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The 1,3-Diaxial Dibromo Interaction

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The non-bonding interaction between two bromine atoms sited 1,3-diaxially on a simple cyclohexane ring is explored by X-ray crystallography. The ring is distorted to allow the bromine atoms an interatomic distance of 3.54 Å.

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Introduction

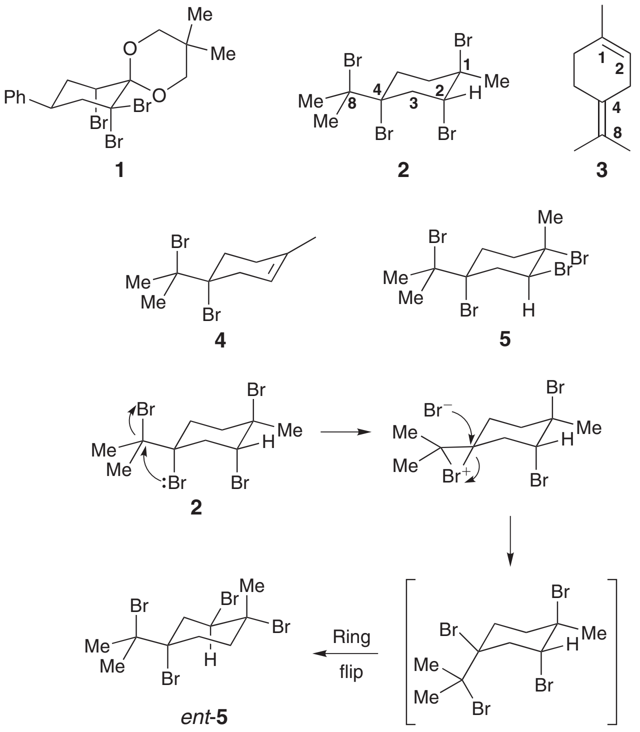
The interatomic distance between two non-bonded atoms situated 1,3-diaxially on an undistorted cyclohexane ring is 1.78 Å. The distance between the two bonded atoms in molecular bromine is 2.29 Å. Therefore, considerable repulsion must occur between two non-bonded bromine atoms placed 1,3-diaxially on a cyclohexane system. A search of the X-ray literature did not provide any simple 1,3-diaxial dibromide cyclohexane structures, but a 1,3-diaxial interaction has been reported[1] for compound **1**. However, the interaction in compound **1** is complicated by both a geminal dibromide and the anomeric effects of the spiro-1,3-dioxane appendage. We now report an examination of the terpinolene tetrabromide **2**.

Results and Discussion

The bromination of terpinolene **3** was first reported by Otto Wallach[2] in 1885 when he prepared a crystalline tetrabromide and noticed its instability even at room temperature. Later workers[3–6] observed two forms of terpinolene tetrabromide. The second, more stable form was obtained either by recrystallizing or melting the unstable form. Interestingly, both these forms have had cell dimensions previously examined by crystallographers.[3,7]

Through NMR spectroscopic examination Venzke[8] showed that the unstable isomer had expected structure **2**. This is formed by initial addition of bromine to the more electron-rich 4,8-double bond of terpinolene **3** to provide dibromide **4** followed by *trans*-diaxial addition of bromine to the 1,2-double bond. The stable isomer has structure **5**, in which Br1 and Br2 are equatorial.

In principal, the rearrangement of **2** to give **5** could proceed by a Barton–Winstein rearrangement either about the C1–C2 bond and involve Br1 and Br2 or about the C4–C8 bond and involve Br4 and Br8. Venzke[8] showed by radioactive bromide labelling that the rearrangement actually occurs about Br4 and Br8 with concomitant ring-flip to avoid the large bromoisopropyl group becoming axial (Scheme 1). At that time it was not possible to determine whether it was Br4 that attacked C8 while Br8 departed (as shown in Scheme 1) or whether the alternative pathway occurred, namely that Br8 attacked C4 while Br4 departed.



Scheme 1.

The rearrangement about Br4 and Br8 (Scheme 1), as opposed to one that might occur about Br1 and Br2, provides the enantiomer of **5** (*ent*-**5**). Since terpinolene **3** is achiral, most of the work on these compounds has been carried out on racemic **2**, and thereby it has not been possible to examine the chirality of **5**. However, Venzke[9] later synthesized chiral isomer **2** and showed that *ent*-**5** is indeed formed after rearrangement.

