsed | Appropriate measured spacings,‡ c.p.s. | $J_{AB}$, c.p.s. | Chemical shifts,§ c.p.s. | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | $\delta_A$ | $\delta_B$ |
| Di-*O*-acetyl | $CCl_4$ | B (1 and 2) | 345.8 | 10, 12 | 4.20 | 10.8 | 140 | 133 |
| | | B (3 and 4) | 330.8 | 9, 11 | | | | |
| | | A (5 and 6) | 335.8 | (11, 12) | 10.15 | 9.85 | | |
| | | A (7 and 8) | 315.8 | 9, 10 | | | | |
| Diol | $CHCl_3$ | B (1 and 2) | 217.6 | 10, 12 | 4.55 | 11.9 | 193 | 123 |
| | | B (3 and 4) | 201.2 | 9, 11 | | | | |
| | | A (5 and 6) | 149.8 | 11, 12 | 11.06 | 10.94 | | |
| | | A (7 and 8) | 127.8 | 9, 10 | | | | |
| Diol | $D_2O$ | B (1 and 2) | 222.2 | 10, 12 | 4.26 | 12.74 | 241 | 171 |
| | | B (3 and 4) | 205.2 | 9, 11 | | | | |
| | | A (5 and 6) | 154.2 | 11, 12 | 10.91 | 12.10 | | |
| | | A (7 and 8) | 131.2 | 9, 10 | | | | |
| Di-*O*-tosyl | $CHCl_3$ | B (1 and 2) | 300.9 | 10, 12 | 3.62 | 12.88 | 196 | 148 |
| | | B (3 and 4) | 284.4 | 9, 11 | | | | |
| | | A (5 and 6) | 252.9 | 11, 12 | 7.82 | 11.88 | | |
| | | A (7 and 8) | 233.2 | 9, 10 | | | | |
| *O*-Isopropylidene | $CCl_4$ | B (1 and 2) | 181.2 | 10, 12 | 3.46 | 11.54 | 205 | 137 |
| | | B (3 and 4) | 166.2 | 9, 11 | | | | |
| | | A (5 and 6) | 116.2 | 11, 12 | 10.99 | 12.31 | | |
| | | A (7 and 8) | 92.9 | 9, 10 | | | | |

*In each case the measurements were made on the signal for the X-proton.

†Average of three to four determinations.

‡These spacings were substituted in either expressions 1 and 2 or 3 and 4 to obtain $J_{AB}$.

§These shifts are those deduced as described in the text.

fractionated to yield 7.32 g (75% yield) of 1,4,4-trideuteriocyclohexanol as a colorless oil. Freshly recrystallized *p*-toluenesulphonyl chloride, 21 g, was added in portions with shaking to a solution of 7.32 g of 1,4,4-trideuteriocyclohexanol in 45 ml of anhydrous pyridine at −2°. The solution was shaken until all the chloride had dissolved, then allowed to warm to room temperature, and set aside for 3 hours. Two milliters of water was added cautiously with shaking. After several minutes, the mixture was poured into 200 ml of water. On chilling, the precipitated oil crystallized. The product was purified by washing with water, drying, and recrystallizing from (1:2) ether/pentane. The white plates, 16 g (87%), melted at 44–45°, the melting point recorded (45) for cyclohexyl-*p*-toluenesulphonate. The 1,4,4-trideuteriocyclohexyl-*p*-toluenesulphonate, 5 g, was dissolved in a solution of 3 g of potassium hydroxide in 10 ml of redistilled diethylene glycol. The mixture was heated under conditions for distillation at 110° and the distillate was collected in a trap cooled in a mixture of solid carbon dioxide and acetone. The organic layer was removed from the distillate and dried over magnesium sulphate. Gas–liquid chromatographic analysis of the product showed it to be pure. The yield of 1,4,4-trideuteriocyclohexene was 1.3 g, 10%. Integration of the NMR spectrum showed the relative intensities of the ethylenic and methylenic hydrogens to be 1:5.8 (expected for I, 1:6). See Fig. 1.

### *1,4,4-Trideuteriocyclohexene-trans-1,2-dibromide in Benzene*

A 4% (w/v) solution of bromine in cold dry benzene was prepared and a slight molar excess was added with stirring to a solution of 117.6 mg of 1,4,4-trideuteriocyclohexene in 1 ml of dry benzene until a permanent pink color remained. The excess bromine was dispelled with a stream of air, the solution passed down a short column of grade 1 alumina, and the eluate concentrated under a spinning-band column to a small volume. The solution was then made up to 1.0 ml with dry benzene containing 0.5% of tetramethylsilane for the NMR experiment.

