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# 2-Bromocyclohexanone Perhydrate—X-ray Crystal Structure and Conformational Effects on Reactivity in Sulfoxidations

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**Abstract**—The remarkably stable crystalline perhydrate **1** derived from α-bromocyclohexanone has been characterised by X-ray crystallography providing the first example of a perhydrate crystal structure. Perhydrate **1** exists in alternative chair conformations in chloroform and tetrahydrofuran with the bromine substituent occupying equatorial and axial positions, respectively. The perhydrate **1** can oxidise sulfides to sulfoxides in good yields in dichloromethane but not in tetrahydrofuran. The requirement for bromine to be equatorial for a stable perhydrate to form is demonstrated using conformationally locked *cis* and *trans* 2-bromo-4-*tert*-butylcyclohexanones in which case only the *cis* isomer **4a** forms a perhydrate. 

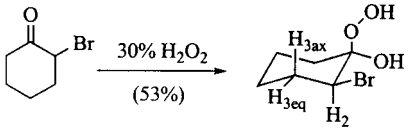
## Introduction

The use of electron deficient ketones as precursors to activated peroxide reagents such as perhydrates[1] and dioxiranes[2] has recently attracted considerable interest. The structural and electronic requirements for activity and selectivity of the ketone precursors are beginning to be probed. Hexafluoroacetone perhydrate is perhaps the best known perhydrate but this reagent must be generated at low temperature (−60°C) using 90% hydrogen peroxide and must be stored at 0°C.[3] The remarkably stable α-bromocyclohexanone perhydrate **1** was first reported by Kharasch in 1958 but no details on stereochemistry were given due to limitations in analytical methods at that time.[4] We now report the full structural characterisation of perhydrate **1**, *the first example of a perhydrate characterised by an X-ray crystal structure* and the importance of stereochemical and conformational effects on reactivity for the oxidation of simple sulfides.

## Results and Discussion

We prepared the perhydrate **1** according to the original procedure[4] that involved admixture of equimolar amounts of α-bromocyclohexanone and 30% hydrogen peroxide (Scheme 1). The crystals formed were filtered and recrystallised from hot toluene (Scheme 1). The perhydrate **1** is a white crystalline solid (mp 82–83°C) and is isolated as a single diastereomer in 53% yield. $^{13}$C NMR spectroscopy ($CDCl_3$) shows a characteristic signal at 101.2 ppm for the perhydrate carbon. $^1$H NMR spectroscopy ($CDCl_3$) shows a double doublet for H-2 with $J_{2,3ax}$=9.2 Hz and $J_{2,3eq}$=4.4 Hz indicating the H-2 and H-3$_{ax}$ to be *trans* diaxial and that the bromine is equatorial. A characteristic signal for the peroxide hydrogen was observed as a sharp singlet at 8 ppm (free peroxide $\delta_H$=7.6 ppm).

In order to determine the relative stereochemistry of the bromo and perhydroxy groups we obtained an X-ray crystal structure, which shows a *cis* disposition between the two groups, with the perhydroxy group axial and bromo equatorial (Fig. 1). The peroxy O–O bond points away from the bromine atom; a suggestion[1] that the structure is stabilised by intramolecular hydrogen-bonding between bromine and perhydroxy is not supported by the crystal structure, although this cannot be ruled out in solution. Both the perhydroxy and the hydroxy OH groups show two-fold disorder of orientation in the crystal structure, and they engage in an extensive network of hydrogen




**1**

**Scheme 1.**

*Keywords*: perhydrate; α-bromocyclohexanone; conformational effects; sulfoxidation; X-Ray structure.