The instability of isomer **2** is undoubtedly the result of 1,3-diaxial repulsion of the two bromine atoms sited at C2

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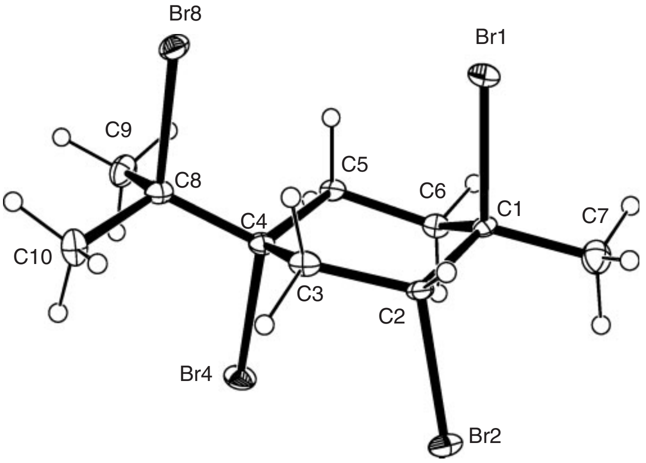

Fig. 1. *ORTEP* drawing of the diaxial tetrabromide **2** (30% ellipsoids).

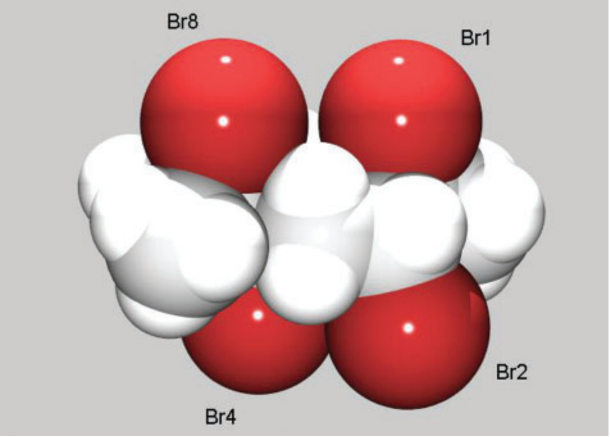

Fig. 2. Space-filling portrayal of compound **2**, viewed with C3 in the centre. The isopropyl methyl groups on the left are eclipsed. The van der Waals radii used in generating the picture were C 1.70, H 1.20, and Br 1.85 Å. The image was created with *ORTEP3* and rendered with *PovRay* version 3.5.

and C4. This interaction cannot be relieved by a simple ring-flip as this would then place the larger bromoisopropyl group in an extremely unfavourable axial environment. In order to examine these effects the X-ray crystal structure of compound **2** has been determined at low temperature (Fig. 1).

The *cis*-diaxial atoms Br2 and Br4 are separated by a distance of 3.54 Å and the cyclohexane chair is distorted to compensate for the closeness of this non-bonded repulsion (the van der Waals radius of Br is 1.85 Å). For comparison, the C2···C4 separation is 2.63 Å. The distortion of the cyclohexane ring is most evident upon inspection of the dihedral angles (C1—C2—C3—C4 39.6°, C2—C3—C4—C5 36.4°, and C3—C4—C5—C6 41.5°). Furthermore, the distortion is localized around the two diaxial Br atoms as shown by the fact that the dihedral angles for C4—C5—C6—C1 (52.2°) and C5—C6—C1—C2 (53.6°) more closely approach the ideal 60° of an undistorted ring. The C2—Br2 and C4—Br4 vectors are tilted by approximately 26° relative to each other, which is consistent with the reported[1] angle (approx. 28°) in spiro compound **1**, but unlike the parallel nature of the two axial bonds in an undistorted chair. The abuttal of Br2 and Br4 in structure **2** is clearly depicted in the space-filling representation illustrated in Fig. 2. The separation between Br1 and Br8 (4.06 Å) is clearly in excess of the sum of their van der Waals radii.