### *1,4,4-Trideuteriocyclohexene-trans-1,2-dichloride in Benzene*

A solution of 124.3 mg of 1,4,4-trideuteriocyclohexene in 1 ml of dry benzene was treated dropwise with stirring with a solution of chlorine in cold dry benzene. The course of the reaction was followed by NMR and the reaction was judged to be complete when the olefinic band disappeared. The excess chlorine was dispelled with a stream of air, the solution passed down a short column of grade 1 alumina, and the eluate concentrated under a spinning-band column to a small volume. The solution was then diluted to 1.0 ml with dry benzene containing 0.5% of tetramethylsilane for the NMR experiments.

### *1,4,4-Trideuteriocyclohexene-trans-1,2-diiodide in Benzene*

Finely powdered iodine, 378 mg, in a vial was cooled in an acetone – solid carbon dioxide mixture and treated dropwise with 127 mg of 1,4,4-trideuteriocyclohexene. The iodine reacted immediately and a reddish-brown solution resulted. The mixture was allowed to reach room temperature, then made up to 1.0 ml with dry benzene containing 0.5% of tetramethylsilane. The solution was used immediately for the NMR experiments.

### *1,4,4-Trideuterio-cis-cyclohexene-1,2-diol*

1,4,4-Trideuteriocyclohexene, 0.7 g, and 2 g of osmium tetraoxide in 30 ml of dry pyridine were mixed at 0° with rapid stirring (14). The mixture immediately set to a mass of brown crystals. After 30 minutes, the mixture was treated with a solution of sodium bisulphite in 60 ml of water and 40 ml of pyridine (15) and the mixture stirred until a clear orange solution was obtained. The solution was thoroughly extracted with chloroform and the extract was dried over magnesium sulphate. Evaporation of the filtered extract left a brown gum from which pure 1,4,4-trideuterio-*cis*-cyclohexane-1,2-diol was obtained as a white crystalline solid by sublimation at 70° and 1 mm pressure. The yield was 0.69 g (70%), m.p. 98° (46).

### *1,4,4-Trideuterio-trans-cyclohexane-1,2-diol*

A solution of 1.44 g of 1,4,4-trideuteriocyclohexene in 5 ml of 98% formic acid was warmed to 45° and treated with 30% aqueous hydrogen peroxide (14) with stirring at a rate to maintain an internal temperature of 55–60°. The addition took 75 minutes. The solution was stirred at 60° for 1 hour, then subjected to steam distillation until 90 ml of distillate was collected. Evaporation of the residual aqueous solution *in vacuo* afforded a yellow gum which readily crystallized. The product, 1,4,4-trideuterio-*trans*-cyclohexane-1,2-diol, was dried and purified by sublimation at 70° and 1 mm pressure. The compound was obtained as a white crystalline solid, 1.30 g (65%), m.p. 101° (literature, m.p. 103.5° (46)).

### *1,4,4-Trideuterio-cis-cyclohexane-1,2-diol Di-p-toluenesulphonate*

A solution of 0.10 g of 1,4,4-trideuterio-*cis*-cyclohexane-1,2-diol in 2 ml of dry pyridine at −5° was treated with 0.60 g of freshly recrystallized *p*-toluenesulphonyl chloride in portions with shaking. When all the reagent has been added, the solution was allowed to attain room temperature and was set aside for 3 hours. A few drops of water were added, and after several minutes the solution was poured into 4 volumes of water. The precipitated oil crystallized. The product was washed with water, dried, and purified by recrystallization from ethanol. The yield was 0.25 g (70%), m.p. 127° (literature (47) m.p. of hydrogen analogue 128.5–129.5°).

*1,4,4-Trideuterio-trans-cyclohexane-1,2-diol Di-p-toluenesulphonate*

Similar treatment of 0.1 g of the *trans*-deuteriodiol with 0.6 g of *p*-toluenesulphonyl chloride afforded 0.2 g (55%), m.p. 105°, of the di-*p*-toluenesulphonate (literature (47) m.p. of hydrogen analogue 109°).