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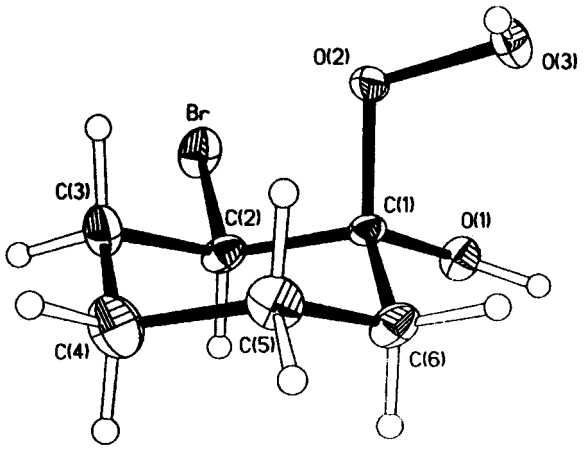
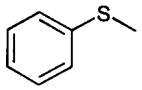
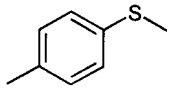
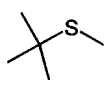



**Figure 1.** Molecular structure of α-bromocyclohexanone perhydrate **1** in the crystalline state.

bonding which links the groups on adjacent molecules; O···O hydrogen-bond distances lie between 2.781 and 2.812 Å, with angles at hydrogen between 152 and 167°. The closest Br···O intermolecular distance is 3.572 Å, with no hydrogen atom directed even approximately along this line, so there is no significant involvement of bromine in the hydrogen bonding scheme.

The perhydrate **1** is able to carry out the sulfoxidation of a range of sulphides giving sulfoxides in good to excellent yields (Table 1) with no overoxidation to the sulfones observed. In comparison with the well known perhydrates of hexafluoroacetone and 1,1,1-trifluoroacetone as oxidants for sulfoxidation, perhydrate **1** possesses intermediate reactivity. For example, transformation of diphenyl sulphide to the sulfoxide with hexafluoroacetone perhydrate is very fast (1 min) whereas 1,1,1-trifluroacetone perhydrate takes several days to oxidise a range of related substrates.[1] Notably hexafluoroacetone perhydrate must be prepared at −60°C using 90% $H_2O_2$, making this reagent unsuitable for use on a large scale. Recently, Sheldon has used perfluoroheptadecan-9-one as a selective and mild catalyst for the epoxidation of a wide variety of alkenes with hydrogen peroxide; after the reaction the catalyst could be recovered and reused without noticable decomposition.[5] Although we have not carried out an extensive survey, it appears that the perhydrate **1** is not a good source of electrophilic oxygen since epoxidation of substrates such as cyclooctene and 1-phenylcyclohexene was very slow. As a nucleophilic oxidant, Baeyer Villiger oxidation was only observed for highly reactive strained ketones such as bicyclo[3.2.0]heptenone (1 equiv. of perhydrate **1** in dichloromethane, 12 h, 92% yield) but not for cyclohexanone or cyclopentanone. Perhydrate **1** may therefore prove useful as a selective oxidant in synthesis since it is easily prepared on scale, although caution should always be exercised when handling organic peroxides and we have not shock tested this material.

**Table 1.** All reactions were carried out in dichloromethane (5 $cm^3$), sulfide (1 equiv.) and perhydrate **1** (1.2 equiv.). The yield was determined by GC (FFAP)

| Entry | Substrate | Time (h) | Sulfoxide Yield% |
|---|---|---|---|
| 1 |  | 4 | 86 |
| 2 |  | 3 | 99 |
| 3 |  | 5 | 80 |
| 4 |  | 1 | 98 |

Importantly we have shown that the perhydrate **1** is the active oxidant and not hydrogen peroxide, which might be liberated in situ. Stirring it in dichloromethane for 24 h showed no decomposition and no free peroxide being formed. Surprisingly no sulfoxidation was observed when using tetrahydrofuran as the solvent with any of the substrates used in Table 1. This lack of reactivity may be due to stabilisation of the perhydrate by H-bonding interactions with the solvent or might reflect the importance of stereoelectronic effects where the relative position of the bromine would affect the electrophilicity of the terminal peroxy oxygen. Interestingly in $d^8$-tetrahydrofuran the $^1$H NMR spectrum of **1** showed a triplet for the H-2 signal with $J$=4.1 Hz indicating that the perhydrate adopts the alternative chair conformation where the bromine is axial (Fig. 2).