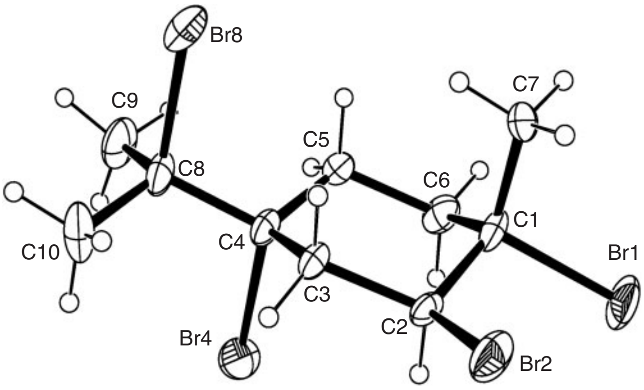

Fig. 3. *ORTEP* drawing of the diequatorial tetrabromide **5** (30% ellipsoids).

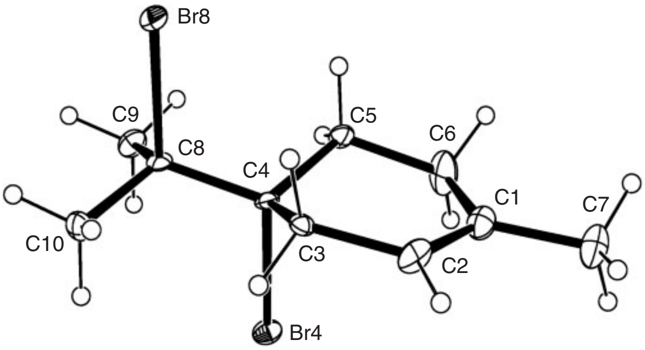

Fig. 4. *ORTEP* drawing of dibromide **4** (30% ellipsoids).

A consequence of this diaxial Br···Br repulsion is that Br4 is pushed towards C8 (Br4···C8 2.84 Å) and Br8 is somewhat further from C4 (2.88 Å). Therefore, we speculate that it is probably attack by Br4 of C8 which initiates the rearrangement to give structure **5** (Scheme 1) rather than attack of Br8 on C4. These distances are reproduced by molecular mechanics calculations using PC Model 8.5 (Br2···Br4 3.49 Å, Br4···C8 2.91 Å, and Br8···C4 2.97 Å).

In relation to previous literature, when transformed to the variant space group $P2_1/a$ (*a* 15.423, *b* 9.915, *c* 9.477 Å, *β* 113.93°), the cell dimensions of compound **2** are consistent with the optical measurements taken on a crystalline sample of 'compound A' reported by Henry and Paget,[3] and earlier still (before the discovery of X-rays!) by Hintze.[7]

The X-ray crystal structure of the isomeric diequatorial tetrabromide **5** (Fig. 3) reveals a relatively undisturbed cyclohexyl ring. The greatest distortions are C2—C3—C4—C5 (44.9°) and C3—C4—C5—C6 (44.3°), with all the other dihedral angles being within 7° of their ideal value. Nevertheless, the Br1···Br2 separation is relatively short (3.48 Å), even more so than the Br2···Br4 distance seen in the structure of compound **2**. However, in compound **5** the cyclohexyl ring is less able to distort in order to relieve this 1,2-interaction. Dibromide **4** (Fig. 4) has no Br···Br contacts and the only distortion of the ring arises from the C1—C2 double bond as expected for a cyclohexene ring system.

Molecular mechanics (MM3) predicts a free energy difference of 10.0 kJ mol^{-1} between isomers **2** and **5**, and suggests that an equilibrium mixture of the two at 27°C might contain approximately 1.7% of unstable isomer **2**. On the other hand, MMX software predicts an energy difference of only 7.0 kJ mol^{-1}, in which case 5.7% of isomer **2** would exist in an equilibrated mixture. NMR spectroscopic examination of pure compound **2** in $CDCl_3$ showed the rapid formation of isomer **5** (H2$_{eq}$ (dt) of compound **2** at δ 4.81 equilibrating with H2$_{ax}$ (dd) of isomer **5** at δ 4.91). After one hour, as well as three, six, and fourteen days (about 25°C in $CDCl_3$), the amounts of isomer **5** present were approximately 5, 58, 83, and 98%, respectively. After 30 days, the mixture had totally rearranged to give isomer **5** with undetectable ($<$0.5%) amounts of isomer **2** present. Although, as previously observed[8] this is not a true equilibrium because olefinic decomposition products are also slowly formed, it does suggest an energy difference of $>$13 kJ mol^{-1} between the two isomers.