*1,4,4-Trideuterio-cis-cyclohexane-1,2-diol Diacetate*

1,4,4-Trideuterio-*cis*-cyclohexane-1,2-diol, 141 mg, was treated with 0.5 ml of acetic anhydride containing a trace of concentrated sulphuric acid as catalyst. The diol dissolved immediately with evolution of heat but the solution soon returned to room temperature and was set aside for an hour. The acid catalyst was neutralized with a little solid calcium carbonate and the filtered solution concentrated to a small volume *in vacuo*. The crude diacetate was purified by elution chromatography on acid-washed alumina using carbon tetrachloride. Evaporation of the eluant afforded diacetate as a colorless oil, 0.2 g (83%), which was characterized by comparison using gas–liquid partition chromatography with an authentic sample.

*1,4,4-Trideuterio-trans-cyclohexane-1,2-diol Diacetate*

Similar treatment of 0.143 g of the *trans*-trideuteriodiol with 0.5 ml of acetic anhydride and chromatographic purification provided the diacetate as a colorless oil, 0.2 g (82%), which was characterized by gas–liquid partition chromatography.

*O-Isopropylidene-1,4,4-trideuterio-cis-cyclohexane-1,2-diol*

A solution of 0.201 g of the trideuterio-*cis*-cyclohexane-1,2-diol in 8 ml of dry acetone and 8 ml of pentane containing 20 mg of *p*-toluenesulphonic acid was refluxed for 60 hours in a Dean-Stark apparatus (48). The residual solution was cooled and treated with 10 mg of solid sodium acetate. The filtered solution was concentrated to a small volume *in vacuo*. The residual oil was purified by elution chromatography on acid-washed alumina using carbon tetrachloride. Evaporation of the eluate afforded the isopropylidene derivative as a colorless oil, 0.15 g (56%). The product was shown to be pure by gas–liquid partition chromatography.

*trans-O-Isopropylidene-1,4,4-trideuteriocyclohexane-1,2-diol*

A solution of 78 mg of the trideuterio-*trans*-cyclohexane-1,2-diol and 9.65 mg of *p*-toluenesulphonic acid in a mixture of 15 ml of 2,2-dimethoxypropane and 5 ml of carbon tetrachloride was heated under reflux for 20 hours. The excess solvents were removed by distillation at atmospheric pressure until the residual volume was about 4 ml. The cooled yellow solution was poured down a silica gel chromatography column covered by a 1-in. section of alumina. The column was developed with carbon tetrachloride and 25-ml fractions of the eluant were collected and concentrated to a small volume by fractionational distillation. The fractions containing the desired product were detected by NMR spectroscopy and combined. The pure product was isolated by preparative gas–liquid partition chromatography on a silicone oil column at 90° and collected in tubes cooled by a mixture of acetone and solid carbon dioxide. The *trans-O*-isopropylidene-1,4,4-trideuteriocyclohexane-1,2-diol, 15 mg (14.5%), produced an NMR spectrum at 100 Mc.p.s. consistent with its structure. Also, it showed the same behavior on gas–liquid partition chromatography as an authentic sample (48).

*4-t-Butyl-2,2,6,6-tetradeuteriocyclohexanone*

A solution of 2.74 g of 4-*t*-butylcyclohexanone in a mixture of 10 ml of anhydrous dioxane and 7 ml of deuterium oxide containing a trace of sodium was sealed in a Carius tube and heated at 100° for 12 hours. The contents were than rapidly extracted with *n*-pentane. Evaporation of the *n*-pentane gave a yellow oil which was treated for a second time under the above conditions for deuterium exchange. The product was isolated by extraction and purified by sublimation. The yield was 2.05 g of a compound with the expected melting point and deuterium content (NMR analysis).

*trans-4-t-Butyl-2,2,6,6-tetradeuteriocyclohexanol*

The tetradeuterioketone was reduced with lithium aluminum hydride in ether and the product was isolated in the usual way. The crude product, m.p. 63–65°, was purified by chromatography as described by Winstein and Holness (49).

*cis- and trans-4-t-Butyl-2,2,6,6-tetradeuterio-1-methylcyclohexanols*

The tetradeuterioketone, 10 g, was reacted with methylmagnesium iodide in ether and the partially crystalline product, isolated in the usual manner, was chromatographed on grade 1 alumina using *n*-pentane – diethyl ether (1:2) for development. Two well-resolved fractions were obtained. The first fraction (cis-isomer) gave a white crystalline material, m.p. 70–71°, after recrystallization from Skellysolve B. The second fraction (*trans*-isomer) melted at 97–98° after recrystallization from ethyl acetate. This latter compound in carbon tetrachloride solution showed absorption in the infrared for intermolecularly hydrogen-bonded hydroxyl which was much more dependent on concentration than was the lower melting, faster moving (chromatogram) former compound. The configurational assignments were made on this basis.

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