In order to test this latter hypothesis we synthesised the conformationally locked 2-bromo-4-*tert*-butylcyclohexanone epimers **4a** and **4b** starting from ketone **2** by bromination of the derived silyl enol ether **3**[6] with *N*-bromosuccinimide (Scheme 2). The bromination reaction gave a 3:4 ratio of separable diastereoisomers **4a** and **4b** in which bromine was shown to reside in the equatorial and axial positions respectively, by examination of the coupling constants for H-2.

Treatment of the isolated equatorial bromoketone **4a** in *tert*-butyl methyl ether with 30% hydrogen peroxide afforded a stable perhydrate assumed to have the structure **5**, by analogy to the formation of perhydrate **1** (Scheme 3).

As for perhydrate **1**, $^1$H NMR spectroscopy ($CDCl_3$) of the perhydrate **5** shows a double doublet for H-2 with $J_{2,3ax}$=9.2 Hz and $J_{2,3eq}$=4.4 Hz indicating that the bromine

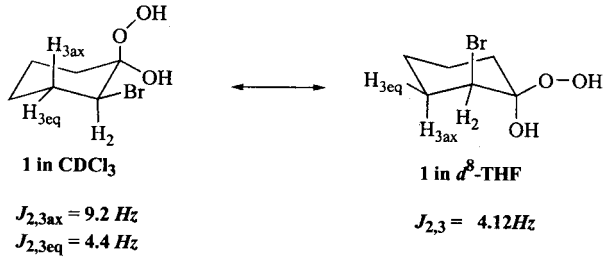
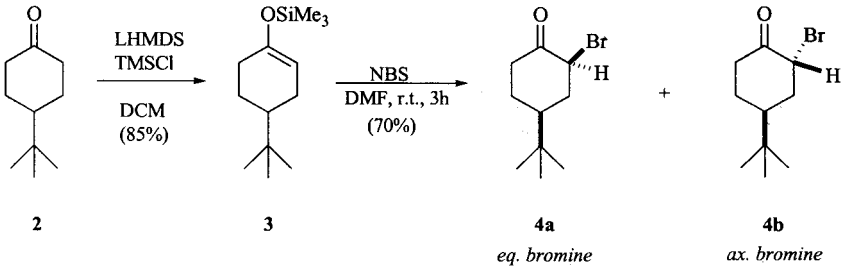
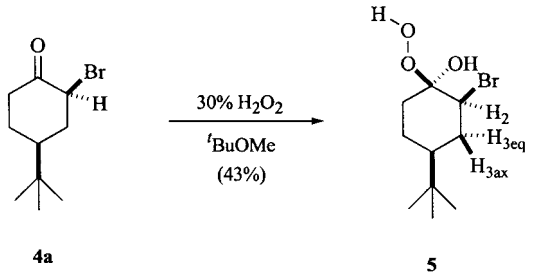



**Figure 2.**




**Scheme 2.**




**Scheme 3.**

has remained equatorial. However, in contrast to the perhydrate **1**, the $^1$H NMR in $d^8$-tetrahydrofuran showed no significant change in appearance for the H-2 signal, reflecting the conformational rigidity of this compound. Oxidation of methyl *p*-tolyl sulfide with the perhydrate **5** in dichloromethane proceeded at a slower rate to that observed with perhydrate **1** (40% conversion in 3 h). The same reaction carried out in tetrahydrofuran resulted in a much slower conversion (6.5% conversion in 3 h).

We therefore conclude that the reactivity of these perhydrates in dichloromethane arises by intermolecular H-bonded interactions (OOH to OH or Br) whereas in tetrahydrofuran this activation is disrupted. The slower rate of reaction with conformationally locked perhydrate **5** in dichloromethane might be explained by a higher energy barrier for the conversion of **5** to **4a** when compared with the conversion of **1** to 2-bromocyclohexanone. Calculations using heats of formation give an energy difference of 3.2 kcal/mol for this transformation in favour of the non-locked system **1**.[7] This difference presumably represents the increased energy barrier for re-establishing the sp$^2$ carbonyl centre in the cyclohexanone ring when its conformational flexibility is limited by the 4-*tert*-butyl substituent. An attempt to form the perhydrate with an axial bromine by treatment of ketone **4b** with 30% hydrogen peroxide resulted in recovery of an equimolar mixture of **5** and **4b**, presumably resulting from acid-catalysed equilibration (pH of $H_2O_2$ solution=3.5) followed by perhydrate formation from ketone **4a**. Repeating the same reaction in phosphate buffer at pH 7 or in dichloromethane with urea-hydrogen peroxide gave no conversion and only recovered ketone **4b**. These results reflect a requirement for an equatorial bromine in order for a stable perhydrate to form. This might be explained either by the anomeric[8,9] lowering of reactivity of the carbonyl group by an axial bromine (efficient overlapping of the $\sigma^*$ and $\pi$ orbitals) or by the inability of perhydrates derived from the axial $\alpha$-bromoketones to experience stabilisation through H-bonding.