The steric interaction of the two bromines at C2 and C4 in compound **2** might be expected to provide a γ-effect upon the chemical shifts of the two relevant carbon atoms, thereby causing them to be more electronically shielded and moved to a higher field in the NMR spectrum. A similar γ-effect might be expected for C6. This is indeed true as the shifts of C2, C4, and C6 (δ 55.0, 73.4, and 36.6, respectively, in compound **2**) move to a lower field (δ 60.8, 79.2, and 40.7, respectively) upon relief of this interaction in compound **5**.

Experimental

^{1}H and ^{13}C NMR spectra were conducted in $CDCl_3$ solutions at ambient temperature and were recorded using both Bruker 400 and 500 MHz spectrometers. Assignments were made using DEPT, HSQC, HMBC, COSY, and double quantum filtered COSY pulse sequences. Correlation experiments for compound **2** were further run at 10°C for improved stability of the compound.

Tetrabromide 2

In a modification of the method of Briggs and Sutherland[10] and Venzke,[8] terpinolene **3** (0.85 g) in ethanol (1.0 mL) and diethyl ether (5.0 mL) at 0°C was treated dropwise with bromine (2.0 g) in cold diethyl ether (3.0 mL). The diethyl ether was then removed at below room temperature and the resultant solid was collected by filtration and washed with ice-cold ethanol. The crystals were stirred with a small volume of acetone at room temperature to achieve a saturated solution. The liquid was decanted off and cooled slowly to -18°C to provide plates of ($\pm$)-(1*RS*,2*RS*,4*RS*)-1,2,4,8-tetrabromo-*p*-menthane **2**, mp 115°C (lit.[3,8] 115–116°C, 119°C). δ_H (on a solution made up immediately before running the spectrum) 4.81 (ddd, H2$_{eq}$), 3.57 (very poorly resolved br d, H3$_{ax}$), 2.93 (very poorly resolved br t, H6$_{ax}$), 2.67 (br d, H3$_{eq}$), 2.43 (ddd, H5$_{ax}$), 2.34 (br d, H6$_{eq}$), 2.08, 2.03, 2.01 (three Me), 1.98 (partly obscured dddd, H5$_{eq}$), consistent with that reported;[8] with $J_{2eq,3ax}$ 2.0, $J_{2eq,3eq}$ 5.2, $J_{2eq,6eq}$ 2.0, $J_{3ax,3eq} \approx -15$, $J_{5ax,5eq}$ -15.0, $J_{5ax,6ax}$ 12.4, $J_{5ax,6eq}$ 3.5, $J_{5eq,6ax} \approx 4$, $J_{6ax,6eq} \approx -15$ Hz. The ^{1}H NMR spectrum showed only trace amounts of isomer **5** (δ 4.91) at time zero, but increasing amounts of isomer **5** were observed as the solution was stored at room temperature. After 30 days, the spectrum showed approximately 98% of compound **5** and isomer **2** could not be detected. δ_C 74.4 (C8), 73.4 (C4), 69.0 (C1), 55.0 (C2), 40.2 (C3), 36.6 (C5 and C6), 33.7 (C7), 31.2 and 30.4 (C9 and C10).

Dibromide 4

Terpinolene **3** (0.85 g) in ethanol (1.0 mL) and diethyl ether (5.0 mL) at 0°C was treated dropwise with bromine (1.0 g) in cold diethyl ether (3.0 mL). The diethyl ether was then removed at below room temperature and the resultant solid was collected by filtration and washed with ice-cold ethanol. The product was recrystallized from acetone (-18°C) to provide plates of ($\pm$)-4,8-dibromo-*p*-menth-1-ene **4**, mp 69°C (lit.[10,11] 69°C), with a ^{1}H NMR spectrum as previously reported[11] and characterized by a resonance at δ 5.30 (br m, H2).