## Experimental

### General

Melting points were determined with a Gallenkamp apparatus and are uncorrected. Elemental analyses were performed by the microanalysis service of the University of Liverpool. Infrared spectra were recorded either on a Perkin Elmer 883 Infrared spectrophotometer or on a Perkin Elmer 1720-X FTIR spectrometer. Solid samples were run as KBr disc and liquid as a thin films. $^1$H NMR spectra were recorded either on a Bruker AC 200 (200 MHz), on a Varian Gemini 2000 (300 MHz) or on a Bruker AMX 400 (400 MHZ) spectrometer for solutions in $CDCl_3$ unless otherwise stated. $^{13}$C NMR spectra were recorded with a Varian Gemini 2000 (75 MHz) or on a Bruker AMX 400 (100 MHz) spectrometer for solutions in $CDCl_3$ unless otherwise stated. The chemical shifts are in parts per million (ppm) using tetramethylsilane as the internal reference. Coupling constants are in hertz (Hz). Mass spectra were recorded with a Fisons TRIO 1000. All solvents and reagents were purified and dried according to standard procedures. Thin layer chromatography (TLC) was performed on silica gel 60-$F_{254}$ (Merck). For column chromatography, silica gel 60 (Merck, 63–200 $\mu$m) was used without pre-treatment.

**1-Hydroxy-2-bromocyclohexyl hydroperoxide 1.** 2-Bromocyclohexanone (12.93 g, 72.65 mmol) was added to hydrogen peroxide solution (30%, 9 cm$^3$, 79.38 mmol) and stirred vigorously over 1 h. The stirring was stopped and the reaction left overnight. The product crystallised to form a white solid, which was crushed in toluene/petroleum-ether. The solid was filtered and washed with the organic solvent. The mother liquor was concentrated under reduced pressure and more product was recovered and filtered. The solids were combined and recrystallised from hot toluene to give the pure perhydrate **1** as a white crystaline solid (8.05 g, 52.5%); (Found: C, 34.28; H, 5.30; Br, 37.73. $C_6H_{11}BrO_3$ requires C, 34.15; H, 5.25; Br, 37.86%); $\nu_{max}$ (KBr)/cm$^{-1}$: 3260, 3175 ($\nu$O–H), 1198 ($\nu$C–C–O); $\delta_H$ (400 MHz, $CDCl_3$): 1.52–1.43 (2H, m), 1.69–1.62 (2H, m), 1.80–1.74 (1H, m), 2.20–2.05 (2H, m), 2.52–2.38 (1H, m), 3.32 (1H, s, OH), 4.30 (1H, dd, $J_{2,3ax}$=9.2 Hz, $J_{2,3eq}$=4.4 Hz, 2-H), 7.98 (1H, s, OOH);); $\delta_H$ (400 MHz, $d^8$-THF): 1.46–

1.39 (2H, m), 1.61–1.54 (2H, m), 2.15–1.89 (4H, m), 4.39 (1H, t, $J_{2,3}$=4.1 Hz), 5.47 (1H, bs, OH), 10.35 (1H, s, OOH); $\delta_C$ (100 MHz, $CDCl_3$): 22.00–24.49 (4-C, 5-C), 30.94 (3-C), 33.46 (6-C), 56.56 (2-C), 101.16 (1-C).

## Crystal structure determination for 1[10]

*Crystal data:* $C_6H_{11}BrO_3$, $M$=211.06, triclinic, space group $P\bar{1}$, $a$=5.5579(6), $b$=6.5299(7), $c$=10.9826(12) Å, $\alpha$=b 76.363(3), $\beta$=84.367(3), $\gamma$=85.686(3)°, $U$=384.92(7) Å$^3$, $Z$=2, $D_g$=1.821 g cm$^{-3}$, $\mu$=5.29 mm$^{-1}$ (MoK$\alpha$, $\lambda$= 0.71073 Å), $T$=160 K. Of 3099 reflections measured on a Bruker AXS SMART CCD diffractometer and corrected semiempirically for absorption, 1732 were unique ($\theta$<28.6°, $R_{int}$=0.0480). The structure was solved by heavy-atom methods and refined on $F^2$ values. Hydrogen atoms bonded to carbon were constrained with a riding model. The O–H groups (hydroxy and perhydroxy) were each found by difference maps to be disordered equally over two orientations, which were refined with geometry restraints. $R$=0.0571 ($F$ values, $F^2>2\sigma$), $R_w$=0.1377 ($F^2$ values, all data), goodness-of-fit=0.995, final difference map extremes (close to Br) +1.39 and −1.17$e$ Å$^{-3}$. Software: Bruker SMART, SAINT, and SHELXTL.

***cis and trans*-2-Bromo-*tert*-butylcyclohexanone (4a and b).** 4-*tert*-Butyl-1-trimethylsiloxycyclohexene 3[2] (2.3 g, 10.17 mmol) was dissolved in DMF (10 cm$^3$) and stirred vigorously. *N*-Bromosuccinimide (2.53 g, 14.24 mmol) was dissolved in DMF (10 cm$^3$) and added dropwise to the reaction mixture. The temperature was maintained at 0°C during the addition then slowly raised to room temperature. After 3 h, the reaction mixture was transferred into a separating funnel and water (100 cm$^3$) was added. The organic layer was extracted and the aqueous layer washed with diethyl ether (4×40 cm$^3$). The organic solutions were combined, washed with brine (40 cm$^3$) and dried over magnesium sulfate. The organic solvent was evaporated under reduced pressure to give a brown oil that was purified by flash-chromatography on silica gel buffered with triethylamine (*tert*-butyl methyl ester - *n*-hexane, 1:13) to give the *cis* and *trans* isomers **4a** and **b**.

*cis*-2-bromo-*tert*-butylcyclohexanone **4a** as a white solid (0.905 g, 38%); mp 64–66°C; (Found: C, 51.52; H, 7.39, Br, 34.83, $C_{10}H_{17}BrO$ requires C, 51.52; H, 7.35; Br, 34.27%); $\nu_{max}$ (KBr)/cm$^{-1}$: 1726 ($\nu$C=O); $\delta_H$ (400 MHz; $CDCl_3$): 0.93 (9H, s, 3x$CH_3$), 1.57–1.46 (1H, m, 5-H$_{ax}$), 1.71–1.63 (1H, m, 4-H$_{ax}$), 1.96–1.86 (1H, m, 3-H$_{ax}$), 2.18–2.11 (1H, m, 5-H$_{eq}$), 2.47–2.38 (1H, m, 6-H$_{ax}$), 2.72–2.64 (2H, m, 3-H$_{eq}$ and 6-H$_{eq}$), 4.69 (1H, ddd, $J_{2,3ax}$=13.3 Hz, $J_{2,3eq}$=6.1 Hz, $J$=1.2 Hz, 2-H$_{ax}$); $\delta_C$ (100 MHz): 27.7 (3x$CH_3$), 28.0 (5-C), 32.8 (4′-C), 40.2 (6-C), 41.2 (3-C), 48.7 (4-C), 56.5 (2-C), 201.8 (1-C); *m*/*z* (EI): 232 and 234 (2.65%, 2.56%) bromine isotopes $[M+H]^+$, 176 and 178 (6.08, 5.58) bromine isotopes, 97 (25.33), 57 (100).