Tetrabromide 5

Isomer **2** was boiled in ethanol (10 min), the solvent was removed, and the resultant solid was recrystallized from acetone (-18°C) to provide plates of ($\pm$)-(1*RS*,2*RS*,4*SR*)-1,2,4,8-tetrabromo-*p*-menthane **5**, mp 122°C (lit.[3,8] 121–122°C).* δ_H 4.91 (dd, H2$_{ax}$), 2.89 (ddd, H6$_{ax}$), 2.84 (dd, H3$_{ax}$), 2.67 (ddd, H3$_{eq}$), 2.54 (ddd, H6$_{eq}$), 2.44 (br ddd, H5$_{ax}$), 2.02 (partly obscured m, H5$_{eq}$), 1.99 and 1.97 (two Me s, H9 and H10), 1.87 (Me s, H7), consistent with that reported;[8] with $J_{2ax,3ax}$ 12.0, $J_{2ax,3eq}$ 4.6, $J_{3ax,3eq}$ -15.1, $J_{3eq,5eq}$ 2.9, $J_{5ax,5eq} \approx -15$, $J_{5ax,6ax} \approx 13.4$, $J_{5ax,6eq}$ 4.0, $J_{5eq,6ax}$ 4.1, $J_{5eq,6eq}$ 2.9, $J_{6ax,6eq}$ -13.9 Hz. The spectrum did not show any sign of isomer **2** (δ 4.81) at time zero or after two months at 25°C. δ_C 79.2 (C4), 73.2 (C8), 65.8 (C1), 60.8 (C2), 45.0 (C3), 40.7 (C6), 34.2 (C5), 31.1 and 30.9 (C9 and C10), 25.4 (C7).

Crystallography

Compound 2

$C_{10}H_{16}Br_4$, *M* 455.87, *T* 150(2) K, monoclinic, space group $P2_1/n$, *a* 9.477(1), *b* 9.915(3), *c* 14.461(3) Å, β 102.87(1)°, *V* 1324.7(5) Å^3, *Z* 4, *F*(000) 864, D_c 2.286 g cm^{-3}, μ 121.16 cm^{-1}, 2336 unique data ($2\theta_{max}$ 50°), *R* 0.0376 [for 1532 reflections with $I > 2\sigma(I)$], wR_2 0.1015 (all data).

Compound 4

$C_{10}H_{16}Br_2$, *M* 296.05, *T* 150(2) K, monoclinic, space group $P2_1/c$, *a* 5.929(2), *b* 10.608(3), *c* 17.65(1) Å, β 95.51(3)°, *V* 1105.0(8) Å^3, *Z* 4, *F*(000) 584, D_c 1.780 g cm^{-3}, μ 72.85 cm^{-1}, 1926 unique data ($2\theta_{max}$ 50°, R_{int} 0.0632), *R* 0.0403 [for 1224 reflections with $I > 2\sigma(I)$], wR_2 0.1055 (all data).

Compound 5

$C_{10}H_{16}Br_2$, *M* 455.87, *T* 293(2) K, monoclinic, space group $C2/c$, *a* 19.690(7), *b* 6.213(1), *c* 23.685(9) Å, β 109.63(3)°, *V* 2729.1(15) Å^3, *Z* 8, *F*(000) 416, D_c 2.219 g cm^{-3}, μ 117.62 cm^{-1}, 2404 unique data ($2\theta_{max}$ 50°, R_{int} 0.0524), *R* 0.0507 [for 1181 reflections with $I > 2\sigma(I)$], wR_2 0.1502 (all data).

Intensity data were collected on an Enraf–Nonius CAD4 four-circle diffractometer using graphite monochromated $Mo_{K\alpha}$ radiation (λ 0.71073 Å) in the ω–2θ scan mode. Data for compounds **2** and **4** were collected at 150 K with the aid of an Oxford Cryostream Cooler, while compound **5** was measured at room temperature. Lattice dimensions were determined by a least-squares fit of the setting parameters of 25 independent reflections. Data reduction and empirical absorption corrections (ψ-scans) were performed with the *WINGX* package.[12] Structures were solved by direct methods with *SHELXS* and refined by full matrix least-squares analysis with *SHELXL97*.[13] All non-H atoms were refined with anisotropic thermal parameters, and H-atoms were constrained at estimated positions using a riding model. The atomic nomenclature defined in Figs 1, 3, and 4 is drawn with *ORTEP3*.[14] The space-filling diagram (Fig. 2) was produced with *ORTEP3* and

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*Despite reports[3,8] that isomers **2** and **5** give a large mixed melting point depression, the two isomers interconvert at their melting point and thus the melting points are dependent upon the rate of heating. We do not consider that the melting point value provides a reliable means for distinguishing between these two isomers.

rendered with *PovRay* version 3.5. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre (CCDC deposition numbers: 262356 for **2**, 262357 for **4**, and 262358 for **5**). Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax +44 1223 336033; email deposit@ccdc.cam.ac.uk, or http://www.ccdc.cam.ac.uk).

Acknowledgments

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