*trans*-2-Bromo-*tert*-butylcyclohexanone **4b** as a colourless oil (0.951 g, 40%);$\nu_{max}$ (film)/cm$^{-1}$: 1721 ($\nu$C=O); $\delta_H$ (300 MHz; $CDCl_3$) 0.93 (9H, s, 3×$CH_3$), 1.51–1.37 (1H, m, 5-H$_{ax}$), 2.01–1.86 (2H, m, 3-H$_{ax}$ and 4-H$_{ax}$), 2.14–2.04 (1H, m, 5-H$_{eq}$), 2.36–2.28 (2H, m, 3-H$_{eq}$ and 6-H$_{eq}$), 3.18–3.06 (1H, m, 6-H$_{ax}$) 4.37 (IH, m, 2-H$_{eq}$); $\delta_C$ (75 MHz): 27.4 (3×$CH_3$ and 5-C), 31.8 (4′-C), 35.6 (6-C), 36.0 (3-C), 40.7 (4-C), 51.5 (2-C), 205.1 (1-C); *m*/*z* (EI): 232 and 234 (1.48, 1.21) bromine isotopes $[M+H]^+$, 176 and 178 (3.65%, 3.43%) bromine isotopes, 97 (18.76), 57 (100).

***cis*-1-Hydroxy-2-bromo-*tert*-butylcyclohexyl hydroperoxide 5.** *cis*-2-Bromo-*tert*-butylcyclohexanone **4a** (2 g, 8.6 mmol) was dissolved in *tert*-butyl methyl ether (3 cm$^3$) and stirred vigorously. A 30% hydrogen peroxide solution was added (1.17 cm$^3$, 10.3 mmol) and stirred for 15 h, the reaction mixture was transferred to a separating funnel, the organic layer was separated and the aqueous layer washed with *tert*-butyl methyl ether (3×1.5 cm$^3$). The organic solutions were combined and dried over magnesium sulfate. The organic solvent was evaporated under reduced pressure to give a white solid. The solid was recrystallised from pentane at -20°C to give white crystals (0.985 g, 43%); mp 57–59°C (Found: C, 44.60; H, 7.24; Br, 29.82, $C_{10}H_{19}BrO_3$ requires C, 44.96; H, 7.17; Br, 29.91%); $\nu_{max}$ (KBr)/cm$^{-1}$: 3560, 3211 ($\nu$O–H), 1176 ($\nu$C–C–O); $\delta_H$ (400 MHz; $CDCl_3$): 0.88 (9H, s, 3×$CH_3$), 1.24–1.16 (1H, m, 4-H$_{ax}$), 1.38–1.27 (1H, m, 5-H$_{ax}$), 1.65–1.57 (1H, m, 6-H$_{ax}$), 1.90–1.71 (2H, m, 5-H$_{eq}$ and 3-H$_{ax}$), 2.28–2.22 (1H, m, 3-H$_{eq}$), 2.64–2.59 (1H, m, 6-H$_{eq}$), 3.4 (1H, br, –OH), 4.25 (IH, dd, $J_{2,3ax}$=12.5 Hz, $J_{2,3eq}$=4.8 Hz, 2-H$_{ax}$), 8.17 (1H, br, –OOH); $\delta_C$ (100 MHz): 23.7 (5-C), 28.1 (3×$CH_3$), 28.2 (4′-C), 33.1 (6-C), 37.5 (3-C), 49.9 (4-C), 58.2 (2-C), 101.7 (1-C)

## Typical sulfoxidation procedure using 1-hydroxy-2-bromocyclohexyl hydroperoxide

1-Hydroxy-2-bromocyclohexyl hydroperoxide (0.169 g, 0.80 mmol) was dissolved in DCM (10 cm$^3$) and stirred. Methylphenyl sulphide (0.100 g, 0.8 mmol) was added to the reaction mixture. After 4 h the solvent was evaporated and the crude was purified by flash-chromatography on silica gel eluting firstly with dichloromethane to give the unreacted sulfide and α-bromocyclohexanone then with ethyl acetate to give methyl phenyl sulfoxide[11] as cloudy yellow oil, (95 mg, 85%).

## Acknowledgements